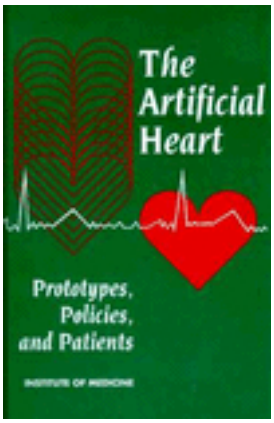

The Artificial Heart: Prototypes, Policies, and Patients

John R. Hogness and Malin VanAntwerp, Editors; Committee to Evaluate the Artificial Heart Program of the National Heart, Lung, and Blood Institute; Division of Health Care Services

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The Artificial Heart

Prototypes, Policies, and Patients

Committee to Evaluate the Artificial Heart Program of the
National Heart, Lung, and Blood Institute
Division of Health Care Services
INSTITUTE OF MEDICINE

John R. Hogness and Malin VanAntwerp, Editors

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NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard to appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

The Institute of Medicine was chartered in 1970 by the National Academy of Sciences to enlist distinguished members of the appropriate professions in the examination of policy matters pertaining to the health of the public. In this, the Institute acts under both the Academy's 1863 congressional charter responsibility to be an advisor to the federal government and its own initiative in identifying issues of medical care, research, and education.

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The image adopted as a logotype by the Institute of Medicine is based on a relief carving from ancient Greece, now held by the Staatlichemussen in Berlin.

COMMITTEE TO EVALUATE THE ARTIFICIAL HEART PROGRAM OF THE NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

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The committee is especially grateful to the authors of its commissioned papers: H. Tristram Engelhardt, Jr., and Kevin W. Wildes of the Center for Medicine, Ethics, and Public Issues at Baylor College of Medicine; Marjorie Funk of the Yale University Department of Epidemiology and Public Health and School of Nursing; Louis P. Garrison, Jr., of the Project HOPE Center for Health Affairs; James H. Maxwell of the Massachusetts Institute of Technology Center for Technology, Policy and Industrial Development; and Gerson P. Rosenberg of the Division of Thoracic Surgery, Pennsylvania State University. The committee also appreciates the opportunities it had to interact with those who participated in its workshops, including these authors and the following: William A. Baumgartner, Johns Hopkins Hospital; G. William Dec, Massachusetts General Hospital; Peer M. Portner, Novacor Division, Baxter Healthcare Corporation; Stuart F. Seides, Washington Hospital Center; and Michael H. Shapiro, University of Southern California Law Center.

The committee was particularly pleased to have as a guest at one of its meetings a heart transplant patient who had been the recipient of a tempo

rary ventricular assist device while awaiting a donor heart. The patient's spouse was also a guest at this meeting. Although these individuals must remain anonymous, their insights into the experience of living with a mechanical circulatory support device, if only temporarily, were very helpful to the committee.

A number of researchers and developers in the mechanical circulatory support field and other knowledgeable individuals provided helpful information and views in response to committee requests. We especially appreciate the contributions by the 23 persons who made presentations at the committee's public meeting and whose names appear in Appendix A. We know that the time limits imposed on their presentations were constraining, although necessary, and thank them for traveling to Washington to state their views in person.

Thanks are also due to the Division of Clinical Decision Making of the New England Medical Center and to the University of Washington School of Public Health and Community Medicine for special assistance in our work.

Finally, and in particular, the committee would like to express its appreciation of the Institute of Medicine (IOM) staff who facilitated the work of this committee. We especially thank Malin VanAntwerp, whose diverse expertise in the fields of health care technology assessment, policy analysis, and medical device regulation was very useful to the study, as well as Jo Harris-Wehling and Holly Dawkins for their many substantive and procedural contributions to the committee's work. All three worked tirelessly to support the committee throughout the study and served capably as primary authors of report chapters. Richard A. Rettig, another member of the IOM professional staff, assisted in drafting the report, and Wallace K. Waterfall, director of the IOM Office of Communications, edited the report. We also appreciate very much the logistical support and manuscript preparation provided by Thelma Cox, the administrative help of H. Donald Tiller, and the assistance of Lisa Chimento and Nina Spruill, financial associates. In particular, the guidance and constant support provided by Kathleen N. Lohr, Deputy Director of the Division of Health Care Services, was invaluable.

Preface

HEART DISEASE causes more than 700,000 deaths each year in the United States alone. Decades of research have led to drugs, medical devices, and procedures that provide effective treatment for many forms of heart disease, yet even today an individual suffering from end-stage heart disease faces a bleak outlook and has few treatment options.

This Institute of Medicine (IOM) study of the artificial heart program of the National Heart, Lung, and Blood Institute (NHLBI) is particularly timely because, after more than 25 years of research, the program is nearing a historic milestone: the first model of a fully implantable, long-term ventricular assist device, designed to reverse the effects of heart failure for many individuals, will undergo clinical trials in 1992. Furthermore, longterm total artificial hearts are under development and scheduled for trials early in the next century. If these devices fulfill their developers' expectations, both the benefits to the patients receiving them and the technology's ultimate impact on the nation's health care system will be dramatic.

The committee's intent was to conduct an independent, comprehensive study of this technology. As the devices are perfected and move into widespread use, this study will, we hope, provide long-term guidance to NHLBI and the broader health care community.

At the same time, because our study has examined a family of technologies, many not yet tried in humans, the IOM committee and its consultants have had to rely on the best possible estimates of these devices' ultimate performance. The issues reviewed here will require periodic reexamination as clinical trial data become available.

This study follows a series of program reviews by groups under the

auspices of NHLBI and its predecessor institutes, dating from 1969 through 1985. The present two-phase study was commissioned by NHLBI's director after a number of events in 1988 indicated the advisability of an independent review of the artificial heart program.

The study's first phase was a planning effort by an IOM committee chaired by Theodore Cooper, M.D., chairman and chief executive officer of The Upjohn Company and former director of the National Heart and Lung Institute. That committee's 1989 report, *The Artificial Heart Program of NHLBI: Plan for Evaluation,* laid the groundwork for the present evaluation by identifying and elaborating on nine questions about NHLBI's future role in artificial heart development. These nine questions have guided this study, and the committee has chosen to examine a number of specific additional issues implicit in responding to these questions.

Much has been accomplished over the 27 years of the artificial heart program's work. Many individual researchers in both academe and private industry have dedicated their careers to development of mechanical circulatory support systems (MCSSs) and warrant commendation for their efforts. All those who played a role in the artificial heart program's creation or who are (or have been) involved in directing and overseeing projects within the program deserve the credit they will appropriately receive once long-term devices come into routine clinical use. Additionally, although past financial support from the private sector has not been as extensive as it is likely to become, the firms and investors that have made possible much of today's research progress should be gratified by its probable outcome.

Rarely has an important advance in health care been such a widely shared undertaking, accomplished in a truly collegial manner among academic researchers, private industry, and government, as has been R&D in the MCSS field. The committee is pleased to be able to comment on the credit that is due to all those involved.

The present study's scope has been limited to long-term devices because those intended only for temporary support are not currently a focus of the artificial heart program. Similarly, we leave to the cardiothoracic surgeons and cardiologists who become expert in applying this technology the task of developing specific clinical indicators for the use of artificial hearts and criteria for the implanting surgeon's appropriate training and experience. These are important topics but are outside the scope of the NHLBI charge and the committee members' expertise.

For some of the same reasons, we have not scrutinized the involvement of the NHLBI Devices and Technology Branch, the sponsor of the artificial heart program, in research concerning biomaterials, cardiovascular imaging, and other technological fields; in some of these areas, NHLBI is virtually the sole source of federal research support. The committee report does look into the appropriateness of using the existing research priority-setting and

funding mechanism for applied research of these types, but did not evaluate the substance of the projects themselves.

Finally, the constraints of producing a document of reasonable length and balance required the committee to focus the written report on those issues not fully discussed by other advisory groups. Consequently, some of the committee's deliberations on more familiar topics are recorded in less depth than might otherwise have been the case. Entire books, for instance, could be and have been written about such concerns as ethical aspects of patient care, but the committee's discussions are distilled in a few pages. A decision was made to focus on issues of particular and perhaps overlooked import, instead of recording the entire depth and range of all the committee's deliberations.

In developing this report, the committee has found itself indebted not only to the 1989 IOM planning committee, but also to those on the previous NHLBI review panels; several from these groups are also members of the current committee. We have not cataloged every recommendation of the prior studies, but their depth and substance have undergirded our work.

The IOM planning committee suggested that the considerations outlined in its report "are appropriate for assessing other complex health technologies." Similarly, this committee recognizes the broad applicability of the concepts, methods, and findings discussed in the pages that follow to decisions by manufacturers, third-party payers, and others. Those interested in the complex arena of government-supported research by academe and industry will also find several research policy issues discussed.

We commend the National Heart, Lung, and Blood Institute for recognizing the importance of studies such as this, conducted by independent groups of individuals with relevant expertise. The committee hopes its report will be useful not only to NHLBI in decisions concerning the future of the artificial heart program, but also to clinicians, policymakers, researchers, health insurers, and others involved in developing, assessing, and applying new technologies that have as their goal the improvement of patient care.

John R. Hogness, Chair
Committee to Evaluate the Artificial Heart
Program of the National Heart,
Lung, and Blood Institute

Contents

The Artificial Heart

Executive Summary

AFTER 27 YEARS, the federal government's program to produce a fully implantable artificial heart is nearing one of its goals: a long-term device that can assist the ailing heart. This report is an evaluation of that program by the Institute of Medicine (IOM), at the request of the National Heart, Lung, and Blood Institute (NHLBI).

Heart disease is the leading cause of death in the United States. Endstage heart disease (heart failure) may be caused by coronary atherosclerosis, hypertension, viral or idiopathic cardiomyopathy, or congenital or acquired defects; it results in perhaps half of the nation's 700,000 heart disease deaths each year. Until now, transplantation has been the only effective treatment for most end-stage heart failure patients, but a severely limited supply of donor hearts has meant that only about 2,000 persons receive transplants each year.

NHLBI's predecessor initiated the artificial heart program in 1964; it has supported a number of academic and industry-based R&D teams since then. A primary goal has been the development of two types of mechanical circulatory support system (MCSS), ventricular assist devices and total artificial hearts, for both temporary and long-term use.

A ventricular assist device (VAD) aids the failing heart but does not replace it. Most current models of VADs are implanted in the abdomen, connected to tubes through which blood is drawn from one of the heart's ventricles and pumped into the circulatory system. A temporary VAD can support either ventricle; two VADs can support both. Such devices usually are employed to assist the left heart, the side primarily affected in most types of heart failure. The second category of MCSS, a total artificial

heart (TAH), is similar in concept to two VADs but replaces the diseased heart.

The long-term TAHs and VADs now being developed are powered by electricity that is transmitted across the skin surface in a transformer-like arrangement; the patient will carry rechargeable batteries on a belt or in an over-the-shoulder pouch. An implanted rechargeable battery provides temporary power for about 20 minutes, so the patient can change the external batteries or bathe.

MCSS use began in 1969 with the first temporary implant to support a patient awaiting a donor heart for transplantation. Temporary MCSSs are now also in routine-but still investigational-use to allow the heart muscle to recover functioning after open-heart surgery or after it has been damaged by an acute myocardial infarction (heart attack). In all, more than 1,300 TAHs and VADs have been used in these temporary applications, including some with the VAD itself placed outside the body. This report, however, focuses on devices intended for indefinite, long-term use to assist or replace the heart.

TECHNOLOGICAL PROGRESS AND BARRIERS

Several developers have made considerable progress toward both VADs and TAHs that are fully implantable. Technological advances have resolved some of the shortcomings observed in the mid-1980s, when Barney Clark, William Schroeder, Murray Haydon, and Jack Burcham received Jarvik-7 TAHs.

The first implantation of a long-term VAD is expected in 1992, in a clinical trial of a device manufactured by the Novacor Division of Baxter Healthcare Corporation. In this NHLBI-sponsored trial, 20 devices will be implanted over a two-year period by researchers at St. Louis University and the University of Pittsburgh. For the evaluation, each patient will be followed closely for two years. Full trial results will thus not be available until 1996 or 1997. Based on years of research including simulated bench testing and animal trials, the developers of this and other long-term MCSSs have confidence in the mechanical capabilities of their devices, but definitive findings about clinical efficacy and effectiveness will not be known for several years.

Estimating the cost of each device, once approved for routine use, is problematic at present. Based on information from developers, the committee expects that a VAD will cost about $50,000 and a TAH about $100,000, expressed in 1991 dollars. In addition, the hospital and physician care required to implant one will probably cost about $100,000, again based on 1991 costs. Costs for postimplantation care depend heavily on the frequency of such events as device problems and complications that require hospitalization.

MAKING DECISIONS ABOUT FUTURE RESEARCH

This study's primary objective is to delineate important considerations in NHLBI's funding decisions about the artificial heart program. Decisions are needed in 1992 about continuing to fund R&D with both types of MCSS. Another VAD developer besides Novacor is nearing the end of its contract for preclinical testing (the last step before clinical trials), and four contracts for earlier-phase R&D work on TAHs expire in September 1993.

Making R&D decisions about MCSSs is not simple. In 1988, NHLBI terminated work under the four TAH contracts so that it could devote additional funding to VAD development. This action generated considerable criticism from organizations interested in cardiac treatment research as well as from several U.S. senators. NHLBI subsequently reinstated the contracts.

In 1989, at NHLBI's request, the IOM began this evaluation of the artificial heart program. In the first phase, a committee was convened to plan a larger study. In its report, that committee formulated nine questions to become the focus of this full study by a second IOM committee; see *The Artificial Heart Program of NHLBI: Plan for Evaluation* (Washington, D.C.: National Academy Press, 1989). This summary reflects the nine questions and this committee's responses to them.

Because of the committee's charge to advise NHLBI about its future decisions in this area, the committee examined the decision-making processes involved in R&D funding. Peer review processes involving nongovernment personnel are used effectively in considering investigator-initiated applications for R&D grants and in certain priority-setting activities, but most other NHLBI decisions are based primarily on subjective professional judgment by the agency's executives and administrators. The committee believes that structured aids to decision making would be helpful to NHLBI in situations for which peer review is not appropriate; it recommends cost-effectiveness analysis (CEA) principles as an aid in making decisions about R&D funding allocations. The committee also identified and ranked as to importance 17 other decision-making criteria; it recommends that NHLBI consider using these criteria as a starting point in developing explicit criteria to aid in the exercise of judgment about R&D funding allocations.

CLINICAL EFFECTIVENESS

Even before human trials of long-term MCSSs begin, predictions of their ultimate effectiveness can be made based on the results of temporary devices used for as long as a year. At least one fully implantable VAD is likely to be approved by the Food and Drug Administration (FDA) for general use by the late 1990s, although the clinical effectiveness of early

model VADs may be lower than that of heart transplantation (which now offers an 80 to 90 percent probability of two-year postoperative survival). As devices improve in reliability and longevity, their effectiveness is likely to approach today's transplantation outcomes. TAHs are being developed on a timetable 5 to 10 years behind VADs, with the first model not likely to be approved by FDA before 2005.

PROJECTED PATIENT NEED

Epidemiological data about the natural course of end-stage heart disease are limited and incomplete. Estimating the number of patients in the United States who will ultimately become candidates to receive a long-term MCSS requires several considerations, among them:

- the effectiveness of the available devices, that is, whether quality of life and the probability of survival are likely to be better or worse than for medical treatment or heart transplantation;
- the number of patients suffering from end-stage heart disease, adjusted for the presence of severe comorbidities and for the proportion who experience sudden death before they would become candidates for an MCSS;
- the relative effectiveness of alternative forms of treatment, both those now in use and others likely to be developed, and thus their impact on the need for an MCSS; and
- the changing demographics and patterns of illness in the U.S. Population.

The extent of third-party payments for implanting MCSSs will also influence the volume of use, but is virtually impossible to estimate this far in advance of FDA approval.

Based on current and projected mortality rates, the committee estimates that between 35,000 and 70,000 patients yearly are in the pool of potential candidates to receive a long-term MCSS, but practical limits (e.g., coverage restrictions by third-party payers, availability of qualified personnel) will hold the growth of this technology's use below this range until about 2010. This estimate assumes that at least one VAD will be approved by FDA by 1999 or sooner and that coverage and payment decisions by policymakers and third-party payers will allow use to increase steadily between 1999 and 2010. The extremes of the potential pool of MCSS candidates correspond to typical upper ages (35,000 for age 75, 70,000 for 85) of patients who may be considered for these devices; however, other than to enable such estimates, no specific upper age limit for MCSS patients should be applied or recommended. Clinically determined criteria should be used in making individual decisions about MCSS use.

Estimating the proportion of all potential MCSS patients who need biventri

cular support and thus a TAH is more difficult. VAD experience during the 1990s will determine, more precisely than is currently known, whether support of only the left ventricle will suffice for most patients or whether a substantial proportion of them will need a TAH. The committee's best estimate, assuming the availability of at least one FDA-approved TAH by early in the next century, is that 10,000 to 20,000 of the total number of potential MCSS recipients in 2010 will need a TAH; the other 25,000 to 60,000 will be candidates to receive a VAD.

The foregoing estimates are for the primary patient group, namely those who are in greatest need and who will receive most of the MCSSs implanted during the first 15 to 20 years of use. Thereafter, if devices are then at least as beneficial as is transplantation at present, others in what the committee has called the secondary group will also become potential candidates. The size of this group is even less certain. It could include as many as 200,000 persons per year after device availability becomes sufficiently widespread, assuming that resources are made available to finance care to such an extent, perhaps by the year 2020.

Two other factors may affect the need for MCSSs during the 2020s or possibly sooner. One is research that is beginning to yield understanding of the basic mechanism of heart failure. If NHLBI's continuing support of research on this topic results in translating this understanding into pharmaceutical advances, it may eventually be possible to slow or even halt the progression of heart disease or to postpone the point at which an MCSS will be needed. These advances are not likely to eliminate the need for MCSSs, but they may reduce the extent of need in both the primary and secondary groups of patients.

The second possible influence on the volume of future MCSS use is the development and implementation of interventions that are more effective in preventing the causes of end-stage heart disease than those currently employed. The committee's epidemiological projections take into account current trends in mortality rates as a result of such measures as hypertension control programs and dietary changes to reduce blood cholesterol levels, but it is possible that additional intervention methods will yield even greater reductions in the incidence of end-stage heart disease.

HEALTH-RELATED QUALITY OF LIFE

Health-related quality of life is important in assessing the effectiveness of MCSSs and other forms of heart disease treatment. Techniques exist to estimate a preference or utility value for each typical health state experienced by patients. Cost-effectiveness analyses are improved by incorporating these values, reflecting patients' quality of life.

Clinical trials of both drugs and medical devices are increasingly assess

ing the quality-of-life aspect of patient outcomes. Among government agencies that fund research, NHLBI's requirement that health-related quality of life be assessed in clinical trials it supports is a pioneering step. All MCSS trials should use standard quality-of-life domains (assessment categories), so that study results can be compared.

MCSS patients and their families must learn to live with this technology for the rest of the patient's life. The committee recommends that all health care providers involved in use of MCSSs develop continuing support programs for patients and their families, to improve quality of life and allow them to learn from each other's experience.

COST-EFFECTIVENESS

Cost-effectiveness analysis (CEA) links the net benefit from using a technology to the cost of providing it. Employing CEA to examine MCSS use is particularly appropriate, because of the committee's wish to assure that the aggregate increases in health care costs resulting from MCSS use will be matched by improved patient outcomes.

Health-related quality of life can be reflected in a cost-effectiveness (C/E) ratio by using quality-of-life utilities that indicate a patient's preferences for particular health states during and after treatment. Quality-adjusted life years (QALYs) are helpful in making comparisons among alternative forms of treatment; C/E ratios are usually expressed as the incremental cost per QALY gained from the particular treatment in comparison with another.

Cost-effectiveness ratios are best evaluated by comparing them with ratios for other forms of treatment for similar diseases. The committee estimates the incremental cost-effectiveness of using a TAH instead of medical treatment as $105,000 per added QALY (in 1991 dollars), a ratio of borderline acceptability. This C/E ratio is considerably less favorable than those for heart transplantation ($32,000 per QALY) and other generally accepted forms of heart disease treatment (e.g., $34,000 per QALY for coronary artery bypass surgery for two-vessel disease with severe angina; $7,000 to $13,000 for percutaneous transluminal coronary angioplasty for severe angina). The TAH C/E ratio is also considerably less favorable than ratios for other forms of treatment of catastrophic diseases, such as an average of about $50,000 per QALY for hemodialysis for end-stage renal disease.

Because the main focus of the report is TAHs, the committee's analysis did not include a specific C/E ratio for VAD use. The initial device cost will be lower than for a TAH, as will some of the detailed probabilities, but the benefit to patients will be very similar. The VAD C/E ratio thus is likely to be somewhat more favorable than the TAH's $105,000 per added QALY. Additionally, if VAD clinical trial results indicate that the commit

tee's performance estimates can appropriately be revised, C/E ratios for both TAH and VAD use will improve; continuing technological improvements in the performance of the devices themselves may also have this result.

The committee believes that the currently estimated C/E ratio for TAH use is not so extreme that it affects the committee's basic conclusionnamely, that federal support for MCSS development should continue for an interim period. By making possible an earlier approval of TAHs for general use, continuing with TAH development for a two-to three-year period may benefit patients who would otherwise die if TAH development is delayed by a suspension of funding. This interim period will also see the availability of better information about the likely effectiveness of MCSSs in 2010 from the clinical trials and continuing temporary use of VADs. Offsetting these benefits is the possibility that, if the borderline C/E ratio is confirmed by forthcoming VAD trial results and leads to the suspension of TAH development at that point, the continued R&D expenditure will yield no return. The committee believes, however, that this possibility is outweighed by the potential future benefit to patients, particularly because a relatively small amount of R&D spending is involved ($5 to $10 million per year).

Estimating cost-effectiveness almost 20 years in the future is fraught with uncertainty, but the technique of sensitivity analysis allows examining the impact of such uncertainties. Varying the key parameters such as costs, complication probabilities, and discount rate shows that the C/E ratio applicable to TAH use is relatively stable.

Cost-effectiveness analysis can also be applied to the consideration of research and development options. The committee used CEA to examine alternative levels of R&D investment during the next phase of TAH development. Based on assumptions of the impact of increased funding on the length of time required to complete R&D and on the future selling price of TAHs, this CEA reveals that increasing the level of R&D funding may yield benefits greater than would otherwise occur, assuming that the underlying $105,000-per-QALY C/E ratio of TAH use is considered acceptable.

APPROPRIATENESS OF USE OF MECHANICAL CIRCULATORY SUPPORT

Among the many unusual aspects of MCSSs is the extent to which they have been scrutinized, decades in advance of their general availability. This study is the seventh originated by NHLBI and its predecessor institutes but the first to be conducted independently.

The committee is concerned that, despite this intense scrutiny, MCSSs may be used inappropriately, a concern similar to those expressed over the years about other new technologies. Inappropriate technology use is

inconsistent with the current emphases in health care on both improving the quality of care and eliminating unnecessary utilization and expenditures.

Given this concern, we note that never before has there been an opportunity such as the one this technology now presents to the health care community. Before VADs and TAHs go into general use, crucial activities can be undertaken to improve the likelihood that these devices will be used appropriately. The committee thus recommends that device developers, NHLBI, and other interested parties take advantage of the period of years during which MCSS development is being completed to participate jointly in the following activities intended to promote appropriate use:

- develop clinical practice guidelines or indications for use, at first on a provisional basis, with later revisions after clinical trial results are reported;
- commission technology assessments that include cost-effectiveness components, based on actual device use, in order to verify and update this committee's work;
- establish a registry of MCSS patients as a means of postmarketing surveillance and perform long-term follow-up studies of an adequate sample of all patients;
- develop guidelines for hospitals, third-party payers, and others to use in determining whether individual physicians have the training and experience necessary to implant MCSSs; and
- work with third-party payers to implement selective coverage programs, to avoid unnecessary and wasteful duplication and thus conserve expensive resources, as well as to ensure that the institutions at which MCSSs are implanted are suitably equipped and staffed to provide this care effectively.

Implantation of an MCSS is not a simple, time-limited treatment episode. Because of the patient's total dependence on the device and because problems can occur at any time, clinical trial subjects should be followed closely during the trials; they and other MCSS patients should be followed, through a registry, for the remainder of their lives. The committee recommends that trials be funded at a level sufficient to allow a full range of physiologic data (e.g., cardiovascular, renal, neurologic, hematologic) to be collected periodically, as well as health-related quality-of-life information and treatment cost data that are sufficient for cost-effectiveness analysis.

Maintaining a registry of MCSS recipients should be considered a routine aspect of this care. Its costs could possibly be supported through payments by hospitals at the time of each implant. Third-party payers would benefit from requiring surgeons and hospitals to agree to provide information to the registry and should provide reimbursement for registry

fees in their payment rates. Patients should also be requested to supply information to the registry on a continuing basis, such as during their periodic visits to check device performance.

For this type of device, long-term follow-up studies are important in order to detect problems that occur after the trial ends or that may not be revealed in the small number of cases included in clinical trials. The committee recommends that NHLBI and the Public Health Service's Agency for Health Care Policy and Research support long-term follow-up studies of an adequate sample of MCSS patients.

PATIENT ACCESS TO MCSSS

Because of the high cost of MCSSs both individually and in the aggregate, as well as their borderline C/E ratios, private third-party payers, Medicare, and state Medicaid programs are likely to resist approving coverage for MCSS implantations. Further, access to this technology by the 30 million or more citizens with inadequate or no insurance is of concern to the committee. The time is ripe for the United States to make clear decisions about access to health care, including costly new technologies.

As with clinical appropriateness, the committee recommends that the time until long-term MCSSs are approved by FDA be used by policymakers at the national and state levels to decide whether at least MCSSs (if not other new technologies also) should be explicitly included or excluded in a package of basic health care services that is applicable to all forms of public and private health insurance. The committee recommends, as well, that policymakers begin to decide about equitable access to MCSSs and other technologies for those without personal resources or insurance, and what trade-offs in access to other services may be necessary to provide MCSS access.

Given the federal budget deficit and other constraints, early policy decisions on access are likely to be made at the state level, such as the efforts currently under way in Oregon and a few other states. For this type of effort to be most effective, the committee recommends that one or more organizations that have the respect of state governments be funded to aid states in considering these decisions.

Medicare, Medicaid programs, and other third-party payers sometimes approve coverage for a new technology but then establish for it a payment rate so inadequate that access to the technology is restricted. The committee believes this is an unacceptable way to ration access to care and recommends that any positive coverage decision include paying for the care at a rate that adequately reimburses the costs of the care, noting that fixing such rates will require accurate cost information.

ETHICAL CONSIDERATIONS

An adequate informed consent process is an important component of any patient's decision to accept an MCSS implantation. Such a process should include a patient's advance directives concerning termination of treatment, as well as the legal designation of a proxy for such purposes. The committee recommends that protocols for all MCSS clinical trials include these requirements and other appropriate ethical safeguards; these requirements also apply to routine MCSS use and should be part of each institution's standard procedures in all long-term MCSS implantations.

RESEARCH AND DEVELOPMENT POLICY ISSUES

Federal support for the development phase of health care R&D is rare; that phase of work is usually funded by industry. The development of MCSSs, however, presents an unusual situation. Because of technological, clinical, and regulatory uncertainties, adequate private-sector financing to develop long-term MCSSs has thus far not been available. Moreover, such support does not appear likely, at least until the first long-term VAD has been approved by FDA. The committee concludes that the potential benefits that patients will derive from these devices, once approved for general use, provide sufficient basis for NHLBI to continue support of R&D for both VADs and TAHs, as well as for other MCSS-related topics such as the development of alternative power sources. International-trade benefits may ultimately be an important outcome of this R&D, but the committee believes that potential benefits to patients should be the primary basis for these expenditures.

Collaborative research is particularly important to continuing R&D in this field in three respects: (1) interdisciplinary collaboration involving biomedical engineers, clinicians, and scientists; (2) collaborative research between academics and researchers in for-profit firms; and (3) formal R&D cost-sharing between government and private-sector developers. The procedures routinely used by NHLBI for the review and approval of proposals for investigator-initiated grants have, to date, also been used for contract awards by the artificial heart program. The committee recommends that peer review groups for MCSS development proposals include appropriate numbers of clinicians, biomedical engineers, and professionals with other relevant expertise (e.g., quality-of-life assessment, cost-effectiveness analysis), instead of the customary preponderance of life scientists. The committee also recommends that NHLBI consider adopting policies and structures governing the artificial heart program (and any similar ones that may exist) that allow for greater flexibility in arranging for collaborative R&D and cost-sharing.

Finally, the committee is concerned that traditional collegial communication among academic researchers may be adversely affected by the increasing support they are receiving from industry and other private-sector financing sources. The committee recommends that academic researchers avoid financial arrangements that restrict open communication and that universities establish policies and procedures that prohibit unreasonable constraints on communication.

REGULATORY DECISIONS ABOUT NEW TECHNOLOGIES

Carrying MCSS R&D through to the development of a marketable device is affected by regulatory activities of FDA and of third-party payers including Medicare. In the past, technical criteria developed by NHLBI for its clinical trials and those applied by FDA in approving devices have not always been consistent. The two agencies are currently working together as the Novacor VAD trial protocol is developed; the committee recommends the continuation of this type of joint activity.

As third-party payers establish MCSS coverage and payment policies, the committee recommends that they recognize all aspects of the technology. Appropriate considerations include clinical benefit to patients-taking into account the information obtained from clinical trials-as well as patient need, access considerations, and the technology's cost-effectiveness.

Coverage approvals may properly be narrow and restrictive initially but should be reconsidered periodically, based on additional clinical evidence of relative safety and clinical effectiveness and the impact of the new information on cost-effectiveness. As has occurred with other cardiovascular technologies (e.g., pacemakers, percutaneous transluminal angioplasty), indications for MCSS use can quite properly be expanded as experience is gained.

DEVELOPMENT OF TOTAL ARTIFICIAL HEARTS

Although the precise number is uncertain, a substantial number of patients to be benefited by MCSSs are likely to need a long-term TAH because a VAD will not provide the biventricular support that they require. Continuing NHLBI R&D funding appears needed if a TAH is eventually to become available for use. Moving into the final preclinical stage of TAH development at this time is premature, however, because the results of early VAD trials will provide useful technological information as well as better information about TAH cost-effectiveness and the number of patients who will need one.

The committee is aware, in developing its main recommendation to NHLBI concerning TAH development, that the estimated cost-effectiveness

ratio for TAH use of $105,000 per added QALY is so unfavorable as to be a possible basis for suspending this R&D program. Further, the committee is aware how little can be said with certainty about the ultimate clinical effectiveness and cost of these devices, if development continues and they are approved for use in 2010 or sooner. In the short-term, however, the cost of continuing to develop both TAHs and VADs can be held in the range of $5 to $10 million per year (in 1991 dollars), a level that is consistent with the artificial heart program's commitments to contracts in these areas in recent years.

The committee therefore recommends that NHLBI continue to support TAH development for an interim period, perhaps by extending the contracts of current TAH developers if their work, through peer review and use of criteria such as those applied by this committee, is deemed worthy of continuing federal investment. Such an interim funding period would allow an opportunity for NHLBI to consider the early results of the Novacor VAD trial and results of continuing temporary VAD use before deciding about the next five-year phase of TAH development. Doing so would also allow the developers to determine whether more funding than customary would enable earlier completion of R&D and, if focused on "manufacturability" (redesign to achieve greater quantity-production efficiency), whether it would yield a lower device selling price. Any changes in third-party payment policies or mechanisms also should be considered at that time. Under this recommendation, NHLBI's commitment to TAHs could be reexamined in 1994 or 1995, taking these factors into account in much the same manner as has the committee, but aided by another cost-effectiveness analysis that reflects updated estimates about projected TAH clinical effectiveness, complications, and costs.

Finally, both the committee's recommendations and any NHLBI action consistent with them should be understood by everyone involved *not* to imply a long-term commitment to TAH development. If clinical performance estimates do not improve as a result of experience during the interim period, NHLBI's proper course in 1994 or 1995 may well be to suspend all support for TAH development until further VAD experience has been gained.

CONTINUED DEVELOPMENT OF VENTRICULAR ASSIST DEVICES

The committee is concerned that, except for the Novacor clinical trial, NHLBI may end its contractual, targeted support for VAD development. Technological limitations or problems may develop with only one model of VAD moving into the clinical-trial phase of R&D; multiple approaches to VAD design may prove to be of significant clinical value. Lower-priced

devices may also result, if more than one manufacturer exists. The committee therefore recommends that NHLBI consider continuing its support for additional VAD development that is judged by peer review to have sufficient scientific merit, for an interim period ending in 1993 or 1994. At that time, further support could be considered in light of initial results from the Novacor trial.

ADDITIONAL RESEARCH

Additional research is needed in two areas. First, any future R&D commitments to MCSSs should not detract from continuing NHLBI support of research aimed at an increased understanding of the mechanisms of heart failure and at developing new approaches to its treatment and prevention.

Second, as previously stated, relatively little is known about the epidemiological aspects of end-stage heart disease, although one current NHLBI-supported study will provide additional information concerning heart disease in patients aged 65 and over. The committee recommends that more epidemiological studies be performed of the natural course of heart failure in persons under age 65, with particular attention to including women and members of minority groups.

USING THIS REPORT

A wide range of persons within and outside the health care community will be able to apply some or all of this report's findings and recommendations. It is both a specific technology assessment that provides detailed guidance to NHLBI and one that can serve as a broader model. The process used in this evaluation and many of its general recommendations should be useful to policymakers at the state and federal levels, third-party payers, and others in the health care system.

1

The Artificial Heart Program: Current Status and History

BY THE LATE 1990s, patients with heart failure may be able to receive a fully implantable device to assist their weakened hearts. A small battery pack will be the only visible evidence of the technology, in contrast to the large console needed to power earlier models of these devices. Five to ten years after assist devices are perfected, a fully implantable total artificial heart (TAH)—a device that replaces the natural heart instead of only assisting it—may be technologically possible.

As soon as 1992, the first patient will receive a fully implantable, longterm ventricular assist device (VAD). The implant will begin a clinical trial of a VAD developed by the Novacor Division of Baxter Healthcare Corporation and is the result of a major effort by the artificial heart program of the National Heart, Lung, and Blood Institute (NHLBI). In the trial, 20 patients will receive the device over a 2-year period, 10 at St. Louis University and 10 at the University of Pittsburgh; each patient will be followed for up to 2 years, and extensive data analysis will be performed. Formal reports of the trial's outcome thus will be available in the latter half of the 1990s.

The longest use of a temporary Novacor VAD (similar but externally powered) in either animals or human beings has been about one year, but the cumulative experience since the first human use in 1984 suggests that the forthcoming trial of the fully implanted model will yield positive results in some patients. Because the two technologies have similar components and face similar problems, the Novacor trial results will have considerable relevance not only for VAD development but also for the future of TAHs. Nevertheless, TAHs are very different devices; replacing a natural heart presents many more challenges than does supporting left ventricular function.

At present, four TAH developers are just beyond the mid-point of NHLBI contracts for continuing R&D. If NHLBI funding continues, the next phase of extensive device readiness testing might require up to five years; this would be followed by another five or more years of clinical trials. TAHs are not likely to be a candidate for wide use until at least 2005.

This report of an Institute of Medicine (IOM) study is primarily intended to help NHLBI determine the extent of its support of the next step of TAH development after the current contracts end in September 1993. The report also considers the need to continue developing additional VAD models and examines issues related to both types of devices, such as appropriateness of technology use and access by patients to this technology. Finally, the report suggests several methods that can assist NHLBI in allocating resources among R&D programs and examines related R&D policy issues. (Temporary-use devices are not considered, except as their experience provides a basis for projecting the performance of long-term devices.)

END-STAGE HEART DISEASE

Consideration of the future role of TAHs and VADs—referred to collectively as mechanical circulatory support systems (MCSSs)—is helped by a basic understanding of the heart's functioning. As Figure 1.1 illustrates, the heart is a double pump. Oxygenated blood from the lungs flows into the left atrium and from there into the left ventricle. The left ventricle pumps the blood via the aorta into arteries throughout the body. After oxygen has been removed in organs and capillaries, the blood flows through veins back to the heart's right atrium and then to the right ventricle. This chamber sends the venous blood to the lungs to be oxygenated, completing a pumping cycle that normally occurs 70 to 90 times per minute.

Because considerably more pumping force is needed to move arterial blood throughout the body than to move venous blood through the lungs, the left ventricle's muscle strength is greater than the right ventricle's and it is also more likely to fail than is the right ventricle. Heart failure is identified as left-sided, right-sided, or both (biventricular); end-stage heart disease occurs when one ventricle (or both) is unable to perform the necessary pumping function. As the name indicates, the typical case of end-stage heart disease becomes steadily more severe, until death occurs.

End-stage heart disease may result from a variety of cardiovascular causes; "heart failure"—sometimes called congestive heart failure—is, technically speaking, not itself a disease but a condition that is caused by many different disease processes. The most common causes of end-stage heart disease and heart failure are hypertension and coronary atherosclerosis (also called coronary artery disease or coronary heart disease, a constriction of the arteries that convey blood to the heart muscle itself). Viral

infections of the heart and idiopathic cardiomyopathy are other major causes of heart failure. As discussed further in Chapter 4, these diseases of the heart result in most of the 700,000 cardiac deaths that occur in the United States each year. A substantial number of these deaths might be postponed by MCSS use; perhaps half of them, however, occur suddenly and without warning as a result of acute myocardial infarction or a sudden fatal rhythm disturbance of the heart.

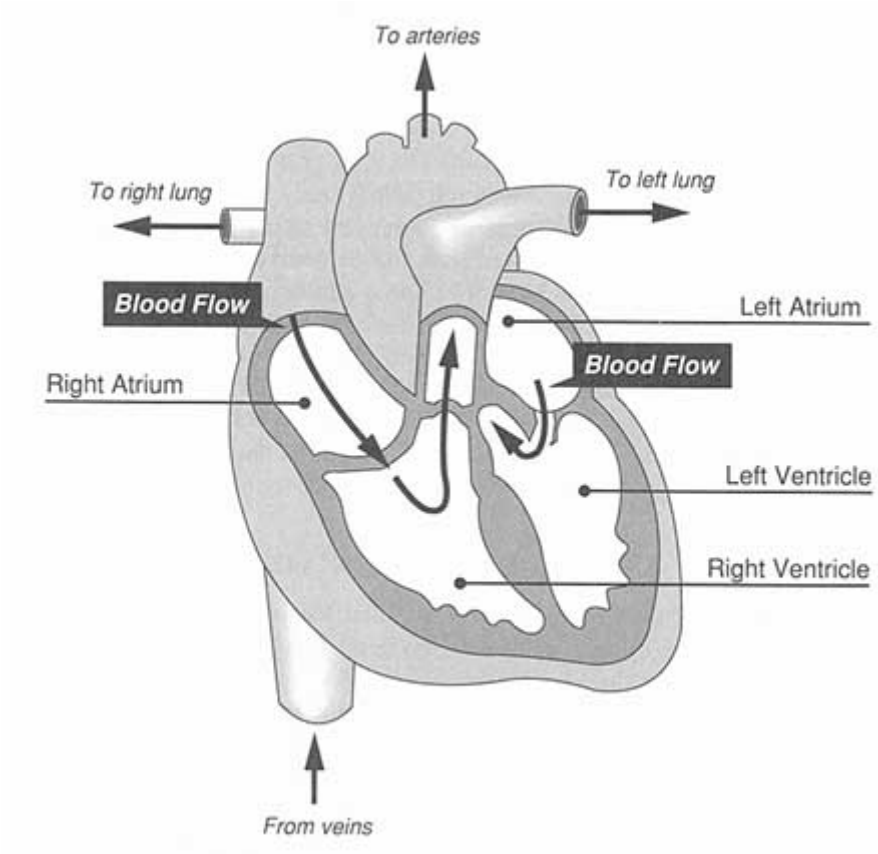

FIGURE 1.1 A simplified drawing of the heart.

The interest in long-term MCSSs is a response to the current limitations on cardiovascular science's ability to prevent or cure end-stage heart disease. The alteration of risk factors for atherosclerosis (e.g., treatment of high blood cholesterol levels and of hypertension, dietary alterations, cessation of smoking) may ultimately reduce the number of patients with end-stage heart disease resulting from coronary artery disease. Patients who already have coronary artery disease may have the natural history of their disease altered, at least temporarily, by coronary artery bypass surgery,

percutaneous transluminal angioplasty, or other similar techniques that are currently the focus of clinical practice and research. Patients with cardiomyopathy or already established heart failure may achieve symptomatic improvement and some prolongation of life with medical therapy, but currently such therapy is palliative at best. Research to further elucidate the cellular mechanisms of heart failure (Francis and Cohn, 1990) may ultimately lead to effective therapy to halt or reverse the progression of disease, but this is not yet possible.

For many heart failure patients, therefore, the treatment of choice is heart transplantation, which is currently achieving five-year survival rates of about 70 percent (Kriett and Kaye, 1990). However, the supply of potential donor hearts is severely restricted. In 1990, 2,085 heart transplants were performed in the United States, up 23 percent from the volume in 1989 (UNOS, 1991). Although the number of donor hearts may continue to increase slightly, there are also a number of factors working against growth in the availability of donor organs generally (IOM, 1991). For the large number of heart failure patients who are unable to receive a transplant, either because of limited donor availability or because they do not meet transplant criteria, the only current alternative is drug treatment. Annual mortality rates of patients receiving conventional medical treatment range from 15 to 50 percent, depending on the severity and rate of progression of the underlying disease.

VADs and TAHs must, therefore, be evaluated as an alternative treatment for end-stage disease within a framework that acknowledges the limitations of heart transplantation and other conventional medical and surgical forms of treatment. Research may eventually lead to successful drug therapy that prevents heart failure, but hundreds of thousands of heart disease patients face serious risk of death until that becomes possible. Any technology such as MCSSs that offers these patients the promise of prolonged functional life thus warrants careful consideration.

HOW LONG-TERM IMPLANTABLE DEVICES COULD HELP

Mechanical circulatory support devices are being developed either to assist or to replace a failing heart on a long-term basis, with the expectation that the patient will resume a relatively normal, productive life. Such devices were under development before the artificial heart program's inception in the 1960s (Norman, 1984).

Ventricular Assist Devices

A ventricular assist device may be implanted in the upper abdomen, chest, or elsewhere (see Figure 1.2). Long-term VADs will normally be

used to assist the left ventricle, connected by large tubes (cannulas) to it and to the aorta. Each pumping stroke of the VAD is coordinated with the left ventricle's contraction, so as to optimize the functioning of both the device and the natural heart.

Inside the VAD's rigid casing, an electrically powered mechanism squeezes a plastic blood sac between two plates; the direction of blood flow is controlled by a pair of valves, the same types used when a natural heart valve must be replaced (e.g., valves from pigs' hearts or ones made of metal and plastic). Electric power is transmitted through the skin in a transformer-like arrangement; in Novacor's design, one of a pair of coils is permanently implanted below the skin and the other is strapped around the waist. An internal rechargeable battery provides power for 20 to 30 minutes, for emergency use or during bathing; external rechargeable batteries

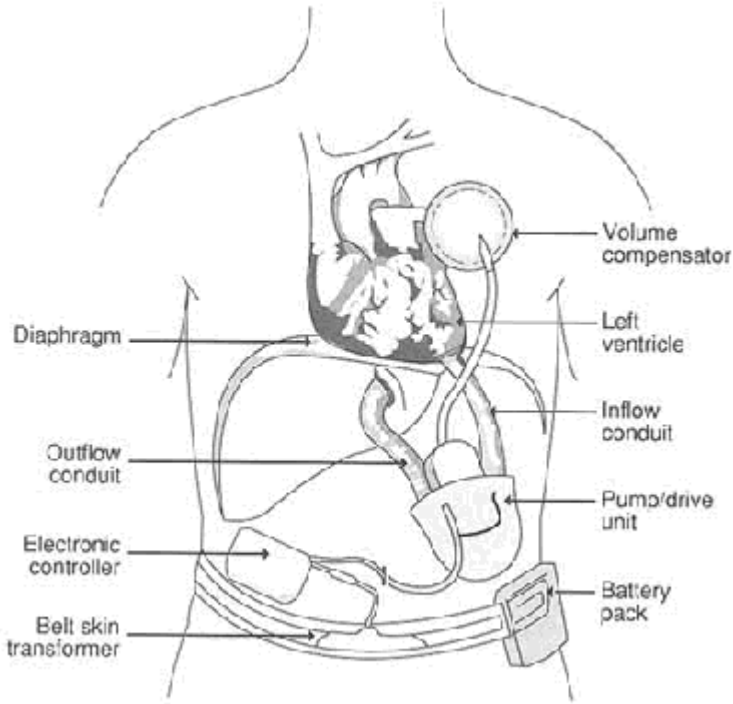

FIGURE 1.2 The Novacor fully implantable ventricular assist device.

are carried on a belt. The external batteries provide power for six to eight hours, so the patient must change to fully charged ones several times per day. A volume compensator or compliance chamber is implanted to accommodate the air displaced by each filling stroke of the pump.

Total Artificial Hearts

A total artificial heart is, in basic design and operation, similar to a VAD, with one power source driving two pumping chambers that perform the ventricles' functions (see Figure 1.3). In the models currently under development, top portions of the natural heart's atria are left in place when the heart's larger components are removed, to facilitate suturing the TAH into position. In models in which the TAH's pumping speed is synchro

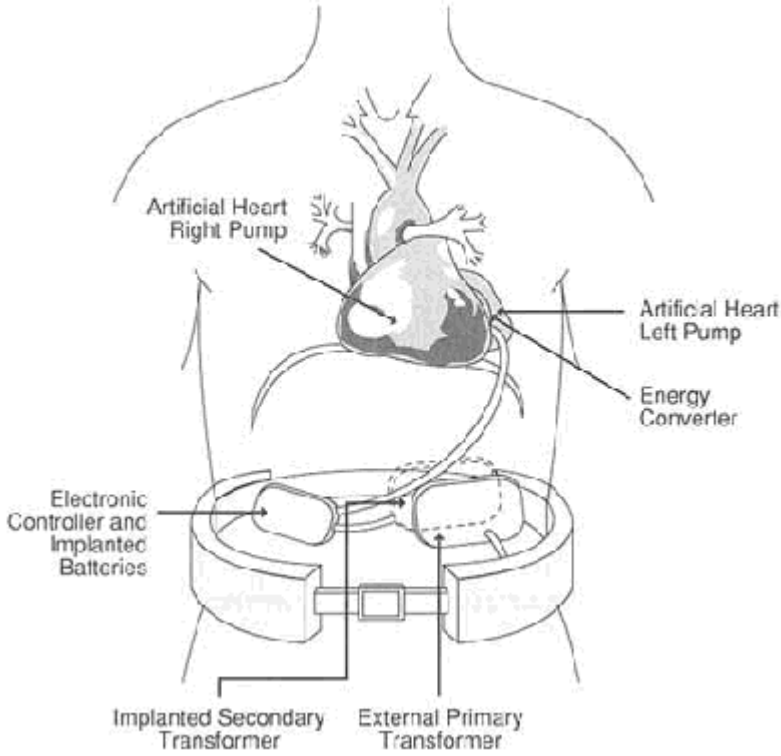

FIGURE 1.3 A fully implantable total artificial heart.

nized to physiological need, those portions of the atria provide the natural electric stimuli so the TAH's speed can increase during exercise and slow during rest.

Depending on when in the patient's disease course a long-term MCSS could be implanted, a TAH may or may not be necessary; as discussed in Chapter 4, further investigation is needed to establish these clinical considerations in detail. Some researchers believe that most patients' needs could be satisfied by a VAD assisting the left ventricle, particularly if it is implanted before serious right heart failure and damage to other organ systems has occurred. Others believe that, regardless of when the implant procedure occurs, a TAH will be needed by a substantial number of end-stage heart disease patients. (In contrast to temporary-use external VADs, a pair of which can be used for biventricular support, developers currently plan to implant only one long-term VAD.)

Temporary Circulatory Support

The current stage of development of long-term fully implantable devices has been made possible by more than 12 years of investigational use of both VADs and TAHs as a temporary support for three classes of patients: those who are awaiting a donor organ for transplant; those who cannot be removed from a heart-lung machine after open-heart surgery but have an anticipated opportunity for recovery in the short-term; and those whose hearts need time and rest to recover function after a myocardial infarction. Hundreds of patients have regained satisfactory cardiac function as a result of temporary MCSS use.

Many forms of temporary VADs have been used. Most have been powered pneumatically by an external pump; in several models the VAD itself is external to the body, with blood cannulas running through the chest wall. A single temporary VAD may assist either of the ventricles, or two VADs or a TAH may be used; the availability of a particular type of device sometimes determines this. Even the Jarvik-7 TAH, used for four U.S. and one Swedish long-term implantations in the mid-1980s, has been employed more than a hundred times worldwide as a temporary device.

THE ARTIFICIAL HEART PROGRAM

The NHLBI mission is to "provide leadership for a national research program in diseases of the heart, blood vessels, lungs, and blood and in the uses of blood and the management of blood resources to improve the health of the nation" (NHLBI, 1990). This responsibility is fulfilled by means of 23 program areas in 3 areas of responsibility, 11 of them pertaining to the cardiovascular system (see Table 1.1).

TABLE 1.1 National Heart, Lung, and Blood Institute Program Areas

Heart and Blood Vessel Diseases	Lung Diseases	Blood Diseases and Resources
• Arteriosclerosis	• Structure and function of the lung	• Bleeding and clotting disorders
• Hypertension	• Chronic obstructive pulmonary diseases	• Disorders of the red blood cell
• Cerebrovascular disease	• Pediatric pulmonary diseases	• Sickle cell disease
• Coronary heart disease	• Occupational and immunologic lung diseases	• Blood resources
• Peripheral vascular disease	• Respiratory failure	• AIDS
• Arrhythmias	• Pulmonary vascular diseases	
• Heart failure and shock	• AIDS	
• Congenital and rheumatic heart diseases		
• Cardiomyopathies and infections of the heart		
• Circulatory assistance (including artificial heart program)		
• AIDS		

AIDS, acquired immunodeficiency syndrome.
SOURCE: NHLBI (1990).

As with other components of the National Institutes of Health (NIH), the principal mechanism for achieving NHLBI's overall mission is the funding of extramural research through investigator-initiated, nontargeted ("RO1") grants. Most of the institutes that make up NIH do not fund later develop-mental stages of medical technologies, focusing instead on fundamental or basic research.

The NHLBI artificial heart program is, however, a notable exception to this generalization. Historically, the funding mechanism for R&D with MCSSs has been targeted contracts, issued following requests for proposals.

From the first appropriation of funds in 1964, one of the program's major goals has been to produce, through focused development, devices for long-term clinical use (see Appendix B for a chronology of the program's activities and others related to it).

Over the years, the artificial heart program has been one of the more closely studied of all NIH activities. Table 1.2 lists the reports previously issued, all by groups under NHLBI's direct auspices.

The artificial heart program now supports six R&D projects through the contract mechanism, with the goals of assessing the Novacor fully implantable VAD and developing other electrically powered, implantable VADs and total artificial hearts. Figure 1.4 shows the projected timetables of these projects as well as of two R01 grants for thermal power development.

Figure 1.5 shows the artificial heart program's historical expenditures, including estimates for the 1990-1991 fiscal year. In addition to the 2 thermal power grants, 29 other grants (including 8 in the category of Small Business Innovation Research awards to small industrial firms) were active as of August 1990 (NHLBI, 1990). This research addresses such areas as cardiac assistance using skeletal-muscle power, specialized MCSSs for pediatric use, and studies of the immune system's response to blood pump implantation.

TABLE 1.2 Previous Evaluations of the NHLBI Mechanical Circulatory Support Program

1969	Cardiac Replacement: Medical, Ethical, Psychological, and Economic Implications; Ad Hoc Task Force on Cardiac Replacement
1973	The Totally Implantable Artificial Heart: Legal, Social, Ethical, Medical, Economic, Psychological Implications; Artificial Heart Assessment Panel
1977	Mechanically Assisted Circulation: The Status of the NHLBI Program and Recommendations for the Future; Report of the Cardiology Advisory Committee
1980	Mechanically Assisted Circulation: Report of the NHLBI Advisory Council Working Group on Circulatory Assistance and the Artificial Heart
1981	Report of the Artificial Heart Working Group
1985	Artificial Heart and Assist Devices: Directions, Needs. Costs, Societal and Ethical Issues; Report of the Working Group on Mechanical Circulatory Support of the NHLBI

SOURCE: NHLBI (1990).

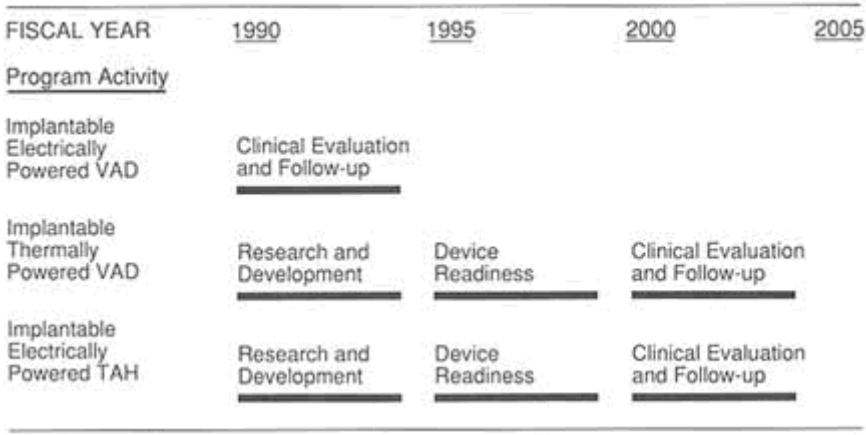

FIGURE 1.4 Estimated timetable for the NHLBI artificial heart program. SOURCE: NHLBI (1990).

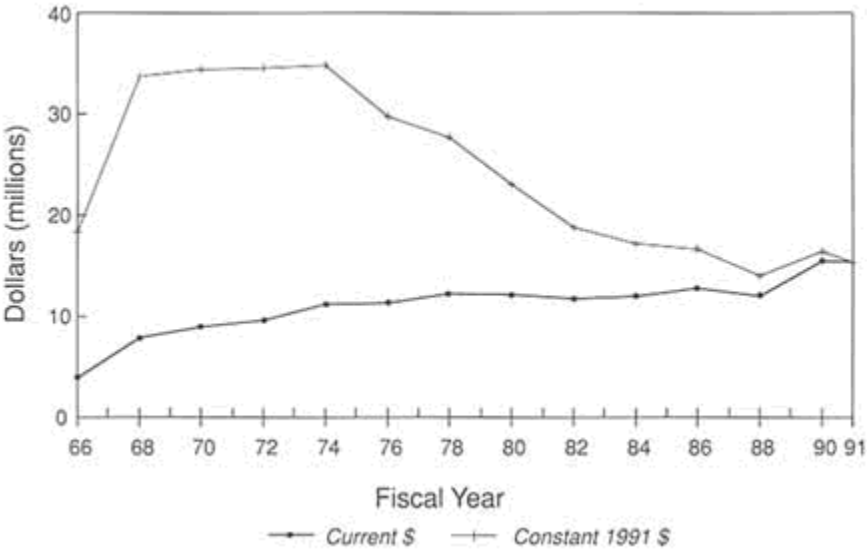

FIGURE 1.5 Total annual expenditures of the NHLBI artificial heart program. SOURCE: NHLBI (1990) (constant dollar adjustments based on U.S. Department of Commerce Biomedical Research and Development Price Index; $4.543 million expended in 1976 transitional quarter not shown).

THE INSTITUTE OF MEDICINE STUDY

This report of a study by the IOM had its origins in a 1988 decision by the director of NHLBI to cancel the four current contracts for TAH development; that decision was later rescinded. Appendix A describes the history and methods of this study in more detail; it also provides details about the preceding planning study that culminated in the 1989 IOM report *The Artificial Heart Program of NHLBI: Plan for Evaluation* (Washington, D.C.: National Academy Press, 1989).

In the 1989 report, the IOM planning committee formulated nine questions to be addressed in this study, as listed in Table 1.3. These questions form the basis for the many topics discussed in the chapters of this report as indicated in Table 1.3. The report's scope is, moreover, broader than the nine questions, including consideration of several issues of R&D policy and decision making.

TABLE 1.3 Nine Questions Identified by the Institute of Medicine Planning Study for the Main Evaluation and Chapters Where Mainly Considered in This Report

1. What are the nature and magnitude of the target populations for which mechanical circulatory support systems (MCSSs) may be applied? (Chapter 4)
2. What are the alternative technologies for preventing and treating end-stage heart disease that may affect the need for MCSSs? (Chapter 2)
3. What is the potential for MCSSs to prevent and treat end-stage heart disease, and what are the current technological and other barriers to their development? (Chapter 2)
4. What is the clinical effectiveness of MCSSs? (Chapter 4)
5. What are the projected costs of research and development of MCSSs? (Chapter 2)
6. What is the cost-effectiveness or cost-benefit of research and development of the various MCSSs, and how does this compare to what is known about the cost-effectiveness or cost-benefit of the research and development of alternative technologies for preventing and treating end-stage heart disease? (Chapters 3 and 6)
7. What should the roles of government and industry be with respect to research and development of MCSSs? (Chapter 9)
8. Should decisions concerning further investment in the artificial heart program depend on whether the current cost-effectiveness or cost-benefit findings indicate the technology is acceptable or unacceptable, or are there additional factors that should be taken into account? (Chapters 3, 5, 6, and 8)
9. How can these findings be used to support decisions on allocation of research funds for artificial heart technologies? (Chapter 3, 6, and 10)

The committee report will also examine methods to enhance communication and cooperation among agencies and others involved in MCSS research in the United States and abroad. (Chapter 9)

SOURCE: Institute of Medicine. 1989. *The Artificial Heart Program of NHLBI: Plan for Evaluation*. Washington, D.C.: National Academy Press.

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2

Total Artificial Hearts: Technological Potential and Research and Development Costs

THIS CHAPTER FIRST ADDRESSES the likelihood of total artificial hearts (TAHs) providing useful treatment of end-stage heart disease. The evaluation examines the current technological potential and limitations of the devices and compares these estimates with data on existing treatments for end-stage heart disease. Then, because actually fulfilling the potential of a technology is directly related to the further research and development provided, current and future funding from the National Heart, Lung, and Blood Institute (NHLBI) are examined. Finally, general considerations for industry R&D decisions, rather than costs, are briefly discussed; determining the costs of future industry R&D for TAHs is not possible.

Since the early 1980s, the major use of TAHs and ventricular assist devices (VADs) (together referred to as mechanical circulatory support systems, or MCSSs) has been for temporary support while the heart muscle recovers function or the patient awaits a donor heart. Appreciable data now exist for *temporary* use of MCSSs. Although such devices have in a few instances functioned for many months, and although a very few TAHs have been implanted with the intent of long-term use, relatively little information exists that is useful for determining the efficacy and risks of *long-term* use. This evaluation of the technological opportunities and barriers in the development of TAHs is therefore based primarily on information from temporary use of TAHs and VADs, animal trials, and in vitro testing.

From these data, it clearly is possible to make a reasonably accurate assessment of the technical state of MCSSs that takes into account their biocompatibility and the mechanical reliability of the systems or components. On other questions, such as long-term technological efficacy, clini

cal complications and effectiveness,[1] and impact on quality of life, it is more difficult to ascertain the future potential of MCSSs. Clinical trials of a totally implantable long-term left ventricular assist device are scheduled to begin in 1992; the data from these trials will have broad implications for continuing development of long-term TAHs and VADs.

TEMPORARY CIRCULATORY SUPPORT

The use of MCSSs for temporary support has evolved, in the absence of totally implantable systems, to meet patient needs and to evaluate the feasibility of mechanically substituting for the pumping action of the heart. These systems have all been connected or "tethered" to cumbersome external power sources by skin-penetrating tubes or wires, limiting acceptance as permanent devices and increasing the risk of infection. They have, however, provided rather substantial and impressive information on pumping efficacy, mechanical reliability, and morbidity and mortality risks that is helpful in predicting the long-term outcomes of using totally implanted devices.

Temporary MCSS use is intended to assist or replace the heart for a limited period of time. Temporary devices support patients until transplantation with a donor heart or while they are recovering from acute depression of cardiac function that is thought to be reversible (e.g., after cardiopulmonary bypass). Although temporary clinical use of MCSSs has been successful in some instances for over a year, the purpose is not to provide permanent circulatory support.

Several MCSSs are currently available for temporary use under a Food and Drug Administration (FDA) investigational device exemption (IDE)[2] (see Table 2.1). Most devices in temporary use are VADs, used to support either the left ventricle, right ventricle, or both. Centrifugal external VADs are not considered here, because their maximum period of use is measured in days.

As of early 1991, the only TAH approved by FDA for temporary investigational use was the Pennsylvania State University heart, also known as the Hershey heart. The Symbion/Jarvik TAH was used for temporary support until 1990, when its IDE was withdrawn by FDA because of questions concerning production and quality control practices on the part of the manufacturer; it is still used for temporary support outside the United States. From an engineering perspective, certain specific MCSS components and

[1] Efficacy is the measure of a medical technology's effect on a disease state under ideal clinical conditions. Effectiveness, in contrast, is the measure of a technology's effect during general clinical use.

[2] FDA grants approval of an IDE for trial use of a device in humans.

designs, such as the electronic control system, are effective whereas other elements of the devices still need improvement. Nevertheless, there is general consensus that MCSSs can temporarily reverse or stabilize a patient's physiologic abnormalities. As with early heart valves and other cardiovascular devices, continued R&D investment is needed to eliminate or minimize complications associated with the devices, to take full advantage of the various strengths of the different device designs, and to expand device capabilities from temporary use to long-term circulatory support.

TABLE 2.1 MCSSs That Are Currently Available

Devices available under investigational device exemptions (IDEs)
Short-term external devices
ABIOMED VAD[a]
Pierce-Donachy VAD[b]
Short-term internal devices
Novacor LVAD[c]
Thermo Cardiosystems LVAD[c]
Pennsylvania State University TAH[c]
Symbion/Jarvik-7 TAH[c], [e]
Devices under development
Long-term internal devices
ABIOMED/Texas Heart Institute TAH[d]
Nimbus/Cleveland Clinic TAH[d]
Pennsylvania State University/Sarns-3M TAH[d]
University of Utah TAH[d]
Novacor LVAD[d]
Thermo Cardiosystems LVAD[d]

[a] Pump on stand adjacent to bed.
[b] Pump strapped externally to the abdomen.
[c] Pump is implantable but connected to an external power source.
[d] Pump is fully implantable, power transmitted through the skin.
[e] No longer available under IDE in the United States. LVAD, left ventricular assist device; MCSSs, mechanical circulatory support systems; TAH, total artificial heart; VAD, ventricular assist device.
SOURCES: Graham and Chalmers, 1989; Macoviak et al., 1990; Rosenberg, 1990.

LONG-TERM DEVICES UNDER DEVELOPMENT

Long-term use of devices is intended to meet a permanent need to assist or replace the heart. The four U.S. development groups currently involved

in developing TAHs under contract to NHLBI are ABIOMED/Texas Heart Institute, Nimbus/Cleveland Clinic, Pennsylvania State University/Sarns-3M, and the University of Utah (see Table 2.1). As of 1991, none of these groups had reached the stage of development appropriate for the initiation of clinical trials.

In the category of VADs, two developers of long-term devices are Novacor and Thermo Cardiosystems, Inc. (TCI). The Novacor long-term implantable VAD is a refinement of that manufacturer's externally powered, temporary VAD. Use of this short-term Novacor VAD in humans has extended in a few instances up to one year. The fully implantable long-term Novacor VAD is beginning its animal trials in 1991 and is expected to enter human trials in 1992. The TCI VAD is a fully implantable device for long-term use that is under development through an NHLBI contract. In vivo trials of the device have been conducted in animals, and a pneumatically driven tethered version has been used for support before transplantation in 33 patients. This VAD uses textured blood-contacting surfaces, enabling the growth of a living lining of endothelial cells within the device that could reduce the likelihood of thromboembolic events.[3] FDA has also approved a TCI electrically powered, tethered VAD for investigational temporary use in five patients (Altman, 1991).

ENGINEERING ASSESSMENT OF MECHANICAL CIRCULATORY SUPPORT DEVICES[4]

Testing of mechanical circulatory devices occurs in three phases: bench testing, also known as in vitro device readiness testing; in vivo trials in animals; and clinical trials in humans. Bench testing of a circulatory support device provides an evaluation of engineering reliability, in particular of its design and manufacture. Animal trials provide biological and physiological information including safety and complications, and are particularly necessary for evaluating whether or not to perform trials in humans. Clinical-trial or investigational use of devices in humans is conducted under an IDE to determine efficacy. All three, used together, help determine the potential benefit of mechanical circulatory support devices and are also specific steps toward FDA approval of the general use and marketing of a device (see Figure 2.1).

[3] Thromboembolism is the blocking of a blood vessel (embolization) by a particle of a blood clot (thrombus) that has broken away from the clot where it formed.

[4] This section draws heavily on a background paper (Rosenberg, 1990) commissioned by the Institute of Medicine committee from Gerson Rosenberg, Ph.D., a bioengineer at Pennsylvania State University.

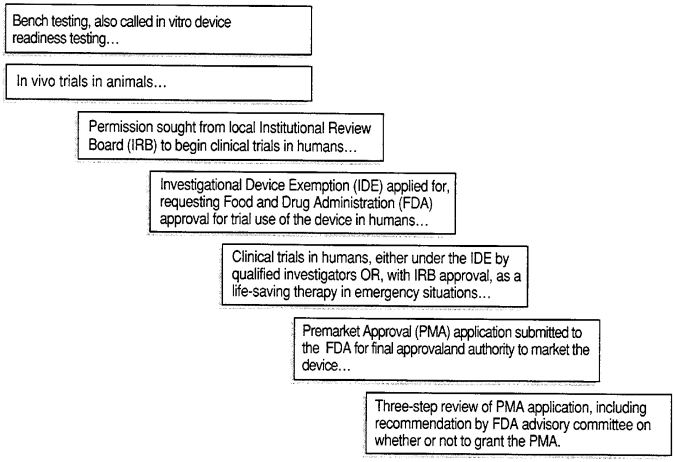


FIGURE 2.1 Testing and approval process for a life-sustaining or implantable medical device.

Mechanical Failure

There are two general kinds of mechanical failure with circulatory support devices. A "soft" device failure occurs when the malfunction is correctable and is not so critical that the patient's life is in immediate danger; a "hard" failure is a major mechanical failure that results in serious risk of death. Based on experience with MCSSs employed for temporary use, the risk of either type of mechanical failure is low.

In one institution, for example, 40 Jarvik TAHs were used over the course of three years. During this time no mechanical failures occurred in the drive system and mechanical dysfunction was limited to one artificial valve that needed to be replaced (Muneretto et al., 1990). Similar positive results are evident in another analysis of reported use, which indicates that of 186 clinical applications of short-term pneumatic TAHs (Symbion/ Jarvik devices for the most part), approximately 1 percent of the patients experienced any mechanical failure, as did approximately 1.5 percent of all those who received one or two VADs (Rosenberg, 1990).

Recent bench testing of the pumping system of the long-term Novacor VAD involved 12 devices operating unattended for 2 years in a simulated in vivo situation. This rigorous reliability testing was, however, a trial of a small number of devices in a simulated environment, and therefore the positive results of the trial are not directly transferable to evaluation of the device's clinical potential. Most notably, saline solution and mechanical

valves, rather than blood and tissue valves, had to be used for the in vitro experiment and the implantable power source was not tested. Nevertheless, the in vitro testing results correlate with the low reported rates of device failure in short-term clinical use. Because failures in such a bench test are most likely to occur during the early stages of the test, the results of the two-year Novacor VAD bench trial support the clinical evidence that mechanical failure of MCSSs is not likely to be a significant limitation on their use.

Device Components as Limiting Factors

Two technical areas of MCSSs that have been inadequately examined are the valves and the batteries. Mechanical wear of valves over time is a particular limitation. The valves currently in use were not designed for use with circulatory support devices but were developed as stand-alone implants, a use that subjects them to less material stress. Valves currently appear to have acceptable but not optimal durability for two or more years of use. Accelerated testing and analysis of stress on the valve elements would enable better estimates of the component's longevity (Rosenberg, 1990).

Longevity of power sources is another concern, despite continuing work on designing next-generation power sources. A primary difficulty is the patient's need to rely on the implanted back-up battery for short periods of time. The longevity of this internal battery must not be significantly impaired by such frequent use, and it must recharge quickly and efficiently enough to be available in an emergency.

One possible solution to the power-source limitation, currently being pursued by a corporation, is the development of a lithium battery (Post and Takeuchi, 1990). Another solution would be thermal power sources; NHLBI has for several years supported two thermal power developers, who reported promising results at the annual contractors' conference in December 1990.[5] A specific advantage of thermal power sources is that the patient would be independent of the external battery pack, with recharging limited to perhaps one hour for every eight hours of continuous operation (Butler et al., 1990; White et al., 1990). Further exploration of alternative power sources might lead to significant improvements in patient quality of life and could obviate the longevity problem of current implantable batteries.

[5] In these implanted thermal power systems, heat from a storage reservoir containing a mixture of lithium fluoride-lithium chloride salts generates energy to drive a piston and power the pump. An advantage of this power system is the elimination of electronic components and several moving parts, with consequently minimized mechanical wear.

The development of safe biomaterials, specifically for surfaces that come into contact with blood, also has been a limitation on MCSS technology; the polyurethane currently in use was developed in the 1960s. The incidence of thromboembolism, a serious clinical complication, is highly responsive to the type and use of biomaterials and the configuration of the pumping chamber. Recent interest in improved biomaterials, including new biomedical elastomers for blood-contacting surfaces, may reduce this barrier to MCSS and other medical device development; two corporations are beginning development of improved biomaterials. Among the goals are materials with improved biocompatibility, fatigue resistance, and ease of manufacture.

The success of further R&D in addressing the problems just enumerated will have a direct impact on levels of clinical complications and quality of life. These levels, in turn, will greatly affect the probability of developing long-term devices that are effective for routine clinical use.

Device Longevity

When calculating the costs of developing a long-term MCSS, a pivotal question is whether the effectiveness of the current devices can eventually be extended beyond two years. Current assumptions about MCSSs are that, with further R&D and the option of easily replacing implanted batteries and other components, device longevity can eventually be extended to 5 and perhaps 10 years. It is also anticipated that component failure or wear will become predictable and that some components can be easily repaired. Although such assumptions of improved device longevity and maintenance have not formed a basis for the committee's evaluation and recommendations, a device with an average 2-year longevity will clearly be used in many fewer patients than one expected to last 5 to 10 years.

CLINICAL COMPLICATIONS WITH MECHANICAL CIRCULATORY SUPPORT DEVICES

There has been extensive temporary use of MCSSs, particularly ventricular assist devices, with over 1,300 documented applications. Of these, 400 patients have been temporarily supported before transplantation and 68 percent of these lived to receive a donor heart (Miller et al., 1990). There do not appear to be significant differences in the outcomes of immediate transplantation and transplantations preceded by MCSS use. The major risk factors for mortality with transplantation after MCSS support are irreversible noncardiac organ dysfunction and infection at the time of transplantation; the same major risks apply when a donor heart is implanted without prior use of an MCSS. When organ dysfunction is moderate and reversible,

mechanical circulatory support can actually normalize liver, kidney, and respiratory function while the patient is awaiting transplantation (McGee et al., 1989; Pifarre et al., 1990).

For patients successfully supported to transplantation, the causes of death vary. With patients who used an MCSS for fewer than 30 days—generally those with the greatest severity of illness—kidney failure, infection, and bleeding had the highest correlation with the patient's death following transplantation. For patients supported for more than 30 days, infection and rejection of the donor heart were the most frequent causes of death, results comparable to those for direct transplantation. These data suggest that, despite an initial risk in implanting the device, there is a relative lack of additional ill effects, once an MCSS is implanted, from duration of use (Miller et al., 1990).

As to clinical complications and biocompatibility, data from the Clinical Registry of Mechanical Ventricular Assistance (Miller et al., 1990) show that the major complicating factors for all MCSS use are bleeding and the subsequent need for reoperation, which occur shortly after initial implantation and are generally related to the severity of illness and consequent alteration in coagulation factors. Kidney failure and infection, respiratory failure, biventricular heart failure during VAD use, and thromboembolism are the other major complications (see Table 2.2). Although particular de

TABLE 2.2 Clinical Complications with Short-Term Use of MCSSs

	Percent of Patients Experiencing the Complication	
	With a VAD (*n* = 1,221)	With a TAH (*n* = 186)
Complication		
Bleeding and reoperation	30	28
Kidney failure	25	19
Infection	17	21
Respiratory failure	16	13
Biventricular failure (VAD only)	16	
Thromboembolic complications	12	13
Emboli	7	9
Thrombi	5	4

LVAD, left ventricular assist device; MCSSs, mechanical circulatory support systems; TAH, total artificial heart; VAD, ventricular assist device.

SOURCE: Combined Registry for the Clinical Use of Mechanical Ventricular Assist Pumps and the Total Artificial Heart, verbal communication to G. Rosenberg, 1990.

vices can excel in specific situations, the overall data are very similar for the short-term use of TAHs and the short-term use of uni-or biventricular assist devices.

The major clinical risks with use of circulatory support devices are, therefore, failure of major organs, bleeding, infection, and thromboembolism. Of these, it is reasonable to predict that the incidence of infection will be lower because the skin-penetrating tubes used with temporary devices will not be necessary with a totally implantable MCSS. Predictions about the implications of long-term MCSS use, however, such as the number of strokes resulting from thromboembolism, can be made less confidently because they depend on current estimates of the future state of the technology.

Data on thromboembolism in particular are very dependent on device design and biomaterials. For all clinical MCSS use for all indications, there is experience of approximately 12 percent either of thrombosis in the device and tubing or of embolism (Rosenberg, 1990) but rates of thromboembolic events vary considerably. These rates depend heavily on factors such as the patient's condition, surgeon's experience, and anticoagulant drug therapies used after implantation, and also on the design of the specific device used. For instance, one group of 12 patients using a VAD with low thromboembolic rates had no such events, whereas 17 percent of 54 patients using another VAD did; both groups received antithrombotic drug therapies (McGee et al., 1989; Termuhlen et al., 1989). To create the best possible device, the optimal combination of MCSS design, components, and materials must be determined (Didisheim et al., 1989; Rosenberg, 1990).

ALTERNATIVE TECHNOLOGIES FOR PREVENTING AND TREATING END-STAGE HEART DISEASE

The conventional treatment modality for end-stage heart disease is medical treatment with pharmaceutical products. When such treatment does not suffice, or when a patient experiences acute difficulties, alternative treatments are considered. Like the use of medication, these treatments can prevent or ameliorate some of the clinical consequences of end-stage heart disease. They are not, however, able to prevent end-stage heart disease itself. Most notable among these current and emerging alternative technologies are: short-term intra-arterial assist devices, surgical techniques for augmenting the function of the heart muscle with a skeletal muscle, and heart transplantation.

Conventional Medical Treatment

The conventional medical treatment of congestive heart failure has evolved over the past century and continues to change with the introduction of new

pharmaceuticals and the acquisition of new understanding about pathophysiologic mechanisms. Medical treatment is first directed at identifying and treating underlying causes and precipitating factors. The work of the heart is reduced by restricting physical activity and by pharmacologically adjusting blood pressure and cardiac function. Digitalis glycosides are used as positive inotropic agents that increase the force of contraction of the failing heart. Salt restrictions and diuretic agents contract intravascular fluid volume and adjust intracardiac pressures to ameliorate the signs and symptoms of vascular congestion. Varying potency and specificity for different portions of the kidney tubule enable these diuretics to be concentrated according to the severity of the disease. Vasodilating drugs reduce the work of the failing heart and thus relieve the symptoms of congestive heart failure. These are the only drugs that have been shown in prospective randomized studies to prolong the survival of patients with congestive heart failure, but to date this has been a short-lived benefit. More potent positive inotropic and vasodilating drugs are available for intravenous use in the intensive care unit for treatment of acute decompensation, but these are not currently practical for long-term management.

In summary, in spite of many advances in the conventional medical therapy of congestive heart failure, the primary goals of therapy remain those of symptomatic relief and palliation of a chronic and inexorably progressive disorder. Ongoing basic and clinical research may offer more hopeful medical therapeutic approaches in the future.

Other Cardiac Assistance Technologies

The intra-aortic balloon pump provides mechanical assistance to left ventricular function on a temporary basis. It is usually inserted into the thoracic aorta through the femoral artery and employs a helium-inflated balloon that deflates in cardiac systole and inflates in diastole. This action reduces the pressure against which the left ventricle contracts and augments diastolic pressure and thus coronary flow. The pump increases cardiac output to a maximum of about 20 percent.

The Nimbus Hemopump[6] is a small device, usually inserted via the femoral artery into the left ventricle, which assists blood flow by propelling blood from the left ventricle to the ascending aorta. It provides greater augmentation of cardiac blood flow than does the intra-aortic balloon pump, but its use is currently limited to several days to a week and it is not yet approved for general use.

Both the intra-aortic balloon and Nimbus blood pumps are generally used

[6] Nimbus Hemopump is a registered trademark.

to maintain patients who are waiting for their hearts to recover normal function after a massive insult to the myocardium, such as might occur after open heart surgery or acute myocardial infarction, or during percutaneous transluminal coronary angioplasty. There are clear applications for their short-term use, but because they can be used for only limited periods of time and because the patient is essentially bed-bound, they are not longterm solutions to end-stage heart disease (Frazier et al., 1990; Macoviak et al., 1990).

Cardiomyoplasty is the process of relocating a skeletal muscle from the back to a position around or near the heart and training it, through electrical stimulation, to contract regularly and thereby aid circulation. Because it takes several weeks to adapt skeletal muscle fibers for this function, cardiomyoplasty is not suitable for emergency circumstances. Having been used investigationally in only a hundred or so patients worldwide, it is not yet clear how much the procedure can improve standard clinical indicators of health.

In summary, pharmaceutical treatment, intra-aortic devices, and cardiomyoplasty can improve or ameliorate the condition of only a portion of patients with end-stage heart disease, typically those in comparatively better health. In particular, these treatment alternatives usually cannot improve the health status of moribund patients (those in New York Heart Association functional Class IV),[7] or postpone their deaths for more than a few weeks. For these patients heart transplantation provides the only available alternative, but is of limited potential given the small supply of donor hearts.

Heart Transplantation

When comparing TAHs with heart transplantation, the first consideration is that the supply of donor hearts, currently about 2,000 annually in the United States, is inadequate and will continue to be insufficient to meet demand. The population currently eligible for donor hearts is a subset of the larger population that would be eligible for TAHs. Given a device that functions well, many of those patients who do not currently receive a donor organ would benefit from a device. Even among those patients who are clearly eligible for transplantation, many will prefer receiving a long-term device to waiting for an available donor heart.

The second consideration is that heart transplantation and circulatory

[7] New York Heart Association functional classification for Class IV: Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased (New York Heart Association, 1964).

support devices are not always suitable for the same individual, and therefore will not necessarily be competing for patients. The criteria for heart transplantation are rather restrictive; there are both absolute and relative contraindications. Absolute contraindications include predictable immune system rejection of the donor organ and comorbidities such as diabetes, cerebrovascular or liver disease, carcinoma, or chronic obstructive pulmonary disease (Graham and Chalmers, 1989). Relative contraindications include overall health too poor to allow waiting for a donor heart; poor tolerance of immunosuppressant side effects; and advanced age, which currently militates against the use of comparatively rare donor hearts. TAHs will have fewer contraindications than transplantation and therefore would be potentially useful for patients who are not eligible for transplantation as well as those who cannot survive the wait for a donor heart.

In the first two years following heart transplantation the most serious risks are infection and immune system rejection of the donor heart. A further risk for heart transplantation recipients, still relatively unexamined for lack of long-term data, is accelerated atherosclerosis of the donor heart. This condition afflicts at least 20 percent of all transplant recipients and may become the most important cause of late mortality or retransplantation (Davies and Al-Tikriti, 1989; Baughman, 1990).

The goals in using circulatory support devices are to prolong life while maintaining an acceptable quality of life. The average survival rate for cardiac transplantation patients after five years is currently about 70 percent. In predicting future use when TAHs and heart transplantation are both available, it will be important to determine whether early TAH performance can be maintained over a 5- and then a 10-year span of clinical use.

SUMMARY OF THE CURRENT AND FUTURE STATE OF TOTAL ARTIFICIAL HEART TECHNOLOGY

Major limitations on long-term, widespread use of mechanical circulatory support are the devices' current power sources, biomaterials, valves, and design. Design challenges include extending device longevity, reducing the size of MCSSs to make them available to smaller adults and children, and improved, smaller configurations of both components and systems. The level of success in overcoming these limitations will directly affect the ultimate usefulness and effectiveness of MCSSs.

In short-term MCSS use, the results of in vitro and in vivo trials indicate that perioperative bleeding, major organ failure, infection, and thromboembolism are the main clinical complications. The data for short-term VADs and TAHs are similar when considered, overall, by category (see Table 2.2) but within the VAD category, performance levels vary in terms of the clinical

complications and overall performance of the specific devices. Long-term use of totally implantable circulatory support devices has not yet occurred; the results of early long-term VAD trials will be crucial in refining current estimates about the long-term routine use of TAHs.

Finally, comparison with other technologies for treating end-stage heart disease indicates that well-performing long-term TAHs could provide care to end-stage heart disease patients that is currently unavailable through heart transplantation, other technologies, or established drug treatment.

RESEARCH AND DEVELOPMENT COSTS OF TOTAL ARTIFICIAL HEARTS

Stages of the Innovative Process

A brief examination of the various stages of the innovation process in medical technology will help to put the research and development process for MCSSs in perspective. Most analysts would propose stages in the innovative process that include basic or fundamental research; applied research and development; product development and testing; introduction to use; and diffusion of use. Two observations about these stages are needed, however.

First, many scientists, implicitly or explicitly, see the stages as a linear progression, in which development and use depend on advances in basic science. But recent observers have begun to demonstrate that the stages often have an iterative relationship to each other: basic research may stimulate further basic research as often as it drives applied research; applied research may feed findings and questions to basic research as it receives vital information from basic research; and development and use of a technology may generate both basic and applied research questions, as well as benefit from research results. Although the dependence of technology on basic science is well established, the frequent contribution of technological advance to scientific progress is less clear but often equally important (Gelijns, 1990).

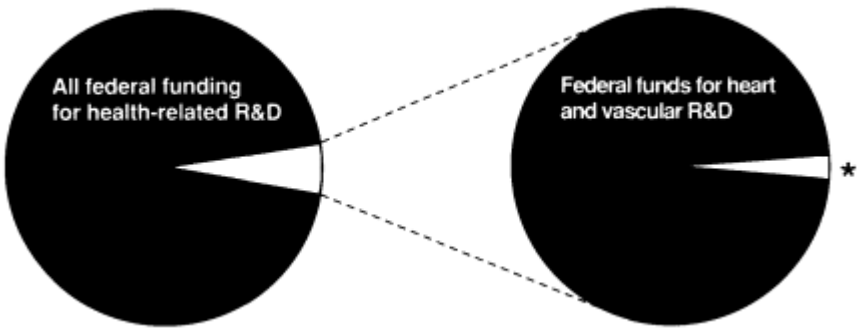
Second, many scientists and engineers involved in the R&D process view "technology-push" as the driving force in innovation, whereas economists and managers tend to place more weight on "demand-pull" as the source of innovation. As Gruber and Marquis (1969) noted long ago, neither of these opposing views is adequate. Successful innovation stems both from the integration of new scientific and technical information and from a recognition of potential market demand. These observations hold for the MCSS R&D process.

Support for the Artificial Heart Program

One purpose of the IOM committee's deliberations is to advise NHLBI in its decision on R&D resource allocations for circulatory support devices. For 1989, estimated federal expenditures on health-related R&D totaled $10.5 billion (IOM, 1990). The federal funds spent specifically on MCSS research and development are disbursed through NHLBI grants and contracts. From the inception of the artificial heart program in 1964 through fiscal year (FY) 1989, a total of $264.4 million has been spent on a wide variety of targeted programs and grants for MCSS R&D (see Figure 1.5).

In FY 1990 estimated costs for MCSS research were $8.2 million in nontargeted grants and $7.3 million in contracts, for a combined total of $15.5 million. This sum represents 2.7 percent of the $581 million allocated by NHLBI to R&D on heart and vascular diseases in FY 1990, and is 1.4 percent of the total NHLBI 1990 budget of $1,072 billion (see Figure 2.2) (NHLBI, 1990a; NHLBI, 1990b).

It is beyond the committee's abilities to precisely estimate the amounts of NHLBI funds needed to carry MCSS development forward. Device developers presented their estimates of further needed funding, but the



Left circle: $10.5 billion, total federal funding for health-related R&D
Right circle: $581.7 million, federal funding for NHLBI R&D on heart and vascular diseases
Asterisk: $13.8 million, federal funding for the NHLBI artificial heart program

FIGURE 2.2 Representation of federal funding for the artificial heart program, FY 1989 and FY 1990. NHLBI, National Heart, Lung, and Blood Institute; R&D, research and development. SOURCES: Division of National Cost Estimates, 1987; IOM, 1990; Office of National Cost Estimates, 1990; NHLBI, 1990a, 1990b, 1991; *Washington Post,* 1990.

committee does not feel comfortable with these figures because they substantially exceed previous levels of NHLBI support. Instead, the committee's best estimates are that for VAD development as recommended (see Chapter 10) about $2 million per year will be needed, over and above the amounts already committed for the Novacor clinical trial, during the early 1990s interim period. Support for further VAD clinical trials may be needed thereafter.

The recommended interim funding of TAH development will likely total $3 to $6 million per year for a two-to three-year period, depending on the number of contracts extended after peer-review consideration of the developers' progress. If development continues thereafter, the support required from NHLBI will likely total, over 10 years, between $30 and $90 million for the two final R&D phases (see Chapter 6).

For all MCSS development, the committee notes the advantages of funding multiple research teams. Existing circulatory support systems differ in terms of design, efficiency, and perhaps susceptibility to clinical complications. Continued R&D on several fronts could make it possible to develop MCSSs with optimal capabilities in all of these areas.

Considering the Costs of Research and Development to Industry

In general, the actual costs of medical technology R&D are not well documented or are unknown, and individual corporations are reluctant to release financial data on their R&D programs (Gelijns, 1990). Nevertheless, a few broad observations are possible. The most data are available for pharmaceutical R&D; it is known, for example, that in 1991 development of the "average" pharmaceutical cost a total of $231 million (DiMasi et al., in press; Grabowski, 1991). Even for pharmaceutical R&D, however, "[a]ctual development costs vary greatly from drug to drug, year to year, and company to company, depending on whether the definitions used are uniform or change, in addition to actual [cost] changes" (Spilker, 1989). For medical devices, the uncertainty and difficulty of comparing cost estimates increase, but it is clear that many factors, including the nature of the device, its stage in the development process, the costs of mass production, and quality assurance and testing requirements, are potential considerations in calculating total costs. Chapters 3 and 9 address other aspects of industry R&D.

CONCLUSIONS

The committee believes that, with the further development likely to occur, the MCSSs currently being developed can reverse the physiological effects of heart failure and improve quality of life for two years or more.

Five-year models appear possible in the near term; however, it is not altogether clear what engineering and materials science advances will be required to achieve highly reliable 5- to 10-year devices. As discussed in Chapter 4, the extent to which MCSSs prolong life and improve its quality will be critical factors in determining their clinical value and the extent of their use.

The committee is uncertain about the costs to NHLBI and industry of the necessary technical improvements in MCSSs and the time required to achieve the necessary level of device longevity. Nevertheless, it does not consider the levels of R&D funding needed from NHLBI to be large enough to constitute, in and of themselves, a reason for discontinuing or cutting back the artificial heart program. The committee further notes the importance of continued funding of multiple research teams so as to profit from the strengths of each.

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3

Decisions for Future Research and Development

THE NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI) must make numerous decisions in coming years about funding in its artificial heart program. The main purpose of this study is to suggest factors to be considered in these decisions, including whether to continue the development of fully implantable ventricular assist devices (VADs) and total artificial hearts (TAHs). As a framework for the specific research and development topics in the balance of the report, this chapter presents explicit decisionmaking criteria and describes several methods for applying them.

As discussed further in Chapter 9, the NHLBI artificial heart program is unusual among health care R&D programs in that government funds have provided almost all of the support for developing the long-term, fully implantable devices that are the subject of this study. In making decisions about activities of the artificial heart program, NHLBI and not-for-profit research organizations use approaches and methods very different from those used by industry in allocating funds to R&D programs (a topic discussed briefly at the end of this chapter).

ALLOCATING RESEARCH FUNDS

Decisions about the use of funds for research and development occur at various levels in any organization involved with R&D. Figure 3.1 illustrates some of the types of decisions made in NHLBI, especially ones that involve the artificial heart program.

Allocations must be made, in total, to each of the three major programs within NHLBI's scope. In each of the 23 clinical program areas, decisions

are needed about the amounts to be allocated for specific targeted research efforts and for nontargeted, investigator-initiated research. Once a specific targeted allocation is fixed, such as the total for all grants under a particular request for applications (RFA) initiative or for funding of contracts for VAD or TAH development, administrators must decide the specific amount allocated to each grant or contract. In general, two methods can be used in the allocation of R&D funds—decision making that is solely judgment based or decisions that are aided by quantitative techniques such as cost

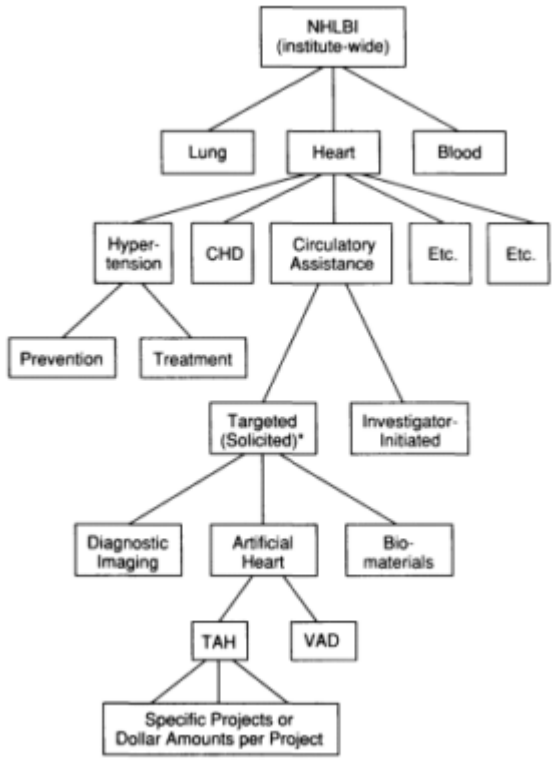

FIGURE 3.1 Levels of R&D resource allocation. The asterisk denotes targeted research that may be accomplished either through R01 grants (by a request for applications) or through contracts (by a request for proposals). NHLBI, National Heart, Lung, and Blood Institute; CHD, coronary heart disease; TAH, total artificial heart; VAD, ventricular assist device; R&D, research and development.

effectiveness analysis (CEA) or by systematic application of explicit criteria.

NHLBI currently relies on peer-or professional-judgment decision making in almost all of its funding-allocation decisions. Using heart and vascular diseases as an example, the NHLBI Cardiology Advisory Committee periodically ranks all proposed new initiatives (RFAs) in priority order. Except for this peer-judgment priority setting for new R&D initiatives, the committee understands that NHLBI does not use quantified methods or assessments of explicit criteria to aid it in deciding about funding allocations at any of the levels indicated on Figure 3.1.

In contrast, in the area of decisions about the scientific merit of specific grants and contracts, NHLBI relies heavily on peer-review judgments that are expressed quantitatively by members of initial review groups (study sections) and ad hoc review committees. Agency officials establish weighted evaluation factors, either general criteria for nontargeted investigator initiated grants or factors that are tailored to a specific area for which proposals have been solicited. Examples of evaluation factors include the feasibility of the proposed approach, the adequacy of the experimental design, and the competence of the investigators.

Study section or review committee members assign priority scores to each factor based on scientific and technical merit; the total scores are then converted to percentiles in order to normalize scores across the various groups. Awards are typically made in the order of assigned percentiles.

JUDGMENT-BASED DECISION MAKING

Traditionally, within NHLBI as in many other organizations, most R&D funding allocation decisions are made on the basis of professional judgment, either individual or collective, about the relative merits of the alternatives under consideration. Rarely is any quantitative approach used, or even a systematic application of specific criteria. General considerations are likely to be implicit in the judgments made, such as these listed in an early draft of Department of Health and Human Services principles for an aborted research planning process:

> Investments in areas of health research should be guided by many factors, including research opportunity, burden of illness measures, demographic trends, public perceptions of the relative importance of different health areas, current state of the art, previous investment and return experiences, near term potential for new breakthroughs, problem areas identified through disease surveillance and investigation of disease outbreaks, interrelationships with other research problems, benefits which may accrue by elimination or improved treatment of disease,

> the perception of those concerned or involved in dealing with social problems or needs, and a continuing retrospective assessment of health benefits attained through research expenditures. (IOM, 1979, pp. 57-58)

At a more practical level, NHLBI administrators, its National Advisory Council, and other advisory committees are likely to consider any relevant spending allocations in previous years, as well as considering several general factors in making funding decisions and recommendations. These factors include:

- the societal and political importance of the various alternative uses for the available funds;
- the magnitude and nature of the clinical needs in each area;
- the ability to make progress in solving the problem addressed by each area; and
- the research capacity (in such respects as facilities and qualified researchers), as well as the perceived degree of scientific-community professional interest, in particular areas.

Any of the foregoing criteria can be described in some detail, and alternatives can be assessed or at least ranked using them. However, this is rarely done. Further, when decision makers face a choice between basic research and applied R&D, other specific considerations may override general criteria. For instance, those in charge of an R&D effort might assess the nature of the problems that need to be addressed during the R&D work. Are the problems to be solved "basic" ones, or technical and practical ones? If the problem is basic, then basic (but perhaps targeted) research should receive the greater part of the research funds; if the problem is technical, the allocation should favor the particular applied research mechanisms that can best achieve the needed engineering and technical solutions.

QUANTIFIED AIDS TO DECISION MAKING

Cost-Effectiveness Analysis

Several resource allocation methods have been developed that take into consideration the cost-effectiveness of R&D alternatives. These typically express in dollar terms both the net benefits yielded by developing solutions to specific problems and the projected R&D expenditures needed to achieve each solution. For example, Weinstein (1983) examined the costeffectiveness of developing and implementing two cancer-prevention research strategies by determining cost-effectiveness ratios that compared the projected benefits of each strategy to their R&D and health care costs.

The calculations also reflected the probability that each R&D effort would accomplish its cancer-prevention goal.

In a similar study, Hatziandreu and colleagues (1988) compared annual spending on research concerning the acquired immunodeficiency syndrome (AIDS), heart disease, cancer, and unintentional injuries (accidents) with the approximate societal cost of each, with costs expressed in several different ways. The study identified current levels of R&D expenditures and related them to such cost measures as deaths caused or years of expected life lost. Such a method could provide valuable information, for example, to Congress or the Office of Management and Budget in making major appropriations or budget decisions.

In a more elaborate consideration of options for vaccine R&D, an Institute of Medicine (IOM) study developed comprehensive estimates of the impact of various contagious diseases (e.g., treatment costs and mortality and morbidity burden) and of the benefits, cost, and probability of successful vaccine development (IOM, 1985). The benefits and costs related to each alternative were combined, using net present value computations for those in future years, resulting in a ranking of the most beneficial R&D efforts to be undertaken.

Application of Methods

In addition to using CEA as an aid to decision making, agency administrators can also use a systematic assessment of compliance with explicit criteria. Such a systematic assessment and a CEA can be employed separately or together in a combined approach. Depending on the type of decision, one method or the other may be more desirable.

For decisions that involve broad options, such as allocating funds between basic research and applied R&D or between alternatives that include combinations of programs with little in common, cost-effectiveness analyses or detailed assessments of criteria are not likely to be feasible. If officials explicitly state applicable criteria, however, they improve the likelihood that their judgment-based decisions will be both more reasonable and more consistent over time, even if they do not evaluate alternatives with precision.

In some instances of this nature, detailed, explicit criteria such as those discussed below can be applied. Assessing criteria in detail can serve, for example, as a check against possible arbitrary decisions that may result from pressures brought by groups with a particular interest in the subject under consideration. In other cases, whether for allocations between broad program areas (e.g., "heart" versus "lung") or between specific target areas within the artificial heart program, using a systematic method will ensure that all relevant factors are considered in the decision-making process.

DECISION-MAKING AIDS SUGGESTED BY THE COMMITTEE

The committee suggests three methods by which NHLBI administrators and others can be aided in making systematic choices among R&D options. Two are described in the sections that follow; the third, to be discussed in Chapter 6 in connection with this study's cost-effectiveness analysis, deals with the allocation of funds within a single R&D program. The two that follow can be used either alone or in combination.

Explicit Criteria for Allocation of Funds

Industrial firms are able to make decisions about the allocation of their R&D funds among specific programs based on return on investment calculations or net present value analysis. Government agencies, philanthropic foundations, and other groups that support health care R&D seldom experience direct monetary benefit from their research commitments, and thus they cannot use financial or economic analysis alone.

Priority-setting criteria have been developed to identify particular areas of health care or specific technologies that warrant intensive clinical study; see, for example, criteria for clinical conditions to be given high priority for examination by the Public Health Service's new effectiveness program (IOM, 1989) and priorities for technology assessments to be conducted (IOM, 1990). Such criteria have only limited usefulness, however, in considering R&D funding allocation decisions.

The committee believed a set of explicit criteria tailored for R&D use would be valuable to NHLBI and others, but a search of the literature did not reveal any listing of explicit criteria, with indications of their importance, that can be considered for this particular purpose. Therefore, the committee undertook a fresh start in exploring the question of R&D allocation criteria. Specifically, it developed through staff research and committee discussion, and proposes here, a total of 18 criteria, ranked in the perceived order of their importance for possible use in allocating research funds (see Table 3.1).[1] It felt comfortable doing so because of the wide range of perspectives and broad expertise in health care delivery and policy represented on the committee.

NHLBI can use these ranked criteria as examples of ones that may be

[1] The categorization of the criteria by degree of importance is based on a survey of committee members, who evaluated each criterion on a scale of choices ranging from I ("unimportant") to 5 ("very important"). The number of respondents (17) is too small for statistical analysis to be of value. Nonetheless, for most of the criteria, there was relatively little difference in view as to importance, which is especially noteworthy considering the diversity of the respondents' backgrounds.

appropriate for its administrators to use in allocating research funds. By suggesting these explicit criteria, the committee hopes to elicit broader discussion, as well as to stimulate NHLBI to use these or other criteria, experimentally at first and then with increasing confidence based on the early experience.

TABLE 3.1 Criteria for Allocating Research and Development Resources Among Competing Programs

More Important Criteria
1. The extent to which anticipated beneficiaries' lives will be extended or their health status and functioning improved, or both, by the research and development (R&D) "output."
2. The approximate number of persons who will benefit directly from each alternative.
3. The probability of success of the particular research effort.
4. The relative cost-benefit or cost-effectiveness anticipated from the use of each alternative.
Important Criteria
5 (tie). The extent to which the proposed research will advance knowledge.
5 (tie). The technology's relevance to the mission of the National Heart, Lung, and Blood Institute (NHLBI).
5 (tie). The expected impact of each technology on overall health care costs, including the cost of manufacturing and using each alternative R&D output.
8. The impact of the technology on patients' families.
9 (tie). The expected impact of each technology on the health care system (e.g., available beds, personnel).
9 (tie). Whether the R&D output will have general applicability or will be either applicable or inapplicable to specific age, sex, or ethnic-racial groups.
11. Specific ethical considerations (e.g., distributive justice) applicable to the technology.
12 (tie). Whether the research is directed at a "halfway technology" (i.e., one that only overcomes a disease's impact or postpones death) or at a technology that prevents or cures disease, such as prevention of coronary artery disease by cholesterol-level reduction.
12 (tie). The cost effectiveness of the R&D output relative to *non-heart* disease technologies.
12 (tie). The extent to which industry or other nongovernmental funds already support the particular research (or are expected to do so).
Less Important Criteria
15. The expected time required for successful implementation of the particular research product.
16. The extent to which allocation of NHLBI resources to the particular research is likely to stimulate private-sector research in the same area.
17. The degree of concern that the technology will be misapplied.
18. The expected impact of each allocation decision, especially with high-cost technologies involving long-term research, on the nation's global standing. (For instance, if it is not developed in the United States, will some other country do so? If so, will the balance of payments or our position of leadership in health care suffer?)

SOURCE: survey of IOM committee members.

Criteria such as those that follow are difficult to apply, as is stated with respect to a number of them. By attempting to apply these or similar criteria to R&D allocation decisions that arise in day-to-day operations, NHLBI is likely both to achieve greater objectivity and consistency in its decisions and also to make a contribution to the management of R&D by other agencies that administer research.

The More Important Criteria

Health and life expectancy gains. The criterion ranked most important by the committee is the degree to which the R&D program's output will extend anticipated beneficiaries' lives or improve their functioning and health-related quality of life, or both; it was ranked as "very important" by all but 3 of the 17 respondents. This criterion encourages allocation decisions that are based on the expected health benefit to individual patients. Life expectancy gains can be estimated by expert clinicians, and improvement in health-related quality of life can be assessed by using estimates of "before and after" measures as well as by explicitly taking the risks of the new R&D output into account.

Using this criterion in isolation does not relate treatment gains to the costs of achieving them. Further, it requires estimating specific treatment outcomes many years in advance and thus carries an even higher degree of uncertainty than other possible criteria.

Again, just as clinical indications for use may broaden over time, a technology's ability to improve patients' health-related quality of life may also change. Thus, the point in time at which the R&D output's effectiveness[2] is being measured should govern estimates of both the benefit it confers on the typical patient and the number of persons benefited.

Finally, the health impact of a particular R&D output may sometimes yield benefits of very different types to different groups. For example, a definitive treatment for a particular communicable disease will directly benefit those whose life is prolonged or health improved by the treatment. Additionally, it will have a broader public health impact that can also be estimated: by reducing the size of the diseased population, it also will

[2] It is important to use in this context "effectiveness," in the manner in which it is classically used, as differentiated from a technology's "efficacy." The latter is determined on the basis of clinical trials, typically performed in academic medical centers with a high degree of care and professional attention from experienced subspecialist physicians and with carefully selected patients. On the other hand, effectiveness is assessed after a technology's diffusion, when it is used by physicians with a range of skills, in a wide variety of settings, and on a wide range of patients. The relative abilities of other health care professionals (e.g., nurses, technologists) may also be relevant.

reduce the future impact of the disease and its attendant direct and indirect costs.

Number of persons benefited. Another of the more important criteria is the approximate number of persons who will benefit directly from a research output. This criterion is an aggregate measure of the R&D program's potential nationwide significance. Using it with only total numbers of projected patients will not reflect the seriousness of the disease being addressed (e.g., degree of disability it causes) or the extent to which successful research is likely to alleviate the disease's impact on affected individuals. Also, it does not provide for consideration of particular demographic groups (e.g., the poor, older persons) who may or may not benefit disproportionately from the R&D output. It is, therefore, not a criterion that should stand alone, despite its clarity and the high degree of importance with which it is viewed by the committee.

One problem in applying this criterion is the need to estimate the size of a potential user population, which is especially difficult during early stages of R&D. Even with a program in as late a stage of development as the long-term ventricular assist device that is about to undergo clinical trials, projecting indications for use that will be implemented when its routine clinical use begins is difficult. Nonetheless, to apply this criterion, decision makers must develop indications for use, based on the best possible estimates of risks versus benefits, and translate them into numbers of prospective beneficiaries.

In health care, even such a needs-based projection may not reflect two other important considerations. First, at least for costly technologies, actual utilization will depend heavily on the extent to which third-party payers decide to pay for the particular R&D output, as well as on the adequacy of payment rates. This consideration will be particularly important for technologies such as mechanical circulatory support systems (MCSSs), insofar as the Medicare program's decisions are concerned, because end-stage heart disease disproportionately affects older persons.

Second, as has occurred in the cardiovascular arena with coronary artery bypass surgery, coronary angioplasty, and the automatic implantable cardioverter defibrillator, indications for use will often broaden as physicians accept the technology's original clinical applications and begin to use it with other patients. Initial utilization projections will likely become obsolete after a few years of routine use, at least to the extent that third-party payers impose no obstacles to such broadening or "slippage."

One limitation of assigning this criterion a high degree of importance is that, when relatively few people are affected by a particular disease, specially targeted R&D support may be needed in order to overcome the

effect of this criterion. For example, special legislation was needed to stimulate the development of "orphan" drugs for rare diseases.

Likelihood of R&D success. The committee ranked the probability of R&D success as another of the more important criteria. Quantifying the likelihood that an R&D effort will achieve its goal is difficult, however, especially at an early stage or even before the activity begins. Probability estimates of success can sometimes be included in CEAs, which would make this a more useful criterion.

Usually, the cumulative probability of success should be the basis for applying this criterion to specific R&D alternatives, because the cumulative probability increases steadily over time. Only if criteria are being applied as of a given date should a time-specific probability be used, such as at the end of a program's particular year.

Cost-effectiveness. The fourth of the criteria ranked by the committee as more important is the relative cost-benefit or cost-effectiveness anticipated from the use of each alternative. In an era of enhanced consciousness about health care costs, using anticipated cost-benefit ratios or costeffectiveness measures (e.g., cost per incremental quality-adjusted life year, or QALY) reflects the relative potential of each R&D output for accomplishing gains in health-related quality of life. As discussed in Chapter 6, cost-benefit analysis (CBA) and cost-effectiveness analysis (CEA) are well recognized as aids to health care decision making; they are particularly valuable if utility measures, assessing the quality of life, are included in the computations.

A method such as CEA also provides a way to reflect costs of alternatives more specifically than may otherwise be possible. A form of treatment that appears to be very costly may, for example, prevent a several-year course of deteriorating health that requires even more costly in patient care. By explicitly considering the long-term costs if the new technology is *not* used as well as the costs of using it, CEA presents to the decision maker the net cost of each new technology as well as its benefits.

CBA and CEA studies have limitations, however. Other nonquantifiable factors must often be considered as part of the evaluation process, such as the other criteria suggested in this chapter. Also, a CBA or CEA often requires the analyst to estimate the values of many different variables, some of which may be uncertain. Sensitivity analysis helps to determine how important the uncertainty is to the decision.

To reflect fully the economic impact of an R&D output, the value of possible spin-offs from that effort would also ideally be considered, as a possible offset against total costs. Several MCSS developers have reported successful spin-offs from this R&D (Appendix C; Poirier, 1990). Some of

these have the potential for major improvements to the quality of health care or even potential value in other fields. Without placing some value on possible research spin-offs, evaluating an R&D program's costeffectiveness would not be complete. Difficulties in forecasting such spin-offs, however, make it unlikely that the choice between R&D options would be affected by differential expectations for spin-off technologies at the time of the R&D decision, unless the options under consideration vary greatly in their amenability to spin-offs.

Important Criteria

Committee members evaluated 10 criteria as important in addition to the 4 just discussed in the "more important" range, but applying as many as 14 criteria in comparing a group of R&D proposals is a daunting prospect. Thus, decision makers may wish to limit their use of criteria such as those that follow to perhaps the four or five that are most applicable to the area and alternatives under consideration. All 10 certainly should not be accorded equal weight.

Advancement of knowledge. The highest ranked of the "important" group of criteria is the extent to which a particular R&D program is expected to lead to basic knowledge that is useful in areas other than the one directly aimed at originally. This criterion or goal is often referred to as "advancing knowledge." It gauges the extent to which targeted research may result in discoveries that are not directly related to the original target, rather than focusing on the basic research itself. The research output may nonetheless be useful in either the alternative under consideration or others.

It is difficult to predict the extent to which an R&D program will produce other useful knowledge. Evaluating options as meeting this criterion will therefore carry considerable uncertainty, especially if the assessment is being done at an early stage of the R&D effort.

The issue of spin-off or spillover discoveries, just discussed in connection with cost-effectiveness analysis, is a related, more concrete example of the value that can result in other fields from targeted research. Still, it may be similarly difficult to evaluate.

Relevance to NHLBI's mission. The relevance of each option to NHLBI's mission is the criterion ranked second highest in the "important" group. Using it may be unproductive, however, because of prior administrative action that, at an early stage, screens out R&D program proposals as irrelevant to NHLBI's mission before they reach the point of formal allocation decisions.

In considering the application of this criterion, NHLBI must recognize

that its mission statement is so broad that it may provide little assessment guidance; this is, unfortunately, true for most large, multifaceted organizations. Still, if the options under review vary considerably in how central or peripheral their goals are to NHLBI's mission, this will be an important criterion to consider.

Impact on health care costs. The expected impact of each technology on overall health care costs, including the cost of manufacturing and using each alternative R&D output, is another important criterion for allocation decisions. Using the long-term fiscal impact of a particular R&D program as a criterion requires assuming that the research is successful and that the output has come into wide use. Doing so puts R&D decision makers in an unusual position. It may require them, for instance, to confront directly the desirability of applying R&D resources toward achieving an ultimate goal that the United States will be unable to afford or, at a minimum, to consider questions of distributive justice that may arise when the R&D output becomes available. Although manufacturing and service industries routinely consider many aspects of the distribution and sale of their R&D outputs from the outset of planning, similar factors are rarely considered in government and not-for-profit R&D decisions. Distributive justice issues can be considered, however, by NHLBI and other R&D agencies.

Several pitfalls may need to be confronted in applying this criterion:

- Various perspectives (e.g., state, federal, private payer) should be discussed and evaluated thoroughly, because implications of a choice may vary widely by perspective.
- Whenever possible, both direct and indirect costs and benefits associated with the new R&D output should be considered, in order to reflect all offsetting reductions.
- Application of this total-cost criterion, without also considering cost *effectiveness,* may stifle innovation. A proposed technology with high projected costs will, in isolation, be viewed adversely by some. In actuality, though, it may be a cost-effective use of resources because of offsetting economic savings or because it provides more substantial health benefits than could be achieved by alternate uses of the resources.
- Long-term health care costs related to a particular R&D proposal are extremely difficult to estimate, making assessments of this criterion uncertain except to the extent that CBA or CEA sensitivity analyses reflect such uncertainties.

Finally, if a technology's use is concentrated within a particular demographic group, projections of the future size of that group should be used in estimating the option's impact on health care costs. The number of older

persons, for instance, will increase greatly in the coming decades. The aggregate cost of applying a technology that is primarily used by older persons is therefore likely to increase at a rate higher than is typical for health care costs generally.

Impact on patients' families. An important criterion that is related to improved life expectancy and health-related quality of life is the effect of the alternative on patients' family members and other caregivers. Its importance will vary depending on the characteristics of each R&D option's goals. If the illness or condition is one in which family members' feelings are likely to have a direct impact on the patient's quality of life, as discussed in Chapter 5, then this criterion may be especially important. Conversely, if family members are typically not involved as caregivers and if the patient's autonomy of decision making about the illness is highly valued, then this criterion should not be applied despite the possible impact on family members. Assessing the effect of an R&D output on family members is even more difficult than it is for patients, particularly in the early stages of an R&D effort, so this criterion should be applied with care.

Nonfinancial impact on health care system. An additional important criterion is the expected impact of each technology on aspects of the health care system (e.g., available beds, personnel) other than the dollar costs of providing the technology. Nonfinancial resources can potentially be a serious constraint on the usefulness of an R&D output; this may be true particularly in the early years of a treatment technology's use as it is applied to a backlog of patients for whom no treatment previously existed. Whether the constraint is one of space—for instance, crowded operating room schedules—or qualified personnel, nonfinancial resource limits may be important with some outputs.

A similar impact may occur when a newly introduced technology has a dramatic effect on the volume of use of other technologies. This occurred, for instance, when thrombolytic therapy was introduced as a treatment for acute myocardial infarction, leading to increased use of coronary angiography and angioplasty (Steinberg et al., 1988).

This criterion thus makes explicit a potential constraint on diffusion that is often not considered but can be important. It is difficult to apply accurately, however, in the early stages of R&D.

Beneficiary demographics. Whether the output will have general applicability or be either applicable or inapplicable to specific age, sex, or ethnicracial groups is another important criterion. This criterion recognizes the possibility of targeting of R&D resources, one type of which is positive targeting that serves beneficiary groups whose needs are qualitatively the

greatest. Such targeting assumes that need can be assessed in a just and equitable manner; as examples, research on cystic fibrosis or congenital heart disease primarily benefits children and research on sickle cell disease primarily benefits blacks. Conversely, targeting that is undesirable from a distributive justice perspective could also be involved, if it benefits one group (e.g., middle-class white males) disproportionately to the demographics or importance of the particular disease, at the same time ignoring other patients' needs.

Depending on how this criterion is assessed, its application may weight the decision-making process either for or against particular population groups; it must therefore be used with great care. Further, it has the potential to allow political considerations to influence R&D resource allocations, if it yields decisions favoring alternatives that benefit particular groups of individuals who have either emotional appeal via the media or greater perceived political power than others. Assessment weightings under this criterion should be as rational and as relevant as possible to the options being considered.

Ethical considerations. The applicability to a technology of such specific ethical considerations as distributive justice is another of our group of important criteria. Two complexities need to be confronted: (1) when ethical principles as discussed in terms of a single technology conflict with one another, such as in the conflict between providing benefit to individuals and fairly distributing the costs of those benefits within society; and (2) when different ethical considerations affect the R&D alternatives being reviewed. The ethical issues raised by heart transplantation and the TAH are an example. The development of the surgical technique of heart transplantation raised issues about the process for equitably distributing very limited benefits, while development of the TAH raises particular issues of access. (See Chapter 8 for further discussion of ethical considerations pertaining to R&D decisions.)

"Halfway" versus "high" technology. A further important criterion is whether the research is directed at a "halfway" technology (i.e., one that overcomes a disease's impact only after it has fully developed, or postpones death) or at a "high" technology that prevents or cures disease, such as prevention of coronary artery disease by cholesterol-level reduction early in life, before the atherosclerotic process begins.[3] By assigning greater weight to high technologies, this criterion would explicitly encourage their devel

[3] These criteria were formulated and the survey undertaken before the committee decided to use the similar "incomplete" versus "complete" distinction discussed in Chapter 8.

opment, as Lewis Thomas espouses (Thomas, 1972). To the degree that high technologies typically produce highly ranked CEA results, this criterion may, in practice, overlap with cost-effectiveness analysis. Further, the committee did not rank this criterion more highly because it is rarely applicable; relatively few disease entities appear to be susceptible to a high technology, at least in the short-term.

Cost-effectiveness related to non-heart disease options. Another criterion is the cost-effectiveness of each R&D output relative to the cost-effectiveness of non-heart disease technologies. In addition to considering the cost-effectiveness of alternative uses of R&D resources within health care, it is also possible, but more difficult, to compare health care research alternatives with R&D programs in other fields. This might be particularly useful in such fields as the environment, where years of life gained, deaths prevented, or added QALYs can be used as a measure in the same manner as in health care. The committee rated this criterion fairly low for two reasons: the general difficulty of comparing such alternatives in quantitative terms, and the belief that such allocation decisions are more appropriately made through the budget process of the administration and Congress.

Extent of existing R&D support. The last of the criteria assessed as "important"—the extent to which industry or other nongovernmental funds already support the particular research (or are expected to do so)—is a useful criterion, when it can be assessed. Application of this criterion minimizes the expenditure of scarce government R&D resources on a goal that can likely be achieved through other funding sources. Still, commitments of private R&D resources can never be considered firm until they occur, so assessing this criterion carries considerable uncertainty until the private support is actually provided.

Less Important Criteria

Time required for implementation. The expected time required for successful implementation of results of the R&D option is another possible criterion. In certain circumstances, it might be a fairly significant one, for instance when considering intensive, time-limited development efforts such as the Small Business Innovation Research program or when the R&D alternatives differ little on other criteria. Usually, however, alternatives that are able to be compared by criteria such as those discussed to this point will not differ greatly in the time required to carry them through to implementation. In contrast, more global programs with goals like "fighting cancer" or "reducing infant mortality" may have widely varying implementation periods.

Likelihood of stimulating private-sector R&D. The extent to which the allocation of NHLBI resources to the particular research is likely to stimulate private-sector research in the same area is related to the previously mentioned criterion concerning the existence of nongovernment R&D support. This criterion recognizes the appeal of leveraging the effect of scarce government resources, in situations in which a multiplier effect can be assumed. It suffers, however, from the same problem as the previous criterion, namely that private R&D commitments can never be considered firm in advance, leading to uncertainty when it is applied.

Application of this criterion requires the government to begin decreasing its R&D support at some point, in the hope that the private sector has been adequately stimulated, but determining that point is difficult. Finally, government-supported research can usually be controlled and monitored more closely than private R&D, in such respects as the steering and data review committees that NHLBI utilizes to oversee clinical trials in this area. Tight control is less likely to occur with private research, as evidenced by the ethical and patient-related criticisms of the mid-1980s cases involving implantation of the Jarvik-7 heart.

Concern about technology misapplication. Although it is an issue that the committee believes is important in relation to MCSSs (see Chapter 7), the degree of concern that an R&D output will be misapplied generally is not viewed in the "important" category. This concern relates to the potential effect of a technology's misuse in terms of quality of care and health care expenditures, as well as to the cost and ability to maximize appropriate use. To the extent that a particular technology is misapplied, resulting for instance in utilization several times greater than anticipated, levels of precision in assessing and applying other criteria considered here may be substantially in error.

Impact on U.S. global standing. The expected impact of each allocation decision on the nation's global standing, especially with high-cost technologies involving long-term research, is another possible criterion, but one that was rated as lowest in importance by committee members. This criterion is illustrated by the following questions: If a particular R&D output is not developed in the United States, will other countries do so? If so, will both the balance of payments and the nation's position of leadership in health care technology suffer?

This criterion reflects an important general national concern, but it is not directly relevant to health care and thus is accorded little weight by the committee. Still, if most long-term production of mechanical circulatory support devices eventually comes from foreign manufacturers and few controls are placed on the devices' use, the aggregate cost of importing

these devices would have considerable impact on the nation's balance of payments deficit. The technology's overall impact on U.S. health care expenditures will be similar, however, whether the devices are manufactured domestically or overseas.

Application of Decision Criteria

A formula. Because all four of the "more important" criteria reflect the number of persons served by an R&D output, their benefit from it, and the cost and likelihood of realizing that benefit, decision makers can combine these criteria into an index of the cost-effectiveness (C/E) of the R&D investment. The rest of this section discusses how that might be done and offers a relatively simple formula that would help to quantify the process, by creating a C/E ratio that expresses the value of each alternative research proposal as the R&D cost per a measure of net health outcome added as a result of applying the specific R&D project's output. This situation was not directly involved in the committee's study, however, so this formula has not been used in this report.

The numerator of the C/E ratio to be calculated is the amortized annual cost of the R&D (amortized over the expected life of the technology, which can for simplicity be regarded as infinite). The denominator of the C/E ratio is the annual net health benefit to the population benefited, less the opportunity cost of the health care resources needed to implement the technology. The opportunity cost represents the amount of health benefit forgone by not using health care resources in other areas. The denominator may be measured in units of health outcome, such as QALYs. Thus, the C/E ratio is calculated as follows:

The numerator, or annualized R&D cost, is

$$C_R = r \times K \times (1 + r)^t,$$

where *CR* is the annualized R&D cost, *r* is the real interest rate, *K* is the capitalized R&D cost, and *t* is the delay time until implementation of the technology, which is assumed to continue indefinitely from that time forward.

The denominator is

$$E = P \times (Q - C/R) \times N,$$

where *E* is the expected annual effectiveness, *P* is the probability of R&D success, Q is the number of QALYs gained per person benefited, *C* is the net treatment cost per person benefited, *R* is the cost per QALY of alternative uses of health resources, and *N* is the number of persons benefited per year.

The value of *R* in the denominator, which represents the cost of gaining one QALY by other health care interventions, can be set initially at $50,000 (approximately the cost per QALY for renal dialysis). The basic $50,000 value can then be varied by way of sensitivity analysis, simultaneously for all programs that are being compared. By recomputing all C/E ratios using, perhaps, $10,000 and then $100,000 per QALY, the effect (if any) of these variations in life-extension valuation on the relative rankings of the R&D options will be revealed. In general, lower values of *R* imply greater opportunity costs for resources diverted to the new technology and, therefore, tend to result in reduced net effectiveness *(E)* when the formula is applied to technologies with high costs.

To simplify the calculations, it is convenient to calculate the number of patients benefited *(N),* annual benefit per patient (Q), and the annual treatment cost *(C)* on an incidence basis. Thus, *N* is the number of patients initiating treatment per year (e.g., receiving a TAH implant), Q is the present value of the total number of QALYs gained per incident case (e.g., compared with not receiving a TAH), and *C* is the present value of the treatment cost per case (e.g., also compared with no TAH). This approach avoids the troublesome problem of converting what may be an uneven time stream of treatment costs into an annual equivalent.

The compound interest factor, $(1 + r)^t$, accounts for the fact that alternative R&D programs under consideration may yield results over very different time frames. This factor (using a typical interest rate such as $r = 0.05$) corrects for the lead time for each R&D effort. It is important that the R&D cost first be capitalized to present value *(K)* before it is annualized over the useful life of the technology, which is assumed to extend from year *t* to infinity.

Applying this ratio to each R&D program under consideration will result in approximate costs per QALY gained that can be roughly compared. The R&D alternatives can then be ranked and evaluated in conjunction with unquantifiable criteria and considerations.

The formula discussed here is a simplification of one developed for what is perhaps the only comprehensive cost-effectiveness analysis of public sector R&D alternatives in health care ever published, an IOM study of vaccine R&D options for the National Institutes of Health (IOM, 1985). Weinstein (1983) offers further examples of applying a similar formula. The full methodology used in the vaccine R&D study will be particularly useful when some of the R&D alternatives produce technologies that are projected to yield net economic savings $(C < 0)$ and others are projected to yield health benefits at a net economic cost $(Q > 0, C > 0)$.

Detailed evaluation of individual criteria. Decision makers can also use, as aids to their decisions, a less formal method instead of or in addition to

ranking C/E ratios, particularly in situations where using CEA requires considerable subjective estimating of values for the formula. Once criteria have been established, such as by selecting from among the foregoing ones, compliance with each criterion can be assessed and the evaluations combined subjectively, based on each criterion's perceived significance. This type of subjective use of explicit criteria provides a more practical alternative to the more rigorous but also more restrictive quantitative scheme implied by the cost-effectiveness formula. If, however, explicit criteria are used in the decision-making process, the result of such a use of systematically applied professional judgment may well be as sound as if only a CEA had been used.

A NOTE ABOUT INDUSTRY RESEARCH AND DEVELOPMENT DECISIONS

The most common consideration of industry, when deciding about an R&D investment, is the expectation of recouping the funds and generating profits from selling the product of the research. Some additional factors affecting R&D investment for Class III medical devices—that is, devices that the Food and Drug Administration (FDA) classifies as implantable or life-sustaining—are considered below. Other considerations in industry investment decision making, such as anticipated device efficacy and policies affecting third-party coverage and reimbursement, are discussed in Chapters 4 and 9.

Several variables may figure significantly in industry R&D decisions, particularly in a decision on whether to invest in MCSS development without NHLBI support. One critical factor is the size of the potential market, which depends on device longevity, potential clinical effectiveness, and third-party coverage and reimbursement. The importance of these factors becomes clear when industry's development of short-term VADs is compared with its current apparent lack of interest in supporting TAH research. Additional crucial factors in health care R&D decisions are the length of time before an investment is recouped and the anticipated difficulty and lack of certainty of obtaining FDA approval. Other typical considerations, particularly with potential Class III devices, include these time and cost factors:

- special testing requirements to determine the product's safety, efficacy, and in vivo durability;
- quality assurance measures that are much more costly for complex medical devices than, for instance, for a chemical compound;
- the length of time before a return on the investment can be realized, because of the delays inherent in the FDA and third-party payer approval processes; and

- the possibility of a substantial exposure to product liability claims, which can be much greater with life-sustaining technologies than with other medical devices, especially because no solution is in sight to what might be called a nationwide product liability crisis.

These considerations are mostly negative ones. They may be at least partially offset by the possibility of revenues from spin-off technologies that emerge from the R&D process, as has occurred with several MCSS developers. Such a potential is, however, difficult to evaluate.

All of these factors are likely to be more important in industry estimates of potential return on investments for long-term TAHs and VADs than are total anticipated R&D costs or the per-unit price of the final device. In the case of TAHs, the companies large enough to make an investment such as would be required to develop a TAH, and carry it through to market, usually have other investment opportunities with far greater certainty of a swift return on R&D costs.

SUMMARY AND CONCLUSIONS

The committee suggests two methods that rely on the formulation and application of explicit criteria to assist NHLBI and other agencies that administer R&D programs in allocating funds among specific programs. The first method simply evaluates R&D options according to explicit criteria. To illustrate the process and form a starting point for NHLBI, the committee identified 18 criteria and ranked them as "more important," "important," or less so; these or similar criteria can be used systematically to provide a rational basis for funding allocation decisions. The second method, useful in some situations, applies cost-effectiveness analysis to R&D program alternatives, thus quantifying one of the most important of the 18 suggested criteria. (Chapter 6 includes an example of a third method, another use of cost-effectiveness analysis, that can aid in decisions within a single R&D program.) Using more explicit criteria, some of them quantitative, can become an increasingly reliable and valuable adjunct to R&D decision making through the exercise of professional judgment.

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4

Clinical Effectiveness and Need For Long-Term Circulatory Support

IN TERMS OF CLINICAL EFFECTIVENESS, long-term mechanical circulatory support systems (MCSSs) must be compared with alternative forms of treatment for end-stage heart disease. Currently, heart disease in all its forms is the leading cause of death in the United States, but transplantation is the only effective treatment for the substantial portion of all heart disease that results in heart failure. For some types of heart failure, pharmaceuticals can reduce symptom levels, postpone death, or both, but most patients either experience sudden cardiac death or deteriorate to end-stage disease, from which they now die if unable to qualify for and receive a transplant.

This is the clinical context in which long-term MCSS use must be evaluated. As Table 4.1 summarizes, today's expectations are that a fully implantable long-term MCSS will ultimately offer patients approximately the same clinical prospects and quality of life as transplantation. Long-term ventricular assist device (VAD) use during the 1990s will clarify selection criteria; some patients will likely be better served by an MCSS, and transplantation will be more desirable for others. Despite the current lack of long-term MCSS experience, the committee must consider this technology's potential clinical impact.

ESTIMATING THE NEED FOR LONG-TERM SUPPORT

Estimating the number of candidates for long-term, fully implantable circulatory support devices is difficult, because no such device has yet seen human use. The reliability and effectiveness of these devices are unknown. Nonetheless, any consideration of the advisability of continuing with MCSS

TABLE 4.1 A Summary Perspective on Treatment Alternatives for End-Stage Heart Disease

	Heart Transplantation	Long-Term MCSS
Advantages and strengths	A physiological answer, not involving any device or visible external evidence of transplant	A mechanical form of treatment not limited by the supply of donor hearts
	No ongoing "upkeep" needed, only medications and periodic tests	No periodic testing needed to detect rejection or other problems
	Current 5-year survival probability is about 70% and may improve	Survival probability is expected to equal transplantation, once in wide use
Risks and limitations	Considerable risk of sudden death while on waiting list for a donor heart	Continuing small but important risk, for TAH recipients, of sudden death as a result of a "hard" device failure
	Substantial risk of diffuse coronary atherosclerosis in donor heart ("chronic rejection"), requiring second transplant or MCSS	Some risk of "soft" device failure, requiring hospitalization for repair or replacement
	Some risk of acute rejection, requiring hospitalization	For the foreseeable future, the MCSS will have a finite life; replacement will thus, ultimately, be needed
	Number of procedures is limited (about 2,000 per year) by supply of donor hearts	Periodic need to replace implanted battery (may, some day, become a simple outpatient procedure)
Inconveniences	Rigorous anti-rejection drug is important to survival	Need to carry batteries and wear electricity-transmitting belt; 2- to 3-times-per-day substitution of recharged external batteries needed; minimal need for drug therapy
Cost (in 1991 $)	One-time cost about $90,000; substantial ongoing costs for anti-rejection drugs, catheterization, and other periodic tests	Estimated $150,000-200,000 one-time cost; low ongoing cost (primarily for battery replacement)
Major complications	Rejection of transplanted organ	Thromboembolic event; bleeding; infection
Most important uncertainties	Extent to which long-term outcome will improve over next 10-20 years; whether supply of donor organs will increase	Unknown impact of long-term device use on physiology; extent to which device longevity will improve (e.g., from 2 to 5-10 years?)

MCSS, mechanical circulatory support system; TAH, total artificial heart.

development must project the clinical effectiveness of these devices in order to estimate how many patients can be expected to receive them. At least three reasons exist for estimating clinical effectiveness and device use:

- to decide whether the number of prospective patients is sufficient to warrant the anticipated R&D costs;
- to assist those who are responsible for beneficiary populations (e.g., third-party payers) in planning their funding needs; and
- to ascertain whether the potential patient volumes and thus the aggregate health care costs of using MCSSs are so large that, added to the already high cost of U.S. health care, the burden would be great enough to become a factor in R&D decisions.

Any estimate of eventual MCSS use involves judging (1) the magnitude of the population dying of cardiac disease or incapacitated by it and (2) the perceived effectiveness of the particular MCSS in delaying death as well as improving the quality of life by ameliorating symptoms. Such estimates must also consider the impact of the alternative therapies and preventive techniques that may be available in the future, as well as the improvement of existing ones.

FROM TEMPORARY TO LONG-TERM USE

The use of long-term implantable devices will certainly be tied closely to their effectiveness in supporting patients' circulation and maintaining a satisfactory quality of life. Evidence of physiologic effectiveness has been growing, based upon the experience of temporary device use (Kormos et al., 1990; Portner et al., 1989; Termuhlen et al., 1989). In more than 400 instances, tethered assist devices have been used to support life in conjunction with cardiac transplantation (Miller et al., 1990b); there has been additional experience with these devices during cardiogenic shock following cardiac surgery or acute myocardial infarction (Miller et al., 1990a).

Present-day MCSSs can provide blood flows to sustain life, with the device itself outside the body or with an external power source driving the pump by means of a transcutaneous line. These devices can, further, meet the demands of moderate patient activity and also reverse multiple organ dysfunction that has resulted from periods of circulatory insufficiency. Also known are the major complications of these devices, such as bleeding, thromboembolism, and infection, with infection the most likely to be reduced by the use of fully implantable devices.

The effects of fully implantable devices on patients' freedom of activity, psychological functioning, and health-related quality of life are not known presently. Reliable, although limited, information as to these factors will not be available until trials of one or more long-term VADs are completed.

PROJECTING DEVICE RELIABILITY AND EFFECTIVENESS

An inescapable relationship exists between a circulatory support device's reliability and clinical effectiveness and the number of potential recipients for it. If, either at an early stage of use or after attempts to improve the device have been unsuccessful, a particular type of MCSS results in patient outcomes that are significantly poorer than heart transplantation, most patients and most physicians will wish to use the device only as a last resort. Death during an unsuccessful wait for a donor heart is obviously less desirable, but many patients faced with these two less-than-favorable options might prefer to take their chances on receiving a donor heart. Even if the MCSS's outcome is poor, however, there will remain a group of patients unsuitable for cardiac transplantation who would wish to use, and who could benefit from, a less-than-desirable alternative, that is, a device that offers some probability of life extension for at least a few months.

Additionally, some patients who are candidates for heart transplantation, faced with a long waiting period during which their activity and comfort levels are sharply restricted, might choose more immediate relief through the use of a device that will not categorically exclude the possibility of a subsequent transplant. In the upcoming Novacor VAD trial, candidates selected for device use will probably not compete with other transplant candidates, because of the need for the study to make the maximum possible contribution to scientific knowledge, an unlikely outcome if some VAD recipients subsequently received a transplant. (Subjects of long-term VAD clinical trials are likely to be persons over age 65 who would not normally be considered for a heart transplantation.) In the future, however, it is entirely possible that implantation of a long-term device will not preclude subsequent transplantation, although the relative effectiveness of the two approaches at that point would be an important factor in any such decision.

At the other extreme, continued research and development may lead to a much improved device that offers a quality of life and a five-year survival probability much better than heart transplantation provides. In that event, more patients will likely become candidates for the implantable device.

In order to estimate the extent of long-term MCSS use, the committee has considered both a range of patients' conditions and a range of device safety and effectiveness characteristics. These, collectively, constitute probable circumstances for device use and make possible a preliminary estimate of the extent of that use. For the purpose of exposition, this chapter and the committee's epidemiology study (Appendix D) identify two patient groups based on their medical conditions and prospects for successful MCSS use. The committee designates these as the primary and secondary groups, as discussed further below.

When early trials of long-term VADs are completed and outcome reports published, interested parties will be able to estimate the future use of these devices much more accurately than is now possible. The same will be true of total artificial hearts (TAHs) after their early trials are completed, probably between the years 2005 and 2010.

Nevertheless, some conclusions can be drawn, based on the current performance of temporary-use devices. For instance, total or "hard" failure of a device or component (resulting in a high risk of immediate death), although it may not be easily corrected, is likely to be relatively rare; by contrast, soft failures are not life-threatening. Although they may be more common, they will rarely be fatal and can be corrected. Further, upper bounds for some types of complications can be estimated; for example, patients with a fully implanted MCSS are almost certain to experience lower infection rates than current temporary-MCSS patients with skinpenetrating power lines.

A direct relationship thus should exist between device performance and clinical effectiveness, except for two factors. First, because soft failures occur gradually or can be predicted, there is time to correct the failure-for instance, by replacing a prematurely worn-out battery-before the patient suffers permanent harm. Second, the extent of a patient's comorbidities may affect what might otherwise be a predictable outcome, given a device's projected performance. Put another way, some patients with certain comorbidities may react very differently to a particular problem or shortcoming of a device than do patients with other types of comorbidities, or none.

RELATING CLINICAL EFFECTIVENESS AND DEVICE USE

Given the current uncertainty about MCSS effectiveness, one approach to estimating the potential patient populations for their long-term use is to explicitly relate a range of projected device characteristics and likely patient outcomes to the number of potential patients under each circumstance. Estimates made today in this manner can be used by the National Heart, Lung, and Blood Institute (NHLBI) in deciding about R&D resource allocations, as well as by others interested in the future of mechanical circulatory support. Table 4.2 summarizes characteristics of three types of devices that will affect patient volume.

Performance of the devices in the three categories can be summarized in this manner:

- A device in category A is one whose characteristics make it particularly desirable, comparing favorably with outcomes of heart transplantation in the early 1990s in terms of five-year survival and complication rates.
- A category B device is somewhat inferior to one in category A, in that survival probability is not as high and complication rates are somewhat

greater. Such a device nonetheless has the potential to improve a heart failure patient's condition from moribund or partially disabled to a reasonable level of functioning, notwithstanding a long-term mortality risk.

- A category C device is one that would likely be used only by patients whose survival is in doubt and for whom transplantation is not available or carries a risk of death during the waiting period that is too great. Although it could be called a "problem" device, a category C device would still offer a reasonable prospect of survival at a moderate functional level for a period of up to two years.

TABLE 4.2 MCSS Device Performance Characteristics Groups

Characteristic	Device A	Device B	Device C
Minimum device survival rate[a]	>70% at 5 years (same as transplantation now)	>80% at 2 years	<50% at 2 years
Rate of surgery to repair or replace soft device failure	10% per year	20% per year	30% per year
Annual rate of thromboembolic events	About 2% (perhaps higher)	2-4% (same as 2 artificial heart valves)	14-20%
Annual rate of infection requiring intensive antibiotic therapy[b]	1%	5%	10%
Other	Compares favorably to 1990 transplantation outcomes	Works well enough to improve patient to NYHA Class I or II	Poor energy transmission; transcutaneous power cable often needed

[a] May be skill-dependent, based on the experience of the personnel at the particular institution, as is the case with heart transplantation.
[b] Complication rates may vary, depending on the severity of the patient's illness.
NYHA, New York Heart Association.
SOURCE: Committee projections based on workshop discussions with experts.

The Role of Comorbidities

The comorbidities suffered by end-stage heart disease patients complicate the task of projecting patient populations for MCSS use. For instance, a psychosocial comorbidity such as alcoholism or cognitive impairment may hinder a patient's ability to adhere to the regimen needed to care for the MCSS, so the patient may require support from a relative or friend

either constantly or periodically. Medical comorbidity (e.g., metastatic cancer, brittle diabetes) may be so serious as to shorten the patient's life expectancy unduly, even if the device works well.

Theoretically, one could use both anticipated device performance and the epidemiology of expected comorbidities to make estimates of potential patient populations for MCSS use; doing so has the potential to be more refined than the two-dimensional approach used here. Unfortunately, the data currently available about coexisting conditions are inadequate to allow such projections with a reasonable degree of certainty. Data are scarce about the natural history of particular forms of heart disease; considering the impact of comorbidities would make the estimates even less certain.

The presence of serious comorbidities has been used in reaching the committee's epidemiological estimates that are discussed below. Less serious comorbidities are not considered, pending additional evidence about their impact on MCSS clinical effectiveness to be derived from forthcoming long-term VAD trials.

OTHER INFLUENCES ON THE USE OF CIRCULATORY SUPPORT DEVICES

Other factors besides anticipated device performance affect the number of potential patients for MCSS use.

The Impact of Other Heart Disease Treatment Technologies

In the United States and some other industrialized countries, both the incidence (the rate at which new cases appear) and the mortality rates of coronary heart disease (CHD) are decreasing, attributable in part to reduced smoking, dietary alterations, and other lifestyle changes. The absolute numbers of individuals who develop heart disease and die of it, however, are projected to increase (Weinstein et al., 1987), largely because of the steadily increasing size of the older population, for whom heart disease is the leading cause of death. In the near future, CHD prevalence, i.e., the number of persons with this disease, is also likely to increase, due both to the increasing population and to extended survival of persons after they are diagnosed as having CHD.

Additionally, neither new measures to prevent CHD nor other forms of treatment appear likely soon to reduce the number of patients who progress to end-stage disease. The volume of surgery to bypass stenosed coronary arteries appears to have reached a plateau, and direct treatment of stenosed coronary arteries by such techniques as angioplasty and atherectomy has been effective for only limited periods. Progression of the disease process has been the rule.

Thus, in spite of therapies that ameliorate symptoms and improve function, the basic disease continues to progress, and the number of individuals eventually coming to an end-stage has not been strikingly reduced by these strategies. Continuing MCSS research should not, however, be considered a substitute for encouraging the diffusion of less dramatic and less costly therapies that have the potential to intervene successfully in the course of heart failure at an earlier stage.

Even heart transplantation does not completely free patients from the possibility of heart failure. Indeed, the anticipated fate of 20 to 30 percent of all transplant patients is failure of the transplanted organ. Hence, even using all current strategies, the number of patients who are potential candidates for long-term mechanical support will not decrease in the near future, although they will seek treatment at a more advanced age.

Further, there are promising gains in understanding mechanisms of the progression of the ventricular dysfunction that occurs in heart failure (Francis and Cohn, 1990). This research may eventually lead to new forms of treatment that slow or even halt the progression of disease and thus reduce the volume of new end-stage patients or, more likely, increase the average age at which the devices may be primarily needed. It is not possible to predict how these new treatments will influence the demand for MCSSs in the next 20 years.

Quality-of-Life Determinants

The clinical effectiveness of all technologies is influenced by the humanness of the patient. The health-related quality of life of patients with end-stage heart disease is a major factor in assessing the outcomes of MCSS use (see Chapter 5). Patients' quality of life and health status, however, should not be equated with the much broader set of determinants that define the context in which patients seek health care. These determinants include (1) personal health habits, health knowledge, and attitudes; (2) social resources and networks of personal contacts; and (3) various economic, educational, and psychologic resources (Patrick and Erickson, 1988; Patrick et al., 1988; see also Bergner, 1985).

Several of these determinants are reported to influence significantly the prognosis and outcomes of patients receiving treatments somewhat similar to MCSS (Lubeck and Bunker, 1982; Evans et al., 1984; Christopherson, 1986; Pycha et al., 1986; NIH, 1987; Kalbfleisch et al., 1989; Vlay et al., 1989). Many patients, health care providers, and third-party payers have an intuitive sense of the importance of these factors and, through various mechanisms, such as patient counseling and case management, attempt to direct or reinforce the influencing factors in a positive direction. Clinical trials, registries, and focused research can add to the understanding of the degree and

direction of specific determinants or combinations for condition-specific populations such as end-stage heart disease patients. Such information will be helpful to all parties involved in discussing prognoses with patients and in making decisions about alternative treatments. Additionally, information on determinants may be useful in the future for determining coverage eligibility for specific high-risk technologies.

Patient Preferences for Life-Sustaining Treatment

The demand for MCSS will also be influenced by patient and family preferences for life-sustaining treatment. Findings of a recent study indicate that only 33 percent of elderly adults facing imminent death, preventable through the use of technology, will opt for life-sustaining treatment; patients indicate that they prefer such treatment only while critically ill but do not desire it after they become permanently unconscious (Danis et al., 1991). The majority prefer not to be kept alive.

Evidence is inconclusive as to what percentage of patients in need of and eligible for heart transplantation or an MCSS will opt for death rather than undergo such a procedure. Several factors have been identified as relevant to the patient's decision making about life-sustaining treatment: degree of independence the patient will retain; presence and severity of comorbidities; perceived quality of life following treatment; clinical prognosis; attitudes and preferences of family and close friends; risk tolerance; prior experiences with death and disease of others; finances; and attitudes and values of the patient about illness, meaning of life, religion, death, and dying (OTA, 1987; Rabinovich and Cohen-Mansfield, 1989; Walden et al., 1989).

Other Factors

Other considerations will also affect individual patients' decisions about a technology such as MCSS. Perhaps the most important is reimbursement, that is, the coverage and payment policies of third-party payers. Chapter 9 examines more fully the effect of third-party payers on MCSS utilization.

EPIDEMIOLOGICAL PROJECTIONS

Previous Studies

Several previous studies have attempted to determine the number of end-stage heart disease patients whose lives might be prolonged by an effective cardiac support or replacement device. Estimates based on mortality statistics, disease incidence, and life expectancy have ranged from 6,000 to 66,000 annually in the United States alone (NHI, 1969; NHLI, 1973; NHLBI, 1980;

Lubeck and Bunker, 1982). The size of the population currently receiving heart transplantations or waiting for them, when adjusted to include those not eligible for transplantation because of age and contraindications, suggests a need for long-term MCSSs of at least 15,000 per year, but other considerations suggest an even greater need.

Researchers at the Mayo Clinic performed a population study in which they reviewed all deaths in Olmsted County, Minnesota, using restrictive criteria for age, associated disease, and time limitations between the onset of life-limiting illness and potential MCSS use. Based on key assumptions that the devices would be offered only to patients under age 70 who are free of major comorbidities and who survive the initial cardiac episode by at least two hours, they projected 11,000 to 23,000 potential users of an effective MCSS device per year nationwide (Kottke et al., 1990). However, major differences between the health and socioeconomic characteristics of Olmsted County residents and of the total U.S. population require careful interpretation of these figures, because many epidemiological markers of heart disease (e.g., incidence and mortality rates) from Olmsted County are substantially lower than those for the nation as a whole.

The Committee's Projection

To update the epidemiological studies just mentioned and form a basis for its own consideration of the need for these devices, the committee commissioned an epidemiological study (Funk, 1991), included in this report as Appendix D. The main focus of the epidemiological study is what we have denominated the primary group of patients who are potential candidates for implantation of a long-term MCSS. This group comprises those in the final phase of end-stage heart disease, functionally either moribund (in Class IV of the New York Heart Association [NYHA] functional classifications) or partially disabled, being maintained on intensive medical therapy (those in the lower portion of NYHA Class III). The primary group thus encompasses patients now eligible for heart transplantation and numerous others who are not eligible for reason of age, transplant-related contraindications that do not apply to an MCSS, or lack of access to a transplant center.

The committee's study found that the primary population of candidates for both forms of long-term MCSS totaled between 30,000 and 60,000 persons in 1990, depending on the age that is considered to be the typical upper limit for device implantation, respectively 75 and 85. The committee notes, however, that these upper age limits are being used exclusively to estimate probable MCSS need; once MCSSs are approved for general use, only clinical factors should be used to select patients to receive an implant. As discussed in Chapter 8, MCSS use should never be denied solely on the basis of chronological age.

The size of the pool of potential MCSS recipients gradually increases (e.g., to an annual range between 35,000 and 70,000 in 2010) as a result of general population growth during this period, in particular as the "baby boom" generation born in the 1940s and 1950s moves into the age range of high heart-disease incidence.[1] This study took into account sudden deaths and serious comorbidities, but it did not consider the nature of the device to be implanted.

This range of sizes for the primary group of potential MCSS candidates encompasses the upper limit of the findings from previous studies of the artificial heart program. The most recent of those, however, was performed seven years ago, at a time when the nature of the devices to be implanted was somewhat less clear than at present.

The committee believes that between 35,000 and 70,000 potential candidates for an MCSS—either VAD or TAH—is a reasonable projection of need as of the year 2010 for the primary patient group. This conclusion assumes that a VAD meeting the characteristics described above as Device B—or, perhaps, Device A—will have completed clinical trials and received approvals from the Food and Drug Administration (FDA) and at least some third-party payers by the turn of the century. Between 1997 (the earliest a VAD is likely to receive FDA approval) and 2010, the annual number of VADs implanted each year will probably increase gradually—from near zero to a number potentially in the 35,000-70,000 range. Because of the short life expectancy of medically treated patients, there is very little year-to-year backlog of patients.

The growth of VAD use will be constrained by several factors: delays in third-party approvals; inadequate payment rates that adversely affect some hospitals' interest in the technology; and the time required for surgical teams, beyond those now experienced in using temporary VADs, to be trained in implanting them. The volume of heart transplant procedures increased gradually during the early 1980s, constrained by similar factors, but plateaued at a much smaller number because of the limited availability of donor hearts.

MCSS use in an annual range of 35,000 to 75,000 may seem high, especially in relation to the 2,085 heart transplants performed in 1990. The projected use range reflects, however, an approximate growth rate between 25 and 35 percent per year, using as starting points a volume of 1,600 (the 1988-1989 number of transplant cases) and 1997 as the earliest possible full

[1] The committee's projections of potential MCSS candidates are for first-time implantations. Particularly in the early years of use, a substantial number of either complete or partial (e.g., the internal battery) MCSS replacements will be needed. Projecting the number of replacements is not possible at this time, other than by using estimates such as the probabilities used in the committee's cost-effectiveness analysis.

year of MCSS use. Neither a potential annual volume between 35,000 and 70,000 nor a 25 to 35 percent growth rate differs greatly from the diffusion rates of other cardiovascular technologies such as pacemakers and coronary angioplasty.

Effect of a Less-than-Ideal Device

As previously discussed, the use of long-term MCSSs will depend heavily on the characteristics of the devices available. This estimate of the size of the potential candidate population assumes a device that has at least the performance characteristics described above as Device B. If a device that meets those characteristics is not developed and approved until early in the next century, this projection should be moved an equal period of time into the future.

Conversely, if forthcoming long-term VAD trials find that the devices perform extremely well—approaching the Device A description in Table 4.2—then the range of potential use projected for 2010 is possibly too low. As soon as a high-performance device becomes available, considerable patient demand can be anticipated, expressed through such routes as legislators, labor negotiations, and patient advocates. The extent of such pressures to make the device available will have a considerable impact on the annual growth in use, as hospitals, third-party payers, and the physicians who care for cardiac patients can be expected to respond to those demands by encouraging coverage approvals. Currently, the limit placed on heart transplantation by the supply of donor hearts is so stringent that no consideration can be given to transplants for patients other than those seriously disabled by their end-stage disease. Pressure to perform transplants at an early stage in the course of patients' illness would thus have been to no avail.

Less Disabled Patients

The foregoing discussion has focused on a primary group of patients who are disabled by end-stage heart disease and who, with few exceptions, will be the individuals receiving long-term MCSSs in the early years of their use. These devices could, however, be used eventually with at least some patients in a much larger group (designated by us and in Appendix D as the secondary group), those whose end-stage disease is now being managed at least temporarily by medication. These patients are able to function within the severe limitations of their disease; some of them may require hospitalization one or more times each year. The committee's review indicates that as many as 400,000 individuals may be included in this secondary group, based on numbers of patients hospitalized for congestive heart failure. (In contrast, those hospitalized for coronary [atherosclerotic] heart disease

are, on average, much less likely to require an MCSS than patients with a primary diagnosis of congestive heart failure.) The limitations of the data are so great, however, that this number may be in error by 100,000 or more persons in either direction.

It is not realistic to consider relaxing the indications for MCSS use to include this much larger group of patients unless the health care system reallocates substantial resources from other areas of health care to pay for these procedures, and develops the resources (e.g., trained surgical teams, facilities) to handle the recurring annual demand from the very seriously ill patients in the primary group. This "break-even" point appears likely to occur in approximately 2010. After 2010, based on the clinical evidence developed in the intervening 15 years of use, clinicians and epidemiologists should be able to define more clearly than is now possible how many of these individuals, somewhat less disabled by their cardiac disease than those in the primary group, can benefit from an MCSS. At this time, the committee's best estimate is that MCSSs of high-performance (category A) characteristics could potentially, at some point in the period between 2010 and 2030, be used in as many as 200,000 patients from the secondary group annually unless, by then, other preventive and therapeutic advances have made substantial inroads into the volume of heart failure patients.

Additional Potential Patients

At some point, probably not before the 2020s, MCSSs likely will be used in limited numbers with two additional patient groups. One group is persons less disabled by their heart failure than those in our secondary group. These individuals are at some risk for sudden death and may have symptoms of their heart disease, particularly if they overexert in relation to their limitations. They are, however, able to function and thus would be interested in an MCSS only if it provided a level of functioning that is considerably improved over their present state, as well as an improved prospect of avoiding sudden death. Some may also wish to become candidates for a long-term MCSS to prevent their condition from worsening. They might be willing to undergo surgery if the MCSS then available offered a very high probability of improving their quality of life and, more important, preventing future decline in their functional capacity.

Second, such a device when developed would also likely be used with some patients suffering from other forms of untreatable heart disease, such as intractable angina or an arrhythmic disorder so severe that it cannot be controlled by an automatic implantable cardioverter defibrillator. Although not heart-failure patients, these individuals would be able to benefit from a high-performance MCSS in much the same manner as those with heart failure.

VENTRICULAR ASSISTANCE VERSUS A TOTAL ARTIFICIAL HEART

The total number of patients likely to benefit from either type of longterm MCSS, and thus potential candidates to receive one, is useful for many purposes. NHLBI is interested specifically in the potential volume of TAH use, however, as one factor in deciding whether to continue that aspect of its artificial heart program.

Current information does not allow a precise estimate of the proportion of patients suitable for an MCSS that will benefit from biventricular support and, therefore, a total artificial heart. It is only a presumption that those suffering from cardiomyopathy-currently half of those receiving heart transplants (Kriett and Kaye, 1990)-have uniform myocardial disease and will require biventricular support. The information from the international registry of temporary MCSS use as a bridge to transplantation does not include etiology. It does identify that biventricular support has been employed in 78 percent of those acutely ill patients (Miller et al., 1990b). An unidentified number of these patients were in acute myocardial failure immediately subsequent to extracorporeal circulation during surgery and procedure-related cardiac ischemia. At present, it is generally accepted that patients are more likely to require biventricular support if they are unable to survive without an MCSS and have as the precipitating factor acute ischemia induced by operation and/or acute myocardial infarction. In contrast, others who are less likely to require biventricular support include individuals with advancing chronic illness manifest by left ventricular failure and characteristically suffering from ischemic heart disease. The international registry prevalence of 78 percent biventricular support does not indicate whether use of this type of support resulted from an evaluation of need, a general policy at the institution, or availability of particular devices, all factors that might have influenced treatment decisions.

Other reports of the need for biventricular support in bridging operations are as low as 36 percent (Kanter et al., 1988). Improvement in right ventricular function in patients receiving a left ventricular assist device (LVAD) as a bridge to transplantation has also been reported (Kormos et al., 1990). An extensive literature on the effects of left ventricular assist on right ventricular function has not been definitive, but it does suggest that the reconfiguration of the ventricles as a result of left ventricular unloading by the LVAD is either neutral or advantageous to right ventricular performance (Farrar et al., 1984; Farrar et al., 1985; Elbeery et al., 1990).

Other factors also affect the choice of a TAH or ventricular support. On the one hand, using a TAH requires removing the patient's natural heart, which eliminates the possibility of even very limited support of the circulation by a badly damaged natural heart if the device fails completely. Thus,

a TAH will be used only when a single long-term VAD will not meet the patient's needs. (No current R&D activity has a goal of two fully implantable VADs.) On the other hand, operative risks increase each time open heart surgery is performed, so any doubt as to the patient's need for biventricular support is likely to be resolved in favor of using a TAH.

Experience with early VAD clinical trials will provide considerable additional information to assist in determining the need for long-term biventricular support. Especially in the early years of long-term VAD use when the volume of implant procedures is limited, patients who are acutely ill and thus may have already suffered damage to other organs will typically be accorded the highest priority to receive a VAD, and these are the patients most likely, from present data, to need biventricular support. As MCSS availability increases, however, surgeons will be able to implant the devices at an earlier point in the patient's deteriorating course of illness. This will probably reduce the proportion of TAHs needed but, because of the increased total volume, the overall need for TAHs will remain approximately stable.

Another factor in the need for TAHs is their present stage of development, on a time line approximately 10 years later than the first model of VAD. Thus, although routine VAD use may begin in the late 1990s, the first FDA approval of a TAH is not likely before 2003 or 2004 at the earliest. By that time, it is probable that third-party payers' experience with long-term VADs will make them more receptive to approving TAH use without lengthy delays.

A final factor in the need for TAHs is that transplantation will remain, for the foreseeable future, the treatment of choice for patients clearly needing long-term biventricular support, such as patients with some forms of cardiomyopathy. The volume of donor hearts probably will not meet the total need from this patient group. Moreover, the need for TAHs is also likely to continue for patients who have rejected a transplanted heart and for clinical reasons cannot receive a second one, as well as for patients for whom transplantation is contraindicated for immunologic or other medical reasons.

Therefore, just as the committee has estimated the potential need for VADs to begin in 1997 and build gradually, it believes there could be a continuing and substantial potential need for biventricular support, much greater than the current annual 1,600-2,000 transplant volume. This need will begin to be satisfied as soon as the TAH development process allows. The ultimate TAH need cannot be estimated precisely but will probably lie in the range of 15 to 25 percent of the total number of MCSSs needed, or a potential of approximately 10,000 to 20,000 as of 2010, depending on the upper age limit of the typical patient. As noted above, once devices are widely available, physicians will be very reluctant to use a TAH when a

VAD appears likely to suffice, so it is improbable that the number of TAHs required could increase to as much as half of the overall need for long-term MCSSs among the primary patient group. Very few TAHs will be needed by the secondary group of patients, however—perhaps 5 percent of the 200,000 potential maximum volume—because intervention is occurring much earlier in the disease process.

Considerable clinical uncertainty also remains. Until VADs have been implanted for two years or longer in a substantial number of patients, clinicians will not be able to know whether VADs represent a solution to the needs of the majority of end-stage heart disease patients. Some unanticipated problem may be revealed, making the VAD less useful than the TAH for defined groups of patients. This constitutes an argument for not suspending the TAH development process, at least until results of long-term VAD use are reported for more than the initial 20 trial patients.

THE NEED FOR MORE RESEARCH

Basic and Clinical Research Concerning Heart Failure

Little is known about the underlying mechanisms of heart failure. The committee is concerned that, whatever action NHLBI takes concerning the artificial heart program, its support of research on mechanisms of heart failure should continue. Additional knowledge about the causes and course of heart failure may soon make possible forms of prevention or treatment that will obviate some patients' need for either heart transplantation or an MCSS, if research that is deemed scientifically meritorious can continue.

Epidemiological Research

Heart disease is the leading cause of death in the United States and many other countries, but there still are deficiencies in knowledge of its epidemiology. In particular, age-, sex-, and race-specific data concerning the natural course of heart failure and other forms of end-stage heart disease in representative populations apparently do not exist. Additional limitations on the ability to estimate numbers of potential MCSS recipients include these:

- There is very little knowledge of comorbidity in end-stage heart disease.
- Hospitalization information is based on discharge data instead of using unique patient identifiers in order to track multiple hospitalizations.
- Hospital discharge diagnostic codes and death certificate entries lack clarity in such respects as the mutual exclusiveness of terms such as coronary heart disease, congestive heart failure, and atherosclerotic heart disease.

NHLBI deserves commendation for its sponsorship of a four-site longitudinal study of heart disease in older patients that is now under way. The committee hopes that additional research on such issues can be initiated, possibly involving patients under age 65 and perhaps drawing on the comprehensive Framingham Heart Study data base. Further, the level of understanding of study results will be improved if the data from major epidemiological studies are made available on "public use" data tapes for analysis by other investigators.

SUMMARY AND CONCLUSIONS

At this point in the development of long-term MCSSs, it is difficult to estimate the precise need for them, were they to be approved for general use. The committee's epidemiological review supports the previous studies that found the ultimate potential total use of both long-term VADs and TAHs to lie at some point in the range of 6,000 to 66,000 per year and probably nearer the high side.

More than a decade will have to pass before a substantial volume of MCSS implantations can occur. The principal limit on growth in use will be uncertainty about the clinical benefits achievable by the devices available at any particular time; technological effectiveness will be the major determinant of these benefits.

The committee concludes that a total volume of initial MCSS use of between 35,000 and 70,000 devices per year could be achieved by the year 2010, based on the projected range of need in the primary group of patients. The committee recognizes the considerable uncertainty inherent in these estimates, which cannot be resolved until many long-term VADs have been implanted for several years and the patients' outcomes reported.

If resources are made available to meet the demand from the primary group, indications for MCSS use may gradually broaden into a larger secondary group of patients, those not yet disabled by their heart failure. The committee estimates that about 200,000 persons in this secondary group could potentially be candidates for MCSS annually, if the devices then available have high-performance characteristics. There is, however, little likelihood that this volume of MCSS use could occur much before 2020.

Until some point in the 2005-2010 period, virtually all the long-term devices implanted will be VADs. Assuming that the first TAH is approved for general use at roughly the mid-point of the 2000-2010 decade, TAH use will increase but probably level off in the 2010s, at a potential maximum volume in the range of 10,000 to 20,000 per year. With the high end of the potential volume and a total implantation cost (in 1991 dollars) of about $200,000, the nation's annual health care bill will increase about $4 billion for TAH use alone, which translates to 0.7 percent of the annual total

health care spending in the United States. With inclusion of 50,000 VADs, the total cost rises to almost $12 billion, or 2 percent of total spending.

The committee concludes that NHLBI should undertake, possibly with the involvement of the Centers for Disease Control, the development of additional epidemiological data about the natural history of end-stage heart disease.

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5

Quality of Life and Mechanical Circulatory Support Systems

> A human being would certainly not grow to be 70 or 80 years old if this longevity had no meaning for the species. The afternoon of human life must also have a significance of its own and cannot be merely a pitiful appendage to life's morning.
> —Carl Jung, The Stages of Life

HEALTH CARE IS BUT ONE of many determinants of the health and quality of life of an individual. Genes, environment, and personal behavior, among other personal, social, and economic factors, have an appreciable impact. Goals and expectations of health care, from the perspectives of the health care provider, patients, and their families, include preventing, managing, and curing disease as well as improving the levels of function and well-being (Stewart et al., 1989).

The use of health technologies, in particular mechanical circulatory support systems (MCSSs), in treating end-stage heart disease raises several important issues about assessing the quality and outcomes of care within the context of the goals and expectations of treatment. In this chapter we focus on one important aspect of treatment alternatives for end-stage heart disease-the quality of life of the patient. A Texas newspaper columnist (Greene, 1990) writing in first person about his experience of heart transplantation shares these thoughts on quality of life:

> One of the meanest things we can say of a person is that he or she is heartless. Coldhearted equals ruthless.... Heart and soul are inextricably mixed in phrase and fable. Where the heart is, . . . there will the soul be also. To tell a male he has heart trouble attacks him in his manhood.... (pp. 28-29)

The discussion that follows attempts to answer such questions as: Why is quality of life important? What is meant by quality of life? What domains of quality of life are relevant to end-stage heart disease patients? What is known about the quality of life of these patients? The final sec

tions of this chapter explore the use of health-related quality-of-life measures in MCSS clinical trials and studies, examine the importance of disease-specific domains and measures, and set forth conclusions of the Institute of Medicine (IOM) committee.

THE IMPORTANCE OF QUALITY-OF-LIFE CONSIDERATIONS

From the Perspective of the Patient

Researchers and clinicians evince much interest in knowing about the quality of life of patients exposed to unconventional forms of therapy for life-threatening conditions. Many of these patients have prolonged hospitalizations, extensive diagnostic testing, and multiple failures of drug therapy. Patients with life-threatening conditions frequently report feelings of anxiety, fear, depression, and loss of control (Cooper et al., 1986); these feelings and the importance patients attach to them need to be considered in assessing treatment options and their outcomes.

Quality-of-life measures can be especially important in assessing the outcomes of care for patients receiving therapies that carry high risks of negative consequences (Falotico-Taylor et al., 1989). Families of these patients are also subject to a considerable range of emotions (e.g., anger, depression, denial, disengagement, guilt) that, in turn, may affect the quality of life of the patient (Christopherson, 1986).

The history of earlier efforts to treat end-stage heart disease patients with mechanical circulatory support devices reflects many emotional and ethical concerns about the clinical and technological environments (Galletti, 1984; Shaw, 1984; Swazey et al., 1989). That history has heightened concern for the "person" with an illness, such as end-stage heart disease, and has confirmed the importance of patients' preferences for balancing quantity of life with quality of life. These preferences are particularly significant when MCSS implantation limits or restricts future treatment options, should the device fail or the patient elect to stop maintaining the device.

"Proximate clinical indicators" or clinical endpoints combine measures of both outcomes and processes of care (IOM, 1991a). They assess care close to the time that treatment is provided and thus take on critical meaning for patients whose life expectancy may be no greater than six months. Patient preferences for health-related quality-of-life outcomes at these interim points of treatment can yield valuable information for care. Additionally, the interaction of the patient and physician has itself been documented as affecting the health status of patients (IOM, 1990; IOM, 1991a).

Methods for Assessing the Quality of Care

Issues relating to the adequacy and equity of the allocation of health care resources challenge the concepts and tools used to measure quality and outcomes of care at a time when medical care and high technology are frequently integrated for achieving a common goal of prolonging life (Furman et al., 1987; Stason et al., 1987; Wenger et al., 1987). For example, Patrick and Bergner (1990) state that health-related quality-of-life measures will be used in the coming decade for ". . . improving the quality of health care and reducing inequities in health" (p. 175).

Therapeutic interventions may have similar biological effectiveness but still differ in terms of quality-of-life outcomes of patients (Falotico-Taylor et al., 1989). Using measures to assess patients' health status provides an opportunity for taking individual preferences for outcomes into account; thus, measuring the net benefit of health care is tailored to the particular patient and extends beyond clinical or physiological measures. This approach allows for more comprehensive technology assessments as well. Worded another way, "more important than the presence or absence of signs, symptoms, or laboratory test values is the patient's response to how treatment affects his or her life" (IOM, 1991a, p. 281).

The conceptual and methodological challenge of assessing the quality and outcomes of care for end-stage heart disease patients is of particular importance. Heart disease not only is the most common cause of death in the United States but also is one of the major causes of sudden death. Patients frequently have high hopes for treatments such as MCSSs, including delay of imminent death or the improvement of quality of life prior to death. As occurred in the mid-1980s with the use of the Jarvik-7 total artificial heart (TAH) for Barney Clark and William Schroeder, this technology attracts much media attention, including major newspapers, tabloids, television, and radio. This attention tends to raise expectations for improved outcomes from the use of high-technology medicine. On the one hand, assessment methods need to be sensitive to the unrealistic expectations of patients, providers, and the public. On the other hand, methods for assessing quality and outcomes of care should include patient-oriented measures that provide more information than the single outcome of death or life.[1]

Additionally, MCSSs pose various challenges for assessing quality-of-life aspects of health outcomes. First, they are more mechanical than physi

[1] The recently released IOM report on computer-based patient records (IOM, 1991b) discusses the opportunities such records provide for improving both the care patients receive and the ability to retrieve information about that care, for purposes such as research.

ological, working in a fashion similar to a pump. Second, their use has the possible unintended consequence of prolonging life for patients who suffer an adverse event and end up in a coma or dependent on another form of long-term mechanical life-sustaining treatment such as a ventilator. Third, in the case of a TAH, the device replaces an organ that has much cultural symbolism. These characteristics are not totally peculiar to MCSSs, but their compounded impact on the conceptual and methodological issues related to assessing outcomes of care should not be overlooked.

Health State Utilities

The role of health state utilities in cost-effectiveness analysis (CEA) is another example of the importance of quality-of-life assessment (see Chapter 6 and a later section of this chapter). Utility is a concept from economics and decision analysis. It refers to the preference for, or desirability of, a particular outcome. The values or preferences assigned to descriptions of the health status of end-stage heart disease patients are utilities. These preferences range from most desirable to least desirable, including states of health that may be considered less desirable than death. Utility assessment provides a means of integrating the value attributed to the worth of life at a given point (state) in time with the quantity of time (months, years) spent in various states (Williams and Wood-Dauphinee, 1989).

Rothenberg and Koplan (1990) summarized the growing interest in utility assessment:

> Finally, although currently our major measures of burden and progress in the chronic diseases remain mortality and longevity, an improved quality of life is likely to emerge as the primary goal of our efforts. The concept of "quality-adjusted life years," now used as a measurement in cost-utility analyses, may well become a concept that has practical significance for the general public. The public may become increasingly sophisticated at health equivalents and valuation, e.g., five years at full activity is worth ten years in a nursing home. Such thinking by both health care providers and consumers may well influence the way medicine is practiced. (p. 292)

Descriptions of the health states of end-stage heart disease patients provide the basis for assigning utilities to these states. As discussed later in this chapter, these health states are operational definitions of the health and quality of life of patients under different treatment options, including conventional medical treatment, MCSS, and heart transplantation.

HEALTH, HEALTH STATUS, AND QUALITY OF LIFE

Health is more than the absence of disease or illness. Thus the accurate assessment of health is not limited to the traditional clinical factors based on anatomical and physiological variables. The variables chosen to evaluate health depend primarily on what aspects of life are considered relevant to health; in turn, the variables used to evaluate the effects of health care interventions depend on the goals of the intervention.

Outcome measures might include the assessment of health-related quality of life in key facets of life experience. Patrick and his colleagues have identified five such facets: (1) life expectancy (or duration of life); (2) impairments, including symptoms, signs, and clinical indicators; (3) physical, psychological, and social functioning; (4) general health perceptions, including self-perceived health status and satisfaction with health; and (5) opportunities, including the stigma or disadvantage arising from ill health and the resilience or future capacity for health (Patrick and Elinson, 1984; Patrick and Erickson, 1988; Patrick and Bergner, 1990).

Health-related quality of life (sometimes called health status) is a concept that incorporates these key facets of life experience in what are called "domains." The most commonly assessed domains are clinical status, physical functioning, mental health or psychological and cognitive functioning, social functioning, role functioning, and general health perceptions. Within these health domains are varying states of health, illness, disease, and wellbeing. Individuals and groups may assign values or preferences, both positive and negative, to these domains. These values are what distinguish "health-related quality of life" from quantity of life (Patrick and Erickson, 1988; Patrick, 1990).

A broader composite of factors contributes to or influences health-related quality of life than are included directly in the more commonly adopted set of domains of health-related quality of life. The influences of this broader set of factors can be positive or negative, and the degree and direction of influence of a given factor will vary among patients and across time for the same patient. Several of these determinants are mentioned in the literature as having particular significance to the outcomes of patients undergoing heart or kidney transplantation, hemodialysis, or coronary artery bypass graft surgery. Such determinants include (1) intensity of health care, personal health habits and attitudes, and use of health services; (2) social resources and networks of personal relationships; and (3) various economic, educational, and psychological resources (Patrick and Erickson, 1988; Patrick et al., 1988; see also Bergner, 1985).

These determinants are the context in which patients seek health care (or, as may be the case, do not seek or receive health services), and thus they, too, affect the outcomes of the encounter (IOM, 1991a). The success of the

Stanford heart transplant program during the 1970s has been attributed, in part, to stringent patient selection criteria that included some of these broader determinants, such as the presence of strong family and social support systems (Lubeck and Bunker, 1982; Christopherson, 1986). A positive outlook on life by the patient, accompanied by intra-psychic strength and interpersonal support systems, creates synergic forces to help the patient, caregivers, and professionals cope with the burdens of end-stage heart disease.

The broader concept of quality of life (in contrast to health-related quality of life) extends the relevant domains to include areas such as the environment and living situation (e.g., housing, neighborhood), employment, religious beliefs, and attitudes toward life and death. Quality-of-life domains might also include the patient's perception of the impact of his or her illness on family members and close friends (Christopherson, 1986). Figure 5.1 depicts the interrelationships of the various factors, including those in the broader quality-of-life construct, that influence the health-related quality-of-life domains.

DOMAINS OF QUALITY OF LIFE RELEVANT TO END-STAGE HEART DISEASE PATIENTS

No consensus or body of empirical research literature exists on the essential set of domains of quality of life for end-stage heart disease patients. Research findings on several diseases and conditions indicate the importance of using both generic and disease-specific tools in assessing quality of life for some patients (Rector et al., 1987; Patrick, 1990; Spilker, 1990). A particular domain, such as role functioning, may be assessed by both or only one of these types of measurement tools. Testing proposed domains through research is one major way of confirming their relevance.

Domains for Utility Assessment

In order to reflect quality of life in CEAs, such as that described in Chapter 6, several steps are necessary; this discussion focuses only on the classification of health states for the assignment of utilities or preferences (the two terms are interchangeable in this context). One of the early activities in a CEA process is the identification or selection of relevant domains of health-related quality of life. Once identified, the domains guide the development of descriptive functional attributes and perceptions of patients in the various health states undergoing analysis. The domains selected for use in this study's CEA of three patient-treatment groups are listed in Table 5.1.

Health state utilities provide the means for assessing trade-offs in health

related quality of life over time. These trade-offs occur among two or more health states defined with two or more domains. For example, social functioning might improve and self-care might deteriorate for a patient between two points in time. Additionally, changes in the patient's expectations can influence the patient's perception of the outcome. Irrespective of the degree and direction of change in any one or more domains, three general health state outcomes are possible. The determination of whether improvement, deterioration, or "no change" has occurred in health status is subjective, depending on the weights and values that are assigned by the individual making the trade-offs among the various states described.

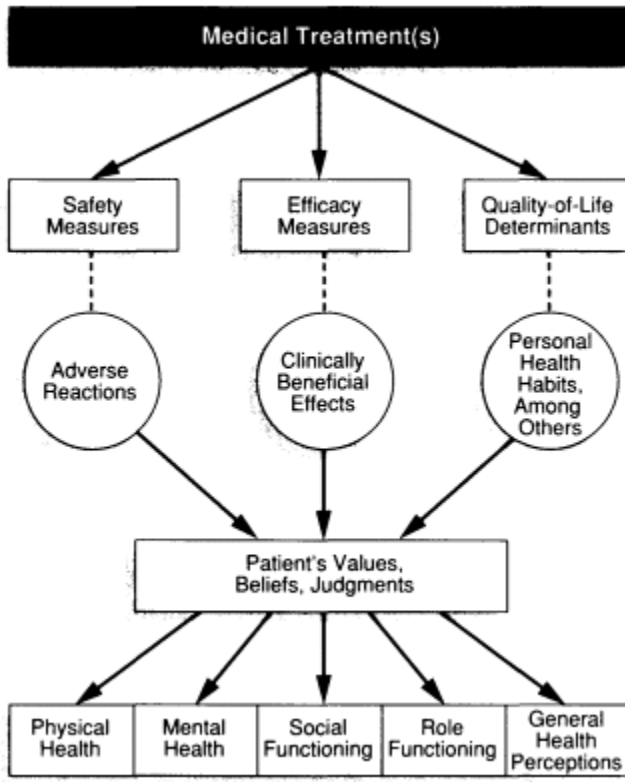

FIGURE 5.1 Model showing, from the perspective of the patient's values, how the interrelationships of clinical aspects of care and a broad composite of quality-of-life determinants influence key health-related quality-of-life domains. SOURCE: Adapted with permission from Spilker (1990).

The results or products of trade-offs can be converted to a quantitative

value, namely preference (utilities) weights to health states.[2] In the committee's CEA (Chapter 6) these weights form the basis for calculating quality-adjusted life years. Appendix E provides more details on the CEA and how utility measures fit into the broader methodology.

TABLE 5.1 Domains for Assessing Utility Measures for End-Stage Heart Disease Health States

Physical
Vitality or energy
Maximum physical activity or limitation
Percent of time in bed during daytime
Mental
Anxiety or depression
Affect or mood
Cognitive
Social
Interpersonal contacts
Role
Role functioning
Self-care
Bathing, dressing, etc.
General health perceptions
Current health
Discomfort or shortness of breath

Other Domains Relevant to These Quality-of-Life Issues

The study committee identified several health-related quality-of-life domains of potential significance to patients considering or having received MCSS treatment, in addition to those used in the health states for the CEA in Chapter 6. The domain that may be unique to the MCSS patient population, given the cultural symbolism of the heart, is that of machine dependence and societal reaction. Two other domains may be relevant not only to MCSS patients but also to other patients treated by exceptional therapies such as transplantation or dialysis: these domains are first, the meaning and purpose of life, and second, spiritual well-being. These three domains are

[2] A more detailed explanation of health state preferences can be found in Froberg and Kane, 1989a, 1989b, 1989c, 1989d; Patrick and Erickson, in press.

discussed here for the purpose of stimulating new research directions and conceptualization on health-related quality of life for patients considering or choosing unconventional forms of therapy in an effort to sustain life.

Machine Dependence and Societal Reaction

The TAH has two characteristics as a medical device that may be of particular significance to the patient's quality of life: It *replaces* rather than *supports* or *assists* a natural organ, and the organ replaced is highly symbolic. These characteristics may have a compounded effect on the MCSS patient. The patient's quality of life may change, positively or negatively, because of the patient's reaction to being machine dependent and to the partial or total excision of his or her heart. The responses of other people, such as family, friends, and even strangers, to the patient as well as the patient's perceptions of these responses may have both positive and negative influences on the patient's self-image.

In some instances, particularly when the TAH technology is new, the MCSS recipient may be perceived as exceptionally brave and appealing to know, and may receive frequent positive responses from friends and acquaintances; the recipient may also find satisfaction from attention provided by the media. In other instances, particularly if TAH use becomes common, recipients may be perceived as "different" or "handicapped" when compared with a "well person." Goffman's term, "spoiled identity" (1963), depicts the potentially negative influence that societal stigmatization can have on one's self-image, an influence that may be quite powerful for TAH patients. The costs that are borne by society or third-party payers to provide MCSS treatment may also raise questions for others as to whether the patient is "worth" the expense; such questions may create doubts in the patient of his or her worthiness.

Other, more philosophical aspects of health status, including some perhaps not yet identified, may be significant for patients treated with a TAH because of the unusualness of a machine heart. For example, will the patient feel like a "whole person"? Will the patient anticipate disengagement from emotions perceived as being centered in the natural heart, such as love? What, if any, relationship will exist between these subjective experiences and the patient's health-related quality of life? How will these experiences be manifest in the patient's behavior and affect other domains such as social functioning?

Meaning and Purpose of Life Versus Fear of Death

The value of living is a personal concept and not one easily measured in quantitative terms. Individuals confronted with life-threatening conditions

may choose treatments that sustain life because, on the one hand, they perceive their present and future life as having meaning and purpose, or, on the other hand, they have a fear of dying. Some patients may struggle with both feelings and, through the therapeutic process, find an increase in the meaning to life and a decrease in fear of dying.

This subjective sense of meaning to life is similar to a sense of personal dignity; one's life has meaning irrespective of external adversities. The domain of meaning and purpose of life differs conceptually from the global domain of life satisfaction. The former implies an actively initiating role of the self (George and Clipp, 1991); the latter implies an act of judgment of an individual on his or her interaction with external or objective life resources or conditions such as illness, socioeconomic status, and relationships to others (Patrick and Erickson, 1988).

Additional concepts in this area of potential relevance to MCSS patients are the finiteness of life, will to live, imminence of death, and readiness for death. These concepts overlap somewhat, but they also have unique elements; to what extent and in what time frame the differences across these concepts are significant and relevant to health-related quality of life for the MCSS patient remain to be confirmed.

Spiritual Well-Being

Social scientists have developed the concepts of religion, religiosity, and spirituality within theoretical constructs useful in research (Ellison, 1983; Payne, 1990; Blazer, 1991). Health services researchers have been slow to adopt or adapt these concepts and theories, perhaps in part because the historical focus of social science in these areas has tended to be on operational measures such as membership and participation in organized religious functions.

Nevertheless, health services researchers recognize that the extended, more broadly defined domains of quality of life include spiritual or religious beliefs. For certain patients, such as those with life-threatening conditions, spiritual well-being may in fact be a significant health-related quality-of-life domain rather than a domain in the more extended general area of quality of life.

QUALITY OF LIFE AND ITS DETERMINANTS FOR PATIENTS WITH END-STAGE HEART DISEASE

Some studies have been published on patients' quality of life after receiving different therapies, procedures, and devices for treatment of heart disease. Little empirical research has been conducted on the quality of life of patients who have received MCSSs (see Ruzevich et al., 1990). The

literature does include anecdotal and case studies of MCSS-treated patients, and quality of life is an often-mentioned characteristic without a standardized definition. Limited inferences on quality of life can be drawn from studies of somewhat similar treatments (such as dialysis) and applied to MCSS patients (Lubeck and Bunker, 1982); broad inferences from studies of patients having illnesses or conditions other than end-stage heart disease should be made only with great caution.

Some of the more common domains of quality of life historically reported by patients include functional levels and symptoms, and recent research includes quantitative measures of these domains (Kaplan and Anderson, 1990). Decreases in functional levels and the presence of discomfort symptoms (e.g., fatigue, breathlessness, sleeplessness) are problems frequently noted by patients with congestive heart failure (Rector et al., 1987; Tandon et al., 1988).

The Medical Outcomes Study (Stewart et al., 1989) provided an opportunity to compare the functional status and well-being of patients with congestive heart failure with the same domains among eight other patient groups having different chronic diseases, including comorbidities. Interrelationships were found among emotional well-being, health perceptions, and physical functioning for both mental and physical disorders in all nine patient groups. Chronic conditions were found to be the factor, among all health measures, that had the greatest negative effect on functioning and well-being. Much of the variance in well-being was not accounted for by the presence or severity of the diseases themselves; other variables such as personal factors and medical care may contribute to the variances (Stewart et al., 1989; Greenfield, 1990).

One must also be careful when drawing conclusions about the impact of particular therapeutic interventions on the quality of life of patients (Walden et al., 1989). In elderly patients with cardiovascular disease, physical and psychosocial symptoms tend to overlap; depression is common and thought to have prognostic significance (Gentry et al., 1987). These researchers report that older people (65 years of age or older) have inappropriately low expectations for functional capacity and other outcome measures following treatment and rehabilitation from a myocardial infarction. These low expectations are correlated with passive rehabilitation behavior as well as behavioral and attitudinal tendencies that perpetuate "sick-role" dependency over long periods of time.

Heart Transplantation

Comparison of the quality-of-life outcomes of organ transplantation with those of other treatments provides some insight to the health status of different patient groups. However, the dearth of research involving control

groups, in particular control groups of patients not accepted for transplantation, leaves many questions unanswered about patient preferences and outcomes of alternate treatments to transplantation.

Similar to patients with congestive heart failure, heart transplant recipients also report impairment of physical functioning but tend to rate their overall quality of life as "good" on subjective evaluations (Evans et al., 1984; Lough et al., 1985). Walden and colleagues (1989) reported that the quality of life of transplant patients differed little from that of survivors of sustained medical therapy. Psychosocial functioning (feelings of anxiety, depression, and hostility) was among the domains studied; both groups scored poorly in this domain. Patients with stable heart failure reported more dysfunction in social and leisure activities than did transplant patients, and heart failure patients viewed their overall functional status to be lower than did heart transplant recipients.

These findings did not support the researchers' expectations that a higher level of emotional benefits would be reported among the heart transplantation study population. The authors are of the opinion that many patients are unwilling to undergo the rigors of transplant surgery to gain only an extension of life; patients want to be guaranteed that the transplant will also improve their quality of life (Walden et al., 1989).

Guarantees are rare in health care, however, and patients react differently to the "unknowns" of health care. For example, organ transplantation involves a high level of uncertainty for many patients: uncertainty of being accepted for a transplant, uncertainty of the availability of an organ within the time constraints, and uncertainty of outcome after transplantation (Christopherson, 1986). Uncertainty is frequently accompanied by fear; thus, the quality of life of implant and transplant patients may be related to the presence and degree of fear, e.g., "fear of sudden death or failure of the graft or machine leading inevitably to death" (Christopherson, 1986, p. 556).

Automatic Implantable Cardioverter Defibrillator

The psychosocial effects of implantation of an automatic implantable cardioverter defibrillator (AICD), a costly new treatment for intractable arrhythmias, have been studied by several investigators. Cooper et al. (1986) reported an association between AICD implantation and multiple physical, social, and psychological alterations; patients tended to report having fears of premature battery failure and shock resulting from the device discharging.

Other investigators of patients having AICD implantation found higher degrees of both anger and anxiety in pre-and postimplantation patients compared with normal controls or with other medically ill populations

(Vlay et al., 1989). These researchers speculate that personality traits of anxiety and anger have the potential to influence outcome adversely.

Pycha and colleagues (1986) also studied the relationship of postimplant adjustments to AICD patients' personality styles, attitudinal and philosophical beliefs about quality of life, severity of the illness, and ability to return to work. Many patients reported having unpleasant feelings during the postimplant stage: anxiety, fear, depression, and loss of security and control; moderate levels of self-doubt and helplessness; and high levels of emotional upset and distress. Most of these feelings decreased over time.

Providing Support in the Postoperative Phase

Assessing health-related quality-of-life outcomes implies that a relationship exists between health care interventions and the patient's health status. Because health care is a continuum of events for the MCSS patient, the postimplantation processes of care, including the patient-provider relationship, have significant potential for influencing clinical indicators or clinical endpoints. Postoperative patient management that includes active interventions such as counseling and educational services can improve patients' quality of life. In many circumstances, family and other significant friends should participate in these sessions (Christopherson, 1986; Pycha et al., 1986; Ruzevich et al., 1990).

Learning in the postoperative phase is not limited to one direction, from health professionals to patients. Patients and family members are a vast resource of knowledge and support, a resource frequently overlooked by health care providers, researchers, and other patients and their families.

Perspectives from Prior Studies of the Artificial Heart

The National Heart and Lung Institute Artificial Heart Assessment Panel (NHLI, 1973) concluded that many patients who will eventually have TAHs will experience anxiety-related psychological burdens and perhaps psychotic reactions. The panel noted that patient concerns may focus on financial worries that in turn may create severe guilt and intrafamilial tensions, feelings of "dehumanization" because of the particular organ replaced with an artificial device, and negative health consequences because of the source of power for the device. (The last of these concerns was noted by the panel because nuclear power was one of three power modes then under consideration.)

An Office of Technology Assessment (OTA) report (Lubeck and Bunker, 1982) on the cost, risks, and benefits of the artificial heart draws some inferences from studies of heart transplant, hemodialysis, and kidney transplant patients for the quality of life of TAH-implanted patients. The study identified several burdens TAH patients may encounter:

- feelings of depression, rapid mood changes, guilt, insecurities about self-image, and insecurities and stress about the potential for sudden death;
- role and identity confusion such as reversal of dependency roles between spouses and difficulties of adjustment to the new role of not being a "sick" patient; and
- inconvenience and anxiety about device maintenance.

The OTA report suggests that the TAH patient's ability to cope may relate to the degree to which society accepts the TAH, especially from the perspective of a general societal concern over a growing dependence on medical technology.

The National Heart, Lung, and Blood Institute (NHLBI) Working Group on MCSS (NHLBI, 1985) noted that even though MCSS recipients will be able to engage in many normal ambulatory activities and moderate exercise, they will not be able to forget about the device. The working group concludes:

> There is no way of predicting with any certainty the quality of life. Considering the clinical circumstances of the recipient when the device is implanted, the anticipated benefits are substantial, but the possible complications and side effects are also significant. Only experience will establish how these balance out. However, it is quite plausible that with appropriate selection of recipients, they will look upon their lives as being of good quality. (p. 27)

IMPLICATIONS OF QUALITY-OF-LIFE CONSIDERATIONS IN CLINICAL TRIALS AND STUDIES OF MECHANICAL CIRCULATORY SUPPORT PATIENTS

Concepts and Methods

Assessing the quality of life in clinical trials and follow-up studies of patients receiving MCSSs is fraught with methodological, funding, and policy issues. For instance, although disease-specific measures for end-stage heart disease patients are important, no consensus exists on whether to incorporate such measures in existing generic instruments or develop unique instruments for this population (Evans et al., 1984; Lough et al., 1985; Wallwork and Caine, 1985; Patrick, 1990; Patrick, in press) On the one hand, some researchers and clinicians question the sensitivity of existing generic instruments to ascertain the preferences of condition-specific populations (Sechrest and Pitz, 1987; Cleary, 1990). On the other hand, most studies of cardiovascular patients use generic measures rather than disease-specific instruments to assess heart disease and treatment effects. Further work is needed in instrument development and validation to deter

mine which domains are important to particular patient populations and, within domains, which components are sensitive to "burdens" perceived by patients (Miles et al., 1988).

The Nottingham Health Profile (NHP) is an example of a generic, validated instrument used to assess the quality of life in studies with cardiac patients (Wallwork and Caine, 1985; O'Brien et al., 1987; see also Falotico-Taylor et al., 1989). Part I of the NHP measures six dimensions of social functioning: physical mobility, pain, sleep, energy, social isolation, and emotional reaction; Part II consists of measures of the effects of health problems in areas such as occupation and sexual functioning.

In contrast, the Living with Heart Failure Questionnaire (LHFQ) was developed for a specific population, namely congestive heart failure patients (Rector et al., 1987). It is a self-administered questionnaire that covers many of the same domains as found in the NHP; the basic difference is in the wording of the individual measures. All 21 questions found in the LHFQ begin with a reference to the patient's condition: "Did your heart failure prevent you from living as you wanted during the last month by making your relating to or doing things with your friends or family difficult?" (Rector et al., 1987, p. 206)

Figure 5.2 depicts the theoretical relationships among different health-related quality-of-life concepts relevant to end-stage heart disease and shows the interactive influences of the disease and behavioral, perceptual, and social determinants (Patrick and Bergner, 1990). This figure reflects the complexity of the subject and, at the same time, points out the importance of a theoretical base for future research studies.

Four perspectives are relevant to the selection of instruments for clinical trials and evaluative studies, such as quality-of-life assessments for end-stage heart disease patients receiving MCSSs or conventional medical or surgical treatment: (1) adequacy of the conceptual content; (2) methodological issues of different measurement strategies; (3) practical considerations relating to data collection, editing, analysis, and interpretation; and (4) the interrelationship of the design and purpose of a study with conceptual, methodological, and practical considerations (Patrick, in press).

Another issue arises when a trial or study includes a cost-effectiveness analysis. Preference-based (i.e., utility) measures are desirable for cost-effectiveness analyses, such as the one described in Chapter 6. Nevertheless, they are frequently challenged for presumed lack of stability, validity, and reliability; further research is needed to determine the best way to undertake such measures.

Other concerns about clinical trials relate to (1) statistical bias, in particular when either study populations do not include variables such as multigeographic and treatment site representation or numbers in such cells are

small; (2) problems with establishing control groups, in particular when study designs are attempting to assess net gains or losses using several outcome measures such as quality of life; and (3) limitations on the followup period because of the short life expectancy of many in both the control and experimental groups (O'Brien et al., 1987; see also Tuteur and Tuteur,

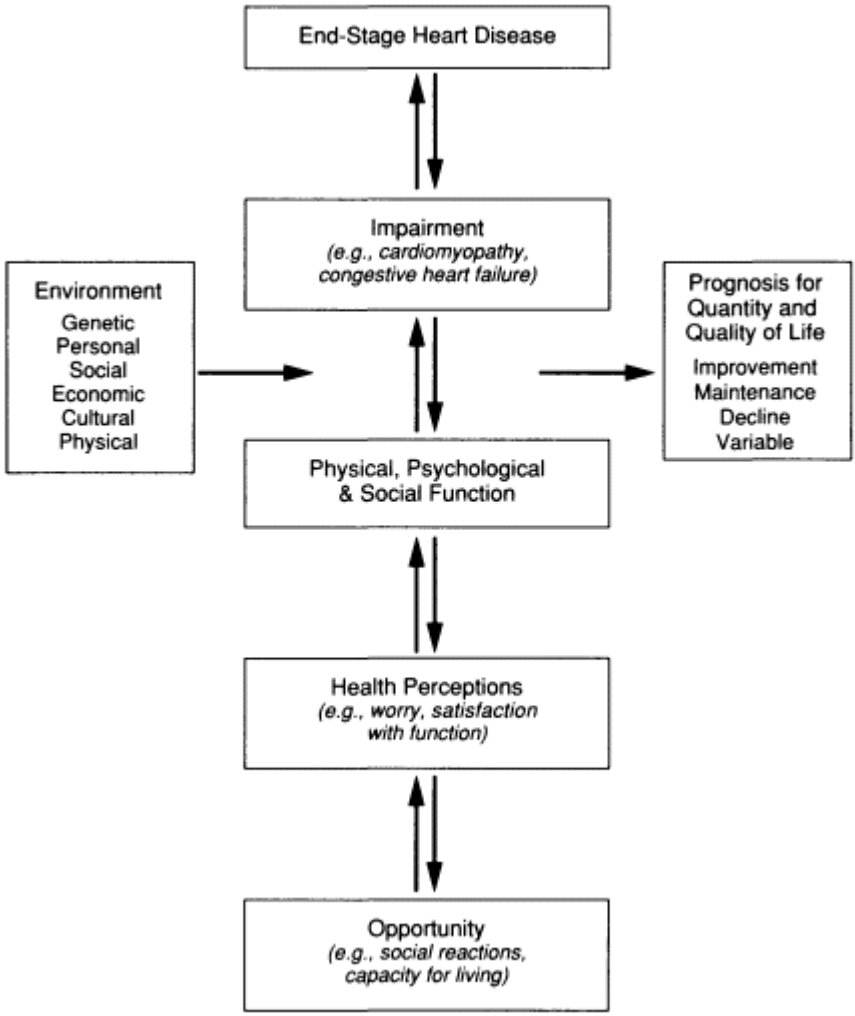

FIGURE 5.2 Theoretical relationships among health-related quality-of-life concepts.
SOURCE: Adapted from Patrick and Bergner, 1990. Reproduced, with permission, from the *Annual Review of Public Health,* Vol. 11, © 1990 by Annual Reviews Inc.

1990). These concerns frequently can be addressed through the study design but resource limitations for conducting clinical trials create pressures to take shortcuts.

To the extent that policymakers judge it to be in the public interest to use public resources to develop the ventricular assist device and TAH, their commitment should include adequate support for comprehensive assessments of health-related quality of life in patients receiving MCSSs during clinical trials and even thereafter. If they do not follow through on such a commitment, major policy decisions addressing access to and equality of health care and patient-physician decision making on the appropriateness of care for end-stage heart disease patients will be made using "convenience" criteria and data that may perhaps be inappropriate or inadequate to the task.

Costworthiness: Patients' and Societal Perspectives

Patients need information that will assist them in making decisions that are costworthy, and individuals should be able to participate in determining which health care interventions are deemed to be costworthy. Just as patients have different goals and expectations of health care, they assign different values to the outcomes of care.[3] Health providers also need information that will help in defining populations for whom clinically effective technologies are appropriate and in planning for the support systems that may enhance quality of life in the postintervention stages (Sechrest and Pitz, 1987; Kaplan and Anderson, 1990).

When differences occur between patients' and society's determinations of the costworthiness of specific health technologies, the greater is the need for information that delineates the domains or outcome measures in which the variations in values and preferences arise. The scarcity of information on outcomes that include health-related quality-of-life measures relative to specific technologies may hinder efforts to make comprehensive coverage decisions that include a criterion on costworthiness.

SUMMARY AND CONCLUSIONS

One important aspect of treatment alternatives for end-stage heart disease is the quality of life of the patient. This chapter discusses the meaning and importance of health-related quality of life within a conceptual frame

[3] The importance of considering patients' preferences in health care decisions is the subject of much work by Wennberg, Mulley, and their colleagues. For more details, see Barry et al., 1988; Wennberg et al., 1988; Mulley, 1989, 1990.

work depicting the relevant domains to be measured. Additional potential domains are proposed that may have special significance for patients considering or choosing unconventional forms of therapy, such as the total artificial heart, for life-threatening conditions.

This review of the concepts and theoretical base of health-related quality of life in the context of end-stage heart disease patients and MCSS interventions supports the following conclusions:

- Quality of life is an important criterion of successful treatment and should be assessed in clinical trials with heart disease technologies.
- A core set of domains for quality-of-life assessment, similar to those used in the utility measures in this report, should be included in all MCSS clinical trials; clinical trials should receive adequate funding to assess health-related quality of life in the core domains. The committee is aware that the Office of the Director of the National Institutes of Health (NIH) has expressed interest in all institutes' incorporating a standard core set of domains in all appropriate NIH-sponsored clinical trials; the committee endorses continued efforts of this nature.
- The need exists to identify and verify a core set of disease-specific domains and respective measures for patients with end-stage heart disease. Such efforts should involve all parties having an interest in the measures, including clinicians treating end-stage heart disease patients.
- The need exists for more research to identify and understand support systems and selected other determinants of health-related quality of life that might be helpful in identifying those patients, among the groups meeting certain clinical conditions, who are more likely to benefit from MCSS treatments.
- The success of the post-MCSS treatment phase is influenced by several variables, including the psychosocial support provided by the team of health care professionals. Attention should be given to the importance of support services for enhancing the patient's quality of life and minimizing the damage or negative aspects of MCSS treatment; services such as primary nursing care in the home, educational and counseling programs to family and informal caregivers, and patient support groups are thought to have particular supportive value. Researchers should be encouraged to increase knowledge in these areas.
- All NHLBI-sponsored research and clinical trials that include cost-benefit or cost-effectiveness analyses should include preference-weighted or utility measures in the analysis design. Utility assessments are important if CEA is to be done correctly.

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6

Cost-Effectiveness Analysis

THE TRADITIONAL ROLE of cost-effectiveness analysis (CEA) is in helping to assess the overall value of specific medical technologies, but it can also be an important aid to decisions about research programs. This chapter considers the projected treatment cost-effectiveness of total artificial hearts (TAHs) and also illustrates a way in which CEA can assist in making decisions about the level of research on a particular technology.

To aid in the committee's work and to provide information about TAHs that will help others as they scrutinize this technology in the years ahead, the committee commissioned a cost-effectiveness study with two goals: (1) to project the cost-effectiveness of long-term TAH use, based on estimates of future device performance, clinical effectiveness, and costs, and (2) to develop information for the National Heart, Lung, and Blood Institute (NHLBI) to use in deciding future investment levels for TAH development. After providing general background, this chapter summarizes the CEA findings and discusses their implications for future TAH development; Appendix E provides the most important data elements and additional detail about the methods used in the analyses.

THE USE OF COST-EFFECTIVENESS ANALYSIS IN HEALTH CARE[1]

CEA and its counterpart cost-benefit analysis (CBA) are analytic techniques for comparing the positive and negative consequences from the use

[1] This section is adapted from the Institute of Medicine (1985a, pp. 137-143); references included in the source have been omitted here.

of alternative technologies. Interest in health care CEA and CBA began to appear in the late 1970s, spurred largely by provider, payer, and consumer concern over increasing health care costs and government spending for health care services.

The uses of CEA and CBA for technology assessment can be categorized either by the type of technology (i.e., drug, medical device, or procedure) or by applications. CEAs and CBAs have been used for a variety of devices, instruments, and drugs. Such assessments require detailed analysis of the process, technical procedures, and personnel using the products; they may employ different analytic methods for diagnostic, therapeutic, or supporting applications.

The principal distinction between CBA and CEA is in the valuation of the effects and benefits of the alternatives. In measuring benefits, a CBA requires that all important effects and benefits be expressed in monetary (dollar) terms. CEA avoids this requirement by calculating the lives (or years of life) saved or lost per dollar expended. Further, assessments of the quality of life of the years saved may adjust or weight differences in health status, or "utilities." These utilities usually range from a value of zero for the state of death up to 1.0 for a healthy state, but a state "worse than death" can receive a negative value; for example, the mean value assigned by the committee's assessment to a moribund end-stage heart disease patient in an intensive care unit or coronary care unit was -0.11, as discussed below.

In performing analyses, all future costs and benefits (including health consequences) should be discounted to their present value in order for them to be compared appropriately with one another. The discount rate attempts to adjust for the fact that a dollar not spent today would earn interest, which could then be made available for future health programs. For long-term projections, low discount rates tend to favor projects whose benefits accrue in the distant future or whose major costs occur in the near term. Accordingly, the selection of appropriate discount rates is often controversial and the use of such rates is usually subjected to sensitivity analysis.

Sensitivity analysis checks the importance of assumptions by testing a range of discount rates, varying the weights used to compute quality-adjusted life expectancy, and testing all important clinical and cost variables over a range, for example, from best to worst case. It is an important means to cope with problems of projections and uncertainties about the future.

Capabilities and Limitations

A CEA or CBA should not serve as the sole determinant of a health care decision, but the process can improve decision making by considering not

only whether the technology is effective but also whether it is worth the cost. In general, a CEA is most useful for making a choice as to the lowest cost technique to achieve a specified objective, benefit, or effect, or for setting priorities among technologies within a limited budget. A CBA is most useful for deciding whether to implement a technology when neither budget constraints nor alternative uses of resources are explicitly known.

Because CEA and CBA consider both economic and health outcomes, they offer promise in their ability to help with policy decisions that affect the quality of care under resource constraints. Social values, ethical considerations, and political realities may well, however, take precedence over analytical results. CEA and CBA techniques can be a useful tool for planning for the future, and prospective analytic simulation models can attempt to predict costs and effects or benefits of competing alternative programs.

The result of a CEA is expressed as a ratio, where the numerator is the total discounted net cost of the intervention for a defined group of patients and the denominator is the aggregate benefits those patients derive from the intervention, also discounted. The denominator is usually expressed in life years (or quality-adjusted life years) gained in relation to another form of (or no) treatment, yielding a cost-effectiveness (C/E) ratio of cost per added life year or quality-adjusted life year. Simply put, the greater the C/E ratio, the less favorable the intervention's effectiveness in relation to its cost.

COST-EFFECTIVENESS OF TOTAL ARTIFICIAL HEARTS

The CEA performed for this committee provides a means of comparing the anticipated clinical benefits and costs of using a TAH with those of other forms of heart disease treatment as well as treatments for other diseases. The CEA examines this technology as of 2010, the earliest likely time when the TAH could be in wide use. It also examines the costeffectiveness of the two main alternatives to mechanical circulatory support systems (MCSSs) for patients with end-stage heart disease: transplantation and conventional intensive medical treatment.

As described in more detail in Appendix E, the CEA was performed using a Markov simulation model that permits variations in assumptions about cost, clinical, and outcome variables. Using a 20-year time frame beginning in 2010 for the model, the typical patient moves through a sequence of potential "states" on a monthly, probabilistic basis. The committee and its consultants developed a number of estimates and assumptions for the CEA concerning the clinical effectiveness of TAH use, heart transplantation, and conventional medical treatment of end-stage heart disease. Costs were also projected, based on estimates such as anticipated lengths of hospital stays both for the initial procedure (implantation, transplantation, or regulation of medication dose) and for necessary device repairs or re

placements as well as various types of complications that were determined to be likely. Costs were estimated in constant 1991 dollars, even though the scenarios were for the 2010-2030 period.

For MCSS use as well as for heart transplantation and conventional medical therapy, individual committee members participated in an assessment of quality-of-life "utility" or preference values. They assigned values to nine typical health states as shown in the appendix to this chapter, where 1.0 denoted full health and 0 denoted death. Because a number of committee members considered being hospitalized with end-stage heart disease as a state worse than death, one of the mean utility values is negative, as shown in Table 6.1. The mean values were incorporated into the cost-effectiveness analysis, yielding figures for estimates of the quality-adjusted life years (QALYs) gained from each type of treatment as well as simple increased life expectancy.

Tables 6.2A and 6.2B summarize the results of the cost-effectiveness analysis for the primary or "base case," applying the best estimates of the various assumptions discussed in Appendix E to the three alternative forms of treatment. The CEA shows that a patient will live an average of 4.4 years after TAH use, before adjusting for quality of life, in contrast with the six months expected if conventional medical treatment is received. Heart transplantation is calculated to provide an average 11.3-year life expectancy, because the committee's consultants estimated complications following transplantation at rates somewhat lower than current ones, in anticipation of improved outcomes between now and 2010. Adjustments for the quality of life reduce the life expectancies for all three forms of treatment. Total costs of TAH use over the average patient's lifetime are substantially higher than for a transplant, primarily because of the device's $100,000 cost.

The cost-utility data assessing the quality of life under the various health states are the group opinions of the committee, not of actual or prospective

TABLE 6.1 Utility Values for End-Stage Heart Disease States by Time Trade-off Method

	Mean Utility		
Patient Group/ Health State	Long-Term Health State	In Regular Hospital Bed	In ICU/CCU
Medical treatment only (moribund)	0.08	0.01	-0.11
TAH recipient	0.66	0.52	0.40
Heart transplant	0.75	0.55	0.42

ICU/CCU, intensive care unit/coronary care unit; TAH, total artificial heart.

patients, as would be ideal and eventually possible. Results of the CEA are thus presented both with and without incorporating these data, that is, both unadjusted and adjusted for the quality-of-life utility values.

TABLE 6.2A Cost-Effectiveness Results for Base Case: Cost and Outcomes by Therapy

Therapy	Aggregate Cost (K$)	LY (yr)	QALY (yr)
1. Artificial heart	$327.6	4.42	2.88
2. Transplantation	$298.2	11.30	8.45
3. Conventional medical treatment	$28.5	0.50	0.03

NOTE: Cost and outcomes discounted at 3 percent per annum; 20-year horizon.
K$, $1,000; LY, life years gained; QALY, quality-adjusted life years

TABLE 6.2B Cost-Effectiveness Ratios for Base Case

Comparison[a]	Incremental Cost (K$)	Change in LY	Marginal Cost/LY (K$/Yr)	Change in QALY	Marginal Cost/ QAYL (K$/yr)
Artificial heart vs. conventional medical (line 1-line 3)	$299.1	3.92	$76	2.85	$105
Transplantation vs. conventional medical (line 2 – line 3)	$269.7	10.80	$25	8.42	$32
Transplantation vs. artificial heart (line 2-line 1)	$-29.4	-6.88	D	-5.57	D

NOTE: Cost and outcomes discounted at 3 percent per annum; 20-year horizon.
[a] Comparing the indicated lines of Table 6.2A
K$, $1,000; LY, life years gained; QALY, quality-adjusted life years; D, dominated (clearly advantageous in both costs and benefits; therefore preferred).

Table 6.2B, comparing both TAH use and heart transplantation with conventional medical treatment, shows that a TAH yields an average increase of 2.85 years in quality-adjusted life expectancy at a net cost of $299,000, for a C/E ratio of $105,000 per QALY gained. Because of transplantation's lower total cost and greater life expectancy, its C/E ratio is $32,000 per added QALY.

Sensitivity Analysis

As discussed in detail in Appendix E, sensitivity analysis to examine the impact on the CEA's results of changing the assumptions for important variables has relatively little impact on the finding of primary interest, the C/E ratio of TAH use in contrast to conventional medical treatment. Increasing each of eight probabilities of key adverse events by 25 to 100 percent increases the marginal cost per QALY only 3 to 11 percent. If all costs are increased 25 percent in addition to all eight of the probabilities, the TAH's cost per added QALY becomes $165,000 instead of $105,000.

Reducing all eight of the variables in combination, as well as reducing costs 10 percent, yields an improvement in the TAH's cost per added QALY from $105,000 to $73,000. Discounting all of the costs and benefits at other than the 3 percent rate used in the base case has little impact; using a 10 percent discount rate yields a TAH cost of $117,000 per added QALY, only 11 percent greater than the $105,000 under the base case.

Implications

It is problematic to evaluate a single, isolated C/E ratio; these ratios must be interpreted in the context of C/E ratios for other uses of resources such as other forms of treatments. Table 6.3 reveals that the cost-effectiveness of a long-term TAH falls above the range of (and thus is considerably less favorable than) C/E ratios for other generally acceptable forms of heart disease treatment. Other applications of some of these interventions have even higher C/E ratios, for instance, coronary artery bypass surgery for very mild angina or care of a low-risk patient in a coronary care unit instead of an intermediate care unit. Such interventions with low-risk patients are generally deemed inappropriate, although they sometimes occur.

Further, the C/E ratio for TAH use is also considerably less favorable than those of other forms of treatment for catastrophic medical problems. The current average cost to the Medicare program for care of a patient with end-stage renal disease is about $30,000 per year, including hemodialysis either at home or in a facility, the latter being the most common form of treatment (IOM, 1991). The cost, and thus the cost-effectiveness, can vary dramatically, however, based on such factors as severity of illness, comorbidities, and whether patients regularly receive the costly drug erythropoietin for treatment of their anemia. Nonetheless, using an approximate utility value of 0.60[2] yields an average C/E ratio of roughly $50,000 per QALY (in

[2] Torrance and Feeny (1989) state a utility of 0.64 for home hemodialysis; because facility based dialysis involves the added inconvenience of trips to the facility three times per week, its utility is presumably somewhat lower.

TABLE 6.3 Summary of Cost-Effectiveness Ratios of Selected Heart Disease Treatments

Treatment	Cost per Life Year or Quality Adjusted Life Year Gained (in 1991 dollars)
Coronary Artery Bypass Graft Surgery	
Left main coronary artery disease	$6,900
3-vessel coronary artery disease	
Severe angina	14,400
Very mild angina, poor LV function	9,500
Very mild angina, good LV function	143,800
2-vessel coronary artery disease	
Severe angina	33,500
Very mild angina	89,900
1-vessel coronary artery disease	
Severe angina	57,400
Very mild angina	899,300
Beta-Blockade Post-Infarction	
High risk	4,400
Medium risk	7,200
Low risk	28,800
Intracoronary Streptokinas	
Inferior infarction	7,500
Anterior infarction	2,900
Coronary Care Units (vs. intermediate care)	
High risk	69,900
Low risk	294,400
Mobile Coronary Care Unit	53,900
Percutaneous Transluminal Coronary Angioplasty	
Severe angina	6,900-12,700
Mild angina	47,200-102,400
Automatic Implantable Cardioverter Defibrillator (AICD)[a]	22,900
Electrophysiologic Testing[b]	32,400
Heart Transplantation[c]	32,000
Implantation of Total Artificial Heart[c]	105,000

[a] For treatment of recurrent life-threatening ventricular arrhythmia, relative to drug treatment.
[b] For treatment of symptomatic bifascicular block, relative to observation; cost updated from 1985.
[c] Relative to conventional medical therapy. LV, Left ventricular.
SOURCES: For last two entries, Appendix E; for percutaneous transluminal coronary angioplasty, Wong et al. (1990); for AICD, S. G. Pauker, personal communication, 1991; for electrophysiologic testing, Beck et al. (1987); for balance, M. C. Weinstein, personal communication, 1991 (all but last two updated from 1988 for inflation by a factor of 1.15).

the case of hemodialysis, each year's cost matches with a year of life gained, because constant treatment is required). Further, Boyle et al. (1983) found a C/E ratio for neonatal intensive care of infants weighing from 500 to 999 grams to be $18,000 per added QALY in 1978 dollars, or $42,600 in 1991 dollars.

Cost-Effectiveness of Ventricular Assist Devices

The primary charge of the committee was to make recommendations about NHLBI's future support for TAH development and the CEA thus focused on that device. CEA can, of course, be applied to a ventricular assist device (VAD) by substituting an estimate of $50,000 as the device's cost instead of the TAH's $100,000 and revising other probabilities appropriately. For example, the impact of hard failure of a VAD is much less severe than with a TAH, as the patient's natural heart may be able to sustain the circulation long enough for the patient to reach a hospital and receive appropriate care such as repair or replacement of the device. While our CEA has not calculated a definitive number, the C/E ratio of VAD use when compared with conventional medical treatment is likely to be somewhat more favorable than the $105,000 for TAH use compared with medical treatment.

Treatment to Prevent End-Stage Disease

Eventually, if the clinical effectiveness of MCSSs approaches that of heart transplantation, these devices will be used with some patients (i.e., the secondary group described in Chapter 4) before their disease has progressed to end-stage. In such a situation, MCSS use will likely halt or slow disease progression, at about the same total cost (including follow-up care) as for end-stage patients.

By definition, as a result of their less severe disease at the time of MCSS implantation, the average life expectancy of this type of patient—without receiving a transplant or MCSS—would be greater than for the moribund patients considered in the committee's CEA. (The impact of quality-of-life adjustments would likely not have a great effect on the CEA's outcome.) Consequently, the cost per added QALY of MCSS use with these earlier-stage patients would be even less favorable than the $105,000 C/E ratio applicable to moribund patients, because the cost would be divided by a smaller number of QALYs added. Only by incorporating into the CEA indirect costs and benefits, such as the added years of productivity gained by avoiding premature death, would intervention earlier in the disease course produce a more favorable result.

COST-EFFECTIVENESS ANALYSIS AND RESEARCH FUNDING LEVELS

Economists have used various analytic tools in approaching decisions about R&D funding, in health care and many other fields. CEAs have been used in studies of a range of research topics, such as choosing from among alternative R&D proposals for cancer prevention (Weinstein, 1983) and vaccine development (IOM, 1985b), the appropriate federal role in R&D (Finneran, 1986), and the balance among R&D investments in various fields (Hartunian et al., 1981; Hatziandreu et al., 1988).

This portion of the committee's CEA has a more limited purpose, which is to assist NHLBI in determining the level of its continuing investment in TAH development during the 1990s. This analysis drew on the cost-effectiveness data generated for the first portion of the study in order to determine the relative cost-effectiveness of three scenarios with varying levels of R&D funding for TAH development after the four developers' current contracts expire in 1993. Under Scenario 1, the primary or base case, two developers would each receive $2 million per year for a five-year period of preclinical device readiness testing, and a 1999-2003 clinical trial of one of these devices would be funded at $2 million per year.

As explained in more detail in Appendix E, TAH developers advised the committee that increased funding levels of TAH development during the 1990s would likely yield long-term benefits, because the additional funding would allow earlier completion of R&D, making devices available for use sooner and thereby extending the lives of some patients who would otherwise die. The added funding would also perhaps reduce the selling price because of resulting design improvements and thus create long-term savings in health care costs, with the TAH selling price lowered from about $100,000 to $70,000 or $78,500, depending on the scenario. More details of Scenarios 2 and 3, describing the effects of the alternative levels of increased funding during the 1990s, are found in Appendix E; this CEA example calculates the benefits that will occur as TAHs come into general use in about 2010.

Under Scenario 2, treatment costs would be increased because an additional one-year cohort of patients would receive TAHs as a result of earlier R&D completion, but those costs and Scenario 2's additional R&D expense would be substantially offset by a lower TAH selling price. The C/E ratio for the patients receiving TAHs in 2008 and 2009 would be $40,000 per added QALY under Scenario 2 and $44,000 under Scenario 3, making it reasonable to undertake the additional R&D expense. Thus, if NHLBI believes that these benefits would flow from the added R&D spending *and* that TAHs will in fact be used in substantial volumes despite their underly

ing borderline cost-effectiveness, it may be beneficial to increase R&D funding over the base-case level of Scenario 1.

Sensitivity Analysis

Sensitivity analyses (see Appendix E) show that the outcomes projected for the additional R&D funding are relatively stable when the assumptions are varied. Even reducing the TAH selling price to $50,000 only drops the C/E ratio to $85,000 per added QALY.

It should be understood that this CEA's results as well as the sensitivity analyses are dependent on a decision that TAHs will be used despite their borderline C/E ratio and that the projected benefits from the increased R&D spending are reasonably certain. If the commitment for continuing development of TAHs under the base case is *not* certain to result in products that the health care system can afford to buy and use, then it would be folly to increase the R&D spending level. The same would be true if it is felt that more R&D funds might well not produce the gains assumed in Scenarios 2 and 3.

Implications

This CEA is useful as an example of how this technique can aid in deciding about funding levels *within* a single R&D program, in contrast with the discussion in Chapter 3 of using CEA as an aid in making funding allocations *among* alternative research programs. It also provides a specific method that the NHLBI can use to help in deciding issues that it must face in the 1990s about continuing to support TAH development and, if so, at what dollar level.

CONCLUSIONS

The Borderline Cost-Effectiveness of Artificial Heart Use

The CEA performed for the committee reveals that the estimated benefits from using a long-term TAH compared with medical treatment yield a C/E ratio ($105,000 per QALY gained) that is considerably less favorable than ratios for both other generally acceptable forms of treatment for heart disease and other treatments for end-stage or catastrophic diseases. The estimates used in developing this CEA resulted in an average life expectancy (LE) of 53 months for TAH patients, substantially below the 11.3 years projected after heart transplantation. While the projected 11.3-year LE of a year-2010 transplant patient anticipates clinical gains over the next two decades, parallel technological improvements in TAHs—building, for in

stance, on more than a decade's clinical experience with fully implantable VADs-may also yield a TAH by 2010 that is more effective than indicated by the performance estimates used in this CEA.

Currently, based on these estimates, the C/E ratio of TAH use is borderline; it remains to be seen what the results of VAD clinical trials will demonstrate about the estimated probabilities and other CEA assumptions. If probabilities of complications and similar events can be reduced as a result of VAD clinical-trial experience, doing so will yield an improved projection of the TAH's clinical effectiveness—and thus an improved cost-effectiveness—that can legitimately be used in future decision making.

NHLBI should, for now, recognize the borderline nature of the TAH's estimated cost-effectiveness in deciding about future support of TAH development; this conclusion is discussed further in Chapter 10. Those developing clinical practice guidelines should also take the TAH's C/E ratio into account, as should third-party payers in their coverage and payment decisions.

Using Cost-Effectiveness to Decide Funding Levels

Applying CEA to a narrowly defined question about a single R&D program allows the long-term effects of such options as alternative funding levels to be examined, in addition to CEA's broader R&D fundingallocation use discussed in Chapter 3. Subject to validation of the underlying assumptions, this portion of the committee's CEA shows that NHLBI may wish to increase its level of investment in the next full-scale phase of TAH development because of the benefits that may be derived, in life years gained, from earlier device availability. There may also be a potential for long-term savings as a result of a lower device cost to hospitals. It is not usually possible to take such considerations as these into account in making decisions about R&D programs, but the committee's CEA example reveals the usefulness of this technique in providing precisely this type of information.

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CHAPTER 6 APPENDIX: DESCRIPTION OF HEALTH STATES

Domain/ Concept	Moribund Patients Receiving Conventional Medical Treatment (No MCSS or Tx)	Patients Who Have Received	
		Long-Term MCSS	Heart Transplant
A: Long-Term Health States			
Physical			
Vitality/energy	Very little	Premorbid normal	Premorbid normal
Maximum physical activity/ limitation	Sedentary only (e.g., TV, reading); no physical activity	Able to return to preillness activity, except for strenuous physical activities	Able to return to preillness activity
% of time in bed during daytime	Almost all in either bed or chair	None	None except during acute rejection
Mental			
Anxiety/depression	Depressed most of time; very anxious	Some anxiety about MCSS failure risk; not depressed	Much anxiety about possible rejection in first year only; some anxiety about effects of long-term immuno-suppression
Affect or mood	Not hopeful about future illness course; also despondent about chance of transplant	Generally positive, with realistic concern about device or battery failure	Generally positive, with realistic concern about rejection
Social			
Interpersonal contacts	Only sees relatives and close friends	Same as premorbid state	Same as premorbid state
Role			
Role functioning	Unable to work or perform major activity	Premorbid normal, except for constant need for available backup power source	Premorbid normal, except during rejection or infection episodes
Self-care			
(bathing, dressing, etc.)	Severely limited	Able to perform all	Limited in self-care during rejection episodes

Domain/ Concept	Moribund Patients Receiving Conventional Medical Treatment (No MCSS or Tx)	Patients Who Have Received	
		Long-Term MCSS	Heart Transplant
General health perceptions			
Current health	Very poor	Good; accepts battery recharging need; realization of total dependene on a mechanical device	Good except during acute rejection or infection
Discomfort (shortness of breath	Periodic *without exertion*	None	None except during acute rejection
Survival expectancy			
	LE is maximum of 6 mos.	Some risk of MCSS failure; 80% probability of LE > 5 yrs.	Some rejection risk; 70-85% probability of LE > 5 yrs.
B: Hospitalization in ICU/CCU			
Emotional well-being and survival expectancy	Depressed and anxious because prognosis is poor	Good state of mind; considerable anxiety about long-term outcome	Good state of mind; mild anxiety about recovery and future
Social/ interpersonal (visitors)	Only closest relatives	Close relatives and friends	Closest relatives and friends
Discomfort	Moderate	Severe	Severe
C. Regular Hospitilization (not ICU/CCU)			
Emotional well-being and survival expectancy	Some anxiety about recurrence of problem	Good state of mind; some anxiety about future problems	Some anxiety about recurrence of problem
Social/ interpersonal (visitors)	Regular visits from relatives	Many visits and telephone calls	Some anxiety about recurrence of problem
Disomfort	Moderate	Occasional	Occasional

MCSS, mechanical circulatory support system; LE, life expectancy; Tx, transplant; ICU/CCU, intensive care unit/coronary care unit

7

The Appropriate Use of Technology

PREVIOUS CHAPTERS HAVE DISCUSSED specific aspects of decisions that the National Heart, Lung, and Blood Institute (NHLBI) must make in coming years about the artificial heart program. This chapter addresses the appropriate use of mechanical circulatory support systems (MCSSs). These devices present a special occasion: Perhaps never before in the modern history of health care technologies has there been such an opportunity to take steps to promote appropriateness of use in advance of a technology's widespread diffusion. The committee believes that this opportunity should be recognized by all those concerned with MCSSs and with the general appropriateness of technology use as one too valuable to be passed by. The anticipated substantial volume of MCSS use and high cost involved are additional reasons to take such early actions.

The past three decades have seen the development of numerous examples of high-technology health care that have yielded important patient care gains. Yet some appear to have been used inappropriately to varying degrees including, in the cardiovascular arena, percutaneous transluminal coronary angioplasty and coronary artery bypass surgery (Cardiology Working Group, 1991).

In principle, subject to discussion elsewhere of such topics as cost-effectiveness, the committee supports the use of long-term ventricular assist devices (VADs) and total artificial hearts (TAHs) to provide optimal patient care. It is concerned, however, about the possibility of their inappropriate use. If NHLBI were in a position to manage how these devices are used after their approval by the Food and Drug Administration (FDA), this report would include specific recommendations for such activities. However, the

responsibility of NHLBI and other components of the National Institutes of Health (NIH) typically ends with clinical trials designed to demonstrate a technology's safety and efficacy.

An emerging technology is rarely scrutinized to the degree reflected in this report and the previous NHLBI evaluations, and none has been so publicly examined this many years in advance of its routine clinical use. The committee is thus able to express its concerns about inappropriate use becoming a problem area for MCSSs and to suggest how those involved with MCSS development and diffusion can minimize the likelihood of inappropriate use. Further, the interim period until general, widespread MCSS use begins provides an unprecedented opportunity to debate, decide upon, and implement a group of mechanisms to promote their appropriate use.

WHAT APPROPRIATE TECHNOLOGY USE IS

The term "appropriateness" has no special definition when applied to the provision of health care services. Appropriateness of use can perhaps best be explained by viewing it as one important aspect of the quality of care, where quality is defined as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge" (IOM, 1990b, p. 21).

Using this definition of quality of care, appropriateness is one of the elements of quality that links health services to "desired health outcomes"; it is "using what works" (Berwick, 1989). Clinical trials and technology assessments help to define what works by determining efficacy, effectiveness, risks, and cost-effectiveness. All of these are important measures in providing quality care or, as the Institute of Medicine (IOM) definition noted, care that is "consistent with current professional knowledge."

This dissection of quality care into small elements reinforces the importance of appropriate care. Appropriateness becomes the bottom line-using what works, only when it is expected to work, and only with those for whom it is expected to work. Consideration of cost leads to the additional conclusion that appropriate care uses resources to produce more improvement in health outcome than could be achieved by alternative uses of those same resources. Later sections of this chapter explore issues relevant to "using what works."

Several groups have studied appropriateness of use of specific technologies. For example, both Wennberg and colleagues (1988) and Chassin and his colleagues at the RAND Corporation (1987) have focused on variations in physician practice patterns, in particular the overuse or underuse of surgical procedures. Appropriateness is a concept that is applicable to any type of health care technology or service, whether a drug, medical device, or medical or surgical intervention and whether new or routinely used.

The Relationship Between Technology Use and Cost

For almost 15 years (Altman and Blendon, 1979), researchers have linked use-and overuse-of technology to the steady rise in health care costs. In some studies, the technologies involved are low in cost on a per-procedure basis but used in large volumes, such as laboratory tests (Fineberg, 1979). Other studies have examined technologies with high capital costs and perprocedure charges in the hundreds of dollars (Hillman, 1986).

Identifying precisely the portion of the year-to-year increase in total U.S. health care expenditures that derives from the use of new technologies is generally considered impossible (Neumann and Weinstein, 1991), as is separately measuring the contribution of inappropriate technology use to total expenditures. Yet, whether on cost or quality-of-care grounds, attention to improving the overall appropriateness of health care services is warranted.

Factors That May Affect Future Use of New Technologies

Technologies that emerge into routine clinical practice in the coming 20 years face a health care environment very different from that of the 1970s and 1980s. Three major factors will affect technology diffusion. First, capital spending for costly equipment is likely to be more constrained than at any time since the Medicare program's enactment in 1965. Tightening limits on revenue from Medicare prospective payment and similar systems of paying for in patient care on a per-admission basis directly affect the hospital "operating profits" that are a major source of capital-budget funds. Restrictions on year-to-year revenue growth have had a particularly dramatic impact on capital spending by hospitals with per-case costs that are higher than payments received, because of the impact of such losses. This situation may, further, become even more restrictive when the Medicare program eliminates "pass through" reimbursement of capital costs and incorporates them into prospective payment.

Second, hospitals and other providers are likely to resist the adoption of technologies that have substantial operating costs on a per-patient basis especially when, as is typical, the cost is not matched by increased revenue from using the technology. Third, resistance to new technologies will also arise because of efforts by large employers to constrain the cost of health insurance for their employees by imposing restrictions in their plans' benefit structures. Continuing federal and state budget deficits that restrain Medicare and Medicaid expenditure increases will have a similar effect. Yet none of these approaches can be counted upon as an ideal restraining mechanism for a technology such as an MCSS once its clinical effectiveness has been established, because the appeal of its life-sustaining capability may overwhelm these restraints.

Past Failures to Limit Technology Use

Efforts to affect the diffusion of technologies, some discarded and others still in use, have relied on either an aggregate or patient-by-patient approach. The most notable of the aggregate approaches was the health planning and certificate-of-need (CON) program initiated by Congress in 1974 (P.L. 93-641) and still in effect in some states. Its provisions were regulatory in nature, prohibiting hospitals from acquiring major capital equipment, undertaking construction, or opening a new service without a CON from the state health planning agency.

Because P.L. 93-641 did not mandate that states require nonhospital facilities (e.g., freestanding diagnostic imaging centers, physician offices) to obtain a CON before acquiring costly technologies, it had only limited impact on the diffusion of costly technologies such as computed tomography scanners and magnetic resonance imaging systems (Hillman, 1986). In part because of the law's ineffectiveness, federal support of the CON process was terminated in the early 1980s. Most of the states retaining their own CON controls have dollar thresholds set so high that they exert little or no restraint on technology diffusion.

Until recently, few controls have existed over the use of technology in the care of specific patients. Since 1972 legislation (P.L. 92-603), professional standards review organizations, now peer review organizations (PROs), have reviewed the appropriateness of hospital admissions and lengths of stay, but rarely the individual components of the care that is provided. Some PROs now review ambulatory care for other payers, as do many managed care providers and payers, themselves, but their impact on technology use has not yet been examined.

Third-party payment restrictions such as those of Medicare Part B have had some effect on technology use in individual cases, in particular when used in physicians' offices and other ambulatory settings or, for inpatients, when a specific physician fee is involved. This is particularly true where the new technology is clearly identified on claims submitted to third-party payers, but coding of services sometimes does not reveal that an unapproved technology has been used.

Concurrent with overall fiscal pressures, patient-by-patient attention to the quality of the care that is provided-and to its cost-is growing. The share of the total insured population whose coverage is "managed" (e.g., by health maintenance organizations or preferred provider organizations) is likely to increase steadily through the 1990s. Additionally, activities of the Public Health Service's Agency for Health Care Policy and Research (AHCPR) are already stimulating the development of clinical practice guidelines for use in patient care decisions (IOM, 1990a), as well as increased attention to comprehensive studies of treatment outcomes with both new and established forms of treatment.

An important question is whether the mechanisms discussed below are seen by policymakers as sufficient to ensure the appropriate diffusion of MCSSs. If they are not, this technology may well provide both an opportunity and a reason for Congress to review the need for new legislation concerning technology use. Past legislative attempts to manage technology diffusion and use, either in the aggregate or case by case, failed because they did not address the problem broadly enough. From today's perspective of continuing increases in health care costs, legislators may well decide the time has come to formulate new mechanisms that, for the first time, effectively manage the diffusion of MCSSs and other costly technologies.

WAYS TO PROMOTE APPROPRIATE USE OF MECHANICAL CIRCULATORY SUPPORT DEVICES

Because of the cost of implanting a long-term MCSS, this technology is likely to receive at least as much attention from third-party payers, health care providers, and others as any previous technology has received. Even that degree of scrutiny, however, may not suffice to prevent inappropriate use that could have an adverse impact on the quality of care and also increase aggregate health care costs substantially, because of the high per patient cost. Several types of activities can promote the appropriateness of MCSS diffusion and use.

Clinical Practice Guidelines

Developing Practice Guidelines

Under the 1989 legislation that established AHCPR, Congress directed that it arrange for the development of clinical practice guidelines to help in assuring the effective and appropriate delivery of health care (Omnibus Budget Reconciliation Act of 1989, sec. 912). AHCPR sought planning guidance from the IOM, which provided one report to the agency in 1990 (IOM, 1990a) and is currently studying additional issues.

Whether developed under AHCPR auspices, independently by physician organizations, or through other means, practice guidelines covering many clinical conditions are likely to be developed and implemented in the coming years.[1] This activity will be an integral part of a broad range of efforts

[1] In addition to defining practice guidelines as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances," the IOM has differentiated them from "medical review criteria" to be used in *assessing* the appropriateness of care (IOM, 1990a). This committee's discussion of clinical practice guidelines should be construed, however, to include the medical review criteria derived from them.

to improve health outcomes and the quality of care. In parallel with the development and use of clinical practice guidelines, strengthened quality assurance programs (including emphasis on the concepts of continuous quality improvement and total quality management) will represent another means of achieving quality-of-care gains, as will increased levels of scrutiny that can be expected from pretreatment payment authorization programs of Medicare and other third-party payers.

Practice guidelines for long-term MCSS use might be developed by the existing Task Force of the American College of Cardiology and American Heart Association that has developed a number of guidelines for the use of cardiovascular technologies; other organizations in the cardiothoracic surgery or cardiology field might also be involved. These or similar groups could also monitor MCSS clinical effectiveness and revise the guidelines at suitable intervals, as clinical experience gained in the early years of routine use clarifies detailed indications for use.

In contrast to many other technologies, the TAH is a special case because of its life-or-death quality and because once implanted in the human body, its use is irreversible. With both VADs and TAHs, the committee concludes that the development of practice guidelines at an early time is important in promoting the appropriateness of their use. In the committee's view, indications for use should be developed and disseminated as soon as possible. They could be developed on a provisional basis during the time FDA is reviewing clinical trial results, or even during the trial, to be revised later based on clinical-use experience. The early availability of such guidelines, developed by experts and reviewed by key professional organizations, would greatly aid third-party payers in making MCSS coverage decisions. The Medicare program may well take the lead in developing MCSS guidelines, because of its substantial stake in the appropriate use of these devices.

Implementing Practice Guidelines

It is not yet clear what incentives and other implementation techniques will be developed for use with practice guidelines. Whatever is used generally, however, such as educational programs and financial incentives, may not be useful with MCSSs because they are a new technology and will be used, at least initially, in only a few hospitals. In the early years, guidelines for MCSS use will be implemented and enforced by two parallel mechanisms. Third-party payers will apply them when considering physician requests for preprocedure authorizations, and hospitals will also likely oversee MCSS use closely because of the high cost involved and the uncertainty of receiving adequate payments.

Appropriate Use of Other Technologies

Those developing indications for MCSS use should not overlook the need to ensure appropriate use of alternative forms of treatment, such as conventional medical treatment for heart failure. One study, for instance (Walden et al., 1989), found that stable heart failure patients survived as long without a transplant, but with intensive medical management, as did those who received a donor organ. A similar result may also occur, at least initially, with MCSS candidates who, for whatever reason, do not receive an implant. The appropriate use of conventional drug treatment for heart failure should therefore not be overlooked in the rush to use MCSSs.

Technology Assessment

Technology assessment and its frequent component, cost-effectiveness analysis (CEA), are increasingly being recognized as useful in determining the most effective future role for new and emerging technologies. They will often be performed as part of the development of practice guidelines.

When a technology assessment or CEA is performed before the technology has diffused widely, the information concerning the new technology may be at a lower level of accuracy than is the case with technologies already in general use. For this reason, terms other than CEA and technology assessment may be more appropriate for estimate-based studies such as the one performed in connection with this evaluation and discussed in Chapter 6.

Nonetheless, a technology assessment should be an integral part of any effort to oversee the diffusion and use of a technology as complex and costly as this one. By assessing particular MCSSs periodically, the information about clinical effectiveness developed for this study can be verified and updated. Other forms of postmarketing surveillance also are important.

The committee concludes that a technology assessment should be performed as soon as data based on actual MCSS use are available and periodically thereafter. It suggests further that appropriate organizations such as the congressional Office of Technology Assessment and AHCPR be charged with conducting such assessments or ensuring that they are carried out.

Postmarketing Surveillance

Postmarketing surveillance of safety and effectiveness after FDA approval for general use, one aspect of scrutiny of a technology, occurs to a limited extent with both new pharmaceuticals and medical devices but not with new surgical procedures that do not involve specific devices. For pharmaceuticals and medical devices, the manufacturer is obligated to re

port to FDA certain adverse reactions and product-related deaths, serious injuries, and malfunctions that have the potential to cause death or serious injury; under 1990 legislation, medical device users will be required to report device-related deaths and serious injuries. New surgical procedures are, of course, developed and diffused throughout the surgical community with no governmental oversight other than what is provided indirectly by providers' quality assurance programs and third-party payers' case review procedures.

These formal requirements reveal unsafe performance more effectively than they identify changing levels of a new technology's clinical effectiveness. Additional requirements may therefore be appropriate and should be considered for MCSSs and similar implantable, life-supporting devices. A 1990 law requires manufacturers of implanted devices to submit a formal postmarketing surveillance protocol for FDA approval after review by an independent review group.

One manner in which routine surveillance can be accomplished is through the use of a patient registry to which physicians who use the device submit data pertaining to specific patients, both at time of implantation and after each follow-up visit. The committee concludes that a registry of long-term MCSS use is highly desirable and suggests that interested parties jointly explore possible mechanisms by which it might be established and funded.

Registries have been created for two cardiovascular technologies, cardiac pacemakers and percutaneous transluminal coronary angioplasty. The latter was supported primarily by NHLBI, at a cost of about $350,000 per year. The current era of severely constrained federal budgets, however, makes it difficult to envision a major commitment to support another registry on the part of either NHLBI or FDA. Other funding means must therefore be considered. The most feasible alternative is probably a registry that is funded, as part of the cost of the implantation, through payments by hospitals when they purchase each device. Further, because of the value of registry data to third-party payers, they could consider making their agreement to pay particular providers for MCSS implantation conditional on the provider's participation in a registry; see the discussion of selective coverage, below. Such arrangements could also provide explicitly for payment levels that support the registry's operation, in recognition of the indirect benefits to payers. Specific provisions as a part of physician fee structures also would enhance future submission of information to the registry by physicians.

A registry's value will be enhanced by consistent, accurate reporting of clinical and technical data both at the time of MCSS implantation and at regular intervals thereafter, if those involved in creating the registry agree in advance on a detailed protocol for data collection by each implantation

and follow-up site. The periodic visits that all MCSS patients will make, to have the performance of their device checked, offers an easy, efficient opportunity for collecting both clinical and quality-of-life data on a continuing basis.

In addition to physician and hospital participation, patients could be asked, as part of the process of granting informed consent to implant the device, to agree to provide periodic information to the registry, such as by responding to questionnaires when visiting their physician or hospital for a device checkup, or through telephone interviews. Patients cannot be required to provide such information but, if the benefits to society at large from their participation are explained adequately, most patients would likely agree to cooperate.

Follow-Up Studies

Clinical trials of new implantable medical devices typically provide for a two-year postimplantation follow-up period, but this is not long enough, with life-sustaining technologies such as an MCSS, to reveal all possible problems. Further, neither a registry nor routine FDA-required postmarketing surveillance is likely to reveal all long-term risks and complications because these mechanisms record only limited information.

Comprehensive long-term follow-up studies are very costly if done properly, and could probably be conducted only with a sample of all persons receiving MCSSs. Nonetheless, NHLBI should support such long-term studies for patients in the clinical trials that it funds, and AHCPR should support studies of patients who later receive an MCSS. A registry, if established, could be used as a pool from which patients can be drawn for more detailed follow-up studies.

Funding of follow-up studies must be adequate to support study designs that have sufficient statistical power to reveal serious problems with the technology. They should also be designed to compare MCSS outcomes with those of alternative forms of treatment such as conventional medical treatment. The level of funding should support periodic measures of patients' quality of life and other nonphysiologic factors, without reducing the amount or quality of the general clinical data that are gathered.

Credentialing for Technology Use

A relatively recent development in managing the use of complex technologies is the formulation and implementation of appropriate requirements calling for specific levels of training and experience, and their documentation, before a physician is allowed to use a new medical device (ECRI, 1987). The committee recognizes the importance of such guidelines as a

means of ensuring patient safety as well as enhancing appropriate technology use but acknowledges that the concept has, by no means, met with wide acceptance and use.

Most credentialing guidelines have been developed by physician organizations and are intended for nationwide use, but their application usually relies on the individual hospital or other provider and its system of clinical privileges. Such guidelines typically apply to new medical devices and surgical procedures. In contrast, the use of new pharmaceuticals is controlled by the item's unavailability until approved by each institution's "pharmacy and therapeutics" or similar committee for entry into its formulary.

The physicians involved in a particular MCSS's development and clinical trials will likely be the early trainers of additional physicians in using the device; these physicians, perhaps through their specialty societies, are the most logical individuals to develop training and experience requirements. Once such guidelines are adopted and disseminated, individual hospitals can and should apply them to limit users of the device to those physicians who are deemed qualified. Third-party payers can also apply them to formulate and announce policies under which they would refuse advance authorizations for unqualified physicians to perform MCSS implantations. Such restrictive payment practices have rarely been applied by third-party payers but are particularly appropriate for a costly, life-sustaining technology of the nature of MCSSs.

Selective Coverage

The Medicare program and several third-party payers in the private sector have developed selective coverage programs applicable to heart transplantation and other high-cost technologies, in effect an extension of the physician credentialing concept to the hospitals in which they practice. These programs achieve a quality-related goal by limiting payment for technology use to specific institutions, sometimes referred to as "centers of excellence," that meet explicit staffing requirements and can document experience (e.g., patient volumes, specific minimum survival rates) with use of the particular technology. Improved safety and quality of care as a result of regular use of the technology by physicians and other health professionals also support this goal. A second goal relates to the lower cost that results from concentrating the service instead of having it offered widely, motivating third-party payers to develop these programs and institutions to offer favorable payment rates.

The selective coverage concept can include provisional approval, based on an institution's experience with analogous types of care. If this is not done, each institution must initially use the technology only with patients who pay for their own care or must somehow absorb the cost of the initial

cases, in order to build the experience base required for selective coverage approval.

In implementing selective coverage, especially if it is to be adopted by numerous health insurers, consistency of criteria on such issues as minimum volumes and provisions for reasonable geographic access is important. To date, however, each insurer has developed its own program details.

The committee concludes that programs of selective coverage for the implantation of long-term MCSSs are desirable. It suggests that third-party payers cooperate in developing coverage policies for MCSS use, recognizing such possible constraints as antitrust laws.

INVOLVING THE RIGHT PARTICIPANTS

Mechanisms to oversee technology use have traditionally been developed in closed processes by either physician groups or third-party payers. With rare exceptions (e.g., Blue Shield of California's Medical Policy Committee, as described by Schaffarzick [1985]), only members or employees of the organization developing the mechanism participate in the process.

The current attention to clinical practice guidelines is causing a reexamination of the past process of developing such measures in private. It is premature to describe the procedures by which diverse parties (including patients) will come to be involved in developing guidelines. Practice guidelines are, however, almost certain not to remain the private preserve of individual organizations, at least not those guidelines formally recognized by AHCPR.

The committee expresses the hope that all activities to promote appropriate MCSS use will be formulated by widely representative groups. Others can also be involved through mechanisms such as advisory committees and public hearings on proposed guidelines.

Certainly, the clinicians and researchers involved in developing MCSSs and in clinical trials are important participants in guideline development because of their intimate knowledge of the devices' impact on patient care. Other less obvious participants should include other physicians and allied health professionals, personnel from NHLBI's artificial heart program, representatives of third-party payers, health services researchers, economists, ethicists, and either MCSS patients themselves or others (e.g., family members, caregivers) who can speak from that perspective.

NIH institutes have not usually participated in overseeing the diffusion of new NIH-sponsored technologies, beyond the consensus development conferences held periodically by the NIH Office of Medical Applications of Research about various diagnostic and therapeutic technologies. The depth of NHLBI's involvement in developing MCSSs is, however, a strong argument for its personnel's participation in formulating mechanisms for

these devices' appropriate use. NHLBI's mid-1980s role in formulating guidelines used to approve heart transplant programs for participation in Medicare serves as a precedent for the agency's involvement in clinicaluse issues. NHLBI officials could also aid in promoting the appropriateness of MCSS diffusion and use by interpreting to AHCPR the reasons that the latter agency should accord high priority to developing guidelines for MCSS implantation and to supporting posttrial studies of MCSS use.

AVOIDING UNREASONABLE PATIENT EXPECTATIONS

To a considerable extent, the public's expectations about MCSSs will be shaped, not by what cardiologists and cardiothoracic surgeons tell patients and their families, but by how the use of these devices is described on television and in newspapers and magazines. MCSS developers and clinical trial investigators have a particularly difficult task ahead, as trials of longterm devices begin. The privacy of patients and their relatives must be respected, but somehow balanced with the public's interest in each patient's day-to-day progress.

Investigators, device developers, and reporters all have roles in portraying the potential and the limitations of these devices realistically. A patient's ability to get out of bed soon after receiving an MCSS may have little or no bearing on long-term survival prospects, and media representatives should be helped to appreciate that long-term results are the true test of the technology's value. Similarly, those involved directly with the sale and implantation of MCSSs have a natural incentive to portray the technology in a positive light. Others knowledgeable about MCSSs, such as representatives of medical specialty societies and NHLBI, may sometimes find it appropriate to offer counterbalancing statements to the media.

In the early years of MCSS clinical trials and routine use, the degree to which reporters and commentators understand this technology's potential and limitations and reflect that understanding to their viewers and readers will have considerable influence on the appropriateness of MCSS use. Public attitudes on the part of such key individuals as union leaders, business executives, and elected officials will likely be influential in early coverage decisions by third-party payers. Only when a large body of clinical data is available will decisions become more readily based on evidence of longterm patient outcomes and quality-of-life gains.

All concerned can learn from the TAH experience of a decade ago (Blakeslee and Shaps, 1986; DeVries, 1988) and plan accordingly. A reasonably informed public will be the best environment for developing reasonable policies about MCSS use.

SUMMARY AND CONCLUSIONS

Each of the mechanisms discussed in this chapter is important in promoting the appropriateness of the use of long-term circulatory support devices. If the law governing FDA allowed it, this committee would recommend that FDA approval of MCSSs for general use be withheld until such measures can be developed, supported financially, and implemented by the relevant parties. The timetable for MCSS development does, however, permit other sectors of the health care community to respond to the concerns and suggestions expressed here. Ample time exists before the first model of a long-term VAD goes into wide use in the late 1990s, and the TAH in perhaps 2005 or 2010, to formulate and implement mechanisms that promote appropriate MCSS use and reduce the likelihood of inappropriate use.

The committee would be reluctant to advise NHLBI to continue its support of MCSS development if it believed that substantial inappropriate use of these devices would occur. The committee regards this eventuality as unlikely, but is nonetheless concerned about what it perceives as the possibility of even a small amount of inappropriate use. It therefore encourages all essential participants to join in the activities discussed in this chapter. VADs and TAHs should benefit the patients who most need them and, at the same time, not excessively burden the nation's health care system with unnecessary expenditures as a result of inappropriate use.

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8

Ethical and Societal Issues

> [D]ramatic, "big ticket" treatments like kidney dialysis and transplantation-or the implantation of an artificial heart at the University of Utah Medical Center in late 1982—are not yet the major strains on the health care budget, but they do crystallize the ethical issues posed by limitations on society's resources. The Commission concluded that these issues cannot be avoided by the sort of response— "give everyone all they need"—that was used for kidney failure. Instead, the Commission turned to the ethical principle of equity. This principle is always a hard one to know how to apply . . .
> —President's Commission[1]

THIS CHAPTER IS ARRANGED in three sections, each addressing aspects of ethical and societal issues in future decisions by the National Heart, Lung, and Blood Institute (NHLBI) about research and development funding allocations in the artificial heart program. The first section provides background on the societal issues of justice that are raised by those complex medical technologies designed to sustain life that are here characterized as "incomplete." These technologies reduce the effects of a disease but neither cure nor totally resolve the underlying condition. Because many of these technologies are in wide use and no longer under development as is the fully implantable total artificial heart (TAH), experience with them can shed light on the ethical and societal issues raised by the TAH.

The second area of concern is ethical issues that the TAH specifically raises for NHLBI and society. Epidemiologically, heart disease is the primary cause of death in the industrialized world. Physiologically, the heart is perhaps more immediately critical than other major organs; the functions performed by the heart are necessary on a minute-by-minute basis. Finally, the heart is an organ with great emotional, symbolic, or religious meaning for most people. For all these reasons, in study after study and commentary

[1] Page 74, President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (1983).

after commentary, terms such as "alluring" are used to describe this technology's potential to reduce suffering and death from heart disease. Because many patients cannot be helped by any technology other than a TAH, the questions of who should and who can have access to the device become critical. The second section of the chapter addresses issues directly pertinent to the TAH such as ethically determining and providing access to care, and developing criteria for use in clinical trials and routine medical practice.

In the final section, methods of protecting individual patients' autonomy are considered in the context of clinical trials and routine use. These issues include the informed consent process, use of advance directives, and NHLBI funding as a means of promoting appropriate clinical investigation and use of new mechanical circulatory support systems (MCSSs).

Although this chapter specifically refers to the TAH, most of the ethical principles discussed, such as the equitable allocation of resources and required informed consent, also apply to long-term ventricular assist devices (VADs). Ethical issues concerned with temporary or bridge use of MCSSs, however, such as their effect on the distribution of donor hearts for transplantation, are not considered. These issues have been examined in detail in other contexts (Annas, 1985; Robertson, 1987; Miles et al., 1988) and are likely to disappear if long-term devices are proven effective and become available for general clinical use.

ISSUES RAISED BY INCOMPLETE TECHNOLOGIES

Health care technologies differ in many ways such as purpose, necessity, ease of use, stage of development, cost, and effectiveness in improving patient longevity and quality of life. One approach to differentiation within a taxonomy of health care technologies is to consider the subset of "incomplete" measures that partially treat or palliate critical medical problems in individuals.[2] The focus here is on those incomplete technologies—ranging from cardiac pacemakers to bone marrow and other types of transplantation to dialysis for end-stage renal disease—whose costs, given finite national resources for health care, raise particular questions about their appropriate and equitable use. Under this category of equitable and appropriate use are decisions about the distribution of benefits and costs, as well as questions about the procedures or mechanisms for ensuring access to the benefits. Whether, how, and in what fashion to make such technologies available

[2] Complete technologies, in contrast, satisfactorily resolve a disease state. An illustration of a complete technology is gallbladder removal, which restores full function to the patient, whereas an incomplete technology might relieve suffering from the disease once it becomes evident.

has raised basic questions about the just distribution of finite benefits and inevitable burdens within a community.

How does a nation ethically distribute benefits and burdens? In its conscious efforts, the United States uses a democratic process (Bellah et al., 1985; Engelhardt and Wildes, 1991). Through mechanisms ranging from established procedures (e.g., legislation, congressional representation, executive decision) to the accumulated precedent of specific decisions, a national consensus or status quo is reached. Such actions are usually influenced by a range of ethical principles such as the desires to avoid doing harm (nonmaleficence) and to do good (beneficence), the just distribution of benefits and burdens, and respect for individual autonomy, as well as by other concerns that can be based on national, individual, or special group interests.[3]

Overall questions of societal priorities, such as the portions of government resources devoted to health care, education, support of the arts, or interstate highways, are not considered here. These are most appropriately determined or influenced by the national political process, and they are beyond the purview of NHLBI or the Institute of Medicine (IOM). Ideally, decisions about allocating federal funds for health care would start with a unified process for determining the proportions of funding for general societal benefits, such as those provided through community-based health measures, and for individual needs, such as those met with incomplete technologies. Currently no such national priority setting is used.

The charge to the IOM committee was to help NHLBI determine whether, and in what amounts, funds should be allocated to continuing the development of TAHs. In determining the appropriate level of federal R&D funding for TAHs, it became necessary to go beyond the issue of resource allocation and consider the societal issues that will arise should TAHs be developed and become available to the public. The NHLBI artificial heart program has been evaluated six times since its inception; it is, perhaps, the most persistently scrutinized program of the National Institutes of Health (NIH). In part, the impetus behind the long-standing discomfort with the NHLBI artificial heart program can be attributed to the recognition that some planning for, and control over, the use of this technology is needed. Such

[3] Four principles—nonmaleficence, beneficence, justice, and autonomy—are recognized as general guidelines for moral action. They also identify several approaches to the issue of justice. The *egalitarian philosophy* emphasizes equal access to those goods that all rational people desire; this philosophy therefore focuses on procedural guarantees of access. *Libertarian and Marxist theories* both emphasize the rights of individuals, with libertarianism focusing on the individual's contribution or merit and Marxist approaches focusing on the individual's needs. *Utilitarianism* applies a mix of criteria so as to maximize public and private utility (Beauchamp and Childress, 1979).

concerns are included in these deliberations, as they were in previous expert assessments of the artificial heart program, because they were significant enough to directly impinge on the committee's ability to address the question of funding allocations.

Specifically, the committee felt unease at the lack of mechanisms for considering the appropriate use of approved TAHs. Health priorities cannot be effectively or reasonably set if the issue under consideration is limited to R&D funding allocation decisions; this is, however, the level at which decisions to continue or halt development are made. As economic constraints become increasingly urgent, gaps in the existing decision-making processes may lead to the use of R&D funding decisions, such as the one under consideration by the committee, as a "last-secure-stopping-point" (Blumenthal and Zeckhauser, 1984). A decision of this nature would limit development and use of the TAH not on the basis of its value, but in an attempt to determine or safeguard national health priorities.

An extreme option considered by the committee was to recommend a halt to NHLBI funding for any TAHs or VADs, on the ground that they are simply too costly to society. Such a decision would indicate that, as a matter of public policy, it is preferable that people die of heart disease than that federal funds be applied to artificially sustaining them at so high a cost. This option, however, raises troubling questions about justice and national priorities for health care. Given its relative lack of ethical expertise, the committee did not feel comfortable making, without a clear national mandate to do so, a recommendation that would potentially affect national policy and thousands of lives. There was, moreover, some question about the acceptability of such a recommendation given "the rule of rescue," a societal tendency to demand that the utmost be done for identifiable individuals who are in critical need (Jonsen, 1986a).

Lester Thurow describes the current dilemma faced by the health care system in allocating expensive incomplete technologies as

> a very high stakes game of Old Maid, where everybody wants to shuffle the deck in such a way that they don't have to tell the patient the bad news. The bad news is, there's something that might be done to help them but we can't, as a society, afford to give it to them. Everybody wants to be in a position to force somebody else to . . . deliver that nasty message.

He continues by pointing out that, far from being simply considerations of economic concerns, these are "ethical questions constrained by economics" (Thurow, 1988, p. 71). For technologies with great potential impact on national priorities and spending, the balance of individual and societal interests must be considered if we are to avoid proceeding blindly or halting the development and use of viable, useful technologies. Health care pri

orities that only become evident in retrospect still function as priorities; they have distributive consequences as substantive as any policy determined through more deliberate or conscious means. As a nation facing increasing economic constraints, we cannot continue to sacrifice optimized and ethical results for the comforts of a pay-as-you-go system.

The inadequacies of the decision process for developing and using technologies such as the TAH mean that R&D allocation decisions inappropriately carry some of the weight of decisions about the technology's use. Either directly or indirectly, NHLBI's decisions about the allocation of public resources for TAH development will respond to the issue of national health priorities. It is therefore part of NHLBI's responsibility as a funding sponsor to encourage other health care policymakers to examine these questions.

Maximizing Benefits in the Provision of Health Care

> Our objective is to use the available resources as efficiently as possible to maximize the health (measured in terms of length and quality of life) of our population. To achieve this objective, decisions about the development or use of a procedure must consider the extent to which the procedure contributes to that objective (its effectiveness), and how efficiently the procedure achieves the objective (its cost-effectiveness) ... This fact creates a burden on anyone who attempts to set policies to guide the use of a procedure. The burden exists for any procedure, but is greater and more urgent for an expensive and potentially widely practiced procedure .... [T]he crucial question is whether there are other things that could be done with the resources that would yield greater benefit. (D. M. Eddy in NHLBI, 1985, p. 56)

As stated above, maximum benefit from the use of resources is desired. But benefits differ and their assessed value is usually shaped by the specific criteria used. Cost-effectiveness as a criterion, for example, is not the only measurement for equitable or appropriate use of resources. In societies based on different ethics, options preferring certain groups such as the sick or poor might be based on effectiveness, without necessarily being based on cost. Measures of benefit alone and cost-effectiveness analysis of several options might result in ethically different and even contradictory conclusions.

But criteria for measuring benefit are needed. Because cost-effectiveness is more objectively determined than benefit, and because it is an economic concept that can be applied in an ethical context, it offers NHLBI a quantitative approach to ethical questions that also uses units of evaluation-dollars-that are within NHLBI's area of responsibility. Despite the lack of answers to such larger ethical questions as the nation's priorities

for health care, NHLBI can appropriately apply cost-effectiveness analysis as a way of helping to address moral and ethical questions.

Criteria other than cost-effectiveness are also relevant, however. This section of the chapter will suggest which criteria are most notable in specific situations. Leaving payment and reimbursement aside, among the often used criteria in health care are the urgency or immediacy of the need and concerns about equitable distribution and use of resources. These and other criteria are relevant to varying degrees, depending on specific goals.

In the provision of care, urgent need is often separated from overall considerations of potential benefit; issues of finite resources or cost-effectiveness are seldom considered in individual cases. The result is an obscuring of both the need to consider multiple goals—helping specific people in immediate need and helping overall improvement of a population's health—and the question of how to maximize both goals.

The difficulty of evaluating benefits can be demonstrated using the differences between incomplete technologies and public health interventions that have broad demographic results. Incomplete technologies offer treatment to individuals who can no longer, and in some cases never could, benefit from public health or preventive interventions. Furthermore, they help individuals who are dying now, whereas public health measures help people who do not appear to be in immediate need. Both approaches are necessary, for both improve health and neither can completely replace the need for the other. But the different "faces" of these approaches can create a disjunction in the perception of need or a lack of attention to criteria such as relative cost-effectiveness. Compared with the urgency of emergency room treatment or implantation of an MCSS in a dying patient, public health measures such as better sanitation, vaccinations, or smoking cessation programs may appear less immediately necessary. Nevertheless, it can be argued that general public health measures usually provide greater overall benefits to a population.[4]

In addition to need and cost-effectiveness, overall substantive justice must be carefully considered. Recent research suggests that, among patients with ischemic heart disease, there are racial variations in the use of

[4] With public health measures such as improved sanitation, the benefits to a population probably have a highly favorable cost-effectiveness value when compared with treatment of diseases. With preventive measures such as vaccination, screening for hypertension, and lifestyle changes, however, a comparison of cost-effectiveness ratios results in the conclusion that "sometimes prevention buys more health for the money; sometimes cure does" (Russell, 1986, p. 111). In general, Russell concludes that prevention provides additional health benefits at additional costs. Decisions should not, however, be based on the assumption that preventive measures are either free or a bargain but, she says, on whether they are the appropriate choice for a particular situation.

cardiovascular procedures such as coronary angiography and coronary artery bypass surgery (Wenneker and Epstein, 1989). If such inequities of access exist, applying only the criteria of cost-effectiveness and immediate presenting need ignores a critical concern.

The various goals of providing health services-including cost-effectiveness, meeting individual needs, and the equitable provision of care-must be considered, along with their differing criteria and mechanisms for access, in a national decision that will balance health costs and benefits between (1) identified individuals with critical needs and (2) overall improvements in the health of the population. The committee was assembled to consider the costs and goals of a specific federal program, the NHLBI artificial heart program. In the process of answering this question, it calls attention to an issue beyond its scope of work or expertise: the need for developing national priorities for the allocation of resources within the health care system.

Conceptualizing Access to Incomplete Technologies

The different levels of benefit in health care elicit varied solutions to the problem of equitable and appropriate access to health technologies. One approach argues against investment in, or coverage for, extremely expensive new technologies on the grounds that the money might be more efficiently used in other areas of health care such as public health measures. Another perspective, noting the piecemeal, de facto nature of funding and reimbursement (Rosenthal, 1979), is that money is not necessarily fungible between the different levels of health care and that prioritizing and funding decisions should be made within categories of technologies with similar purposes.

Given this second argument, the approach to the category of incomplete technologies has significant consequences for the questions of equity and access. On the one hand, if incomplete technologies are seen in a historical and legal framework, policymakers might consider it more important to be consistent and equitable than to weigh the effects of such individual decisions on total spending for expensive incomplete technologies. Such an approach is evident in the argument that TAHs should be available to all who need them because renal dialysis is available. This approach, however, does not recognize the fact that health care resources are, and will always be, limited.

On the other hand, if incomplete technologies are seen as a necessarily limited segment of health care efforts and their costs-perhaps defined as a rough proportion of all funds spent on health care-then the most beneficial technologies within the category should be funded, with benefit measured using various indicators such as relative cost-effectiveness, need, and

existing inequities. This "limited resources" model would parallel the peer-review system for awarding NIH research grants where, as funds become available in a fiscal year, the most highly valued forms of research are financed until there is no more money.[5]

Proponents of the legal, individual-focused model would argue that, if dialysis and the TAH are within the same magnitude of costs and costeffectiveness, TAHs should be available to patients with end-stage heart disease. Conversely, if the limited resources model is applied, current funding of the end-stage renal disease program might militate against the development and provision of TAHs, at least with federal funds, on the grounds that we cannot afford it at this time. Consideration of both models might lead to the establishment of options for reconciling them, such as a comprehensive nationwide or statewide position on access to selected incomplete technologies.

In *Habits of the Heart* (1985), Bellah, Madsen, and colleagues argue that individualism, and not equality, is the preeminent value in American society. Our traditions encourage us to think of justice as a matter of guaranteeing equal opportunities and access for individuals through laws and political procedures, and as a consequence we have become knowledgeable about procedural and even distributive justice. They suggest, however, that such an approach does not guarantee substantive justice, which considers the overall societal effectiveness of procedural and distributive guarantees when resources are limited and there are competing valid demands. This committee was not constituted to resolve such major issues on the nation's health care agenda, but it does urge that attempts at their equitable resolution become a high-priority agenda item for the appropriate federal and state policymakers.

[5] Although the NIH peer-review system could serve as an example for determining priority levels within the category of incomplete technologies, several immediate considerations come to mind. First, peer-review study sections concentrate on specific research disciplines. Multidisciplinary approaches would have to be developed for considering a range of technologies (IOM, 1990, pp. 92-100). Such ranking of a range of technologies according to criteria is currently being done, on the state level, in Oregon. Second, a review process for determining the appropriateness and merit of technologies would have to be based on stated national priorities. Setting these priorities would, perhaps, be best carried out by a standing national commission. Third, the category of "peers" would undoubtedly have to be expanded to include citizens other than physicians, researchers, and ethicists. National or state priorities should be set with adequate consultation of many sectors of the community, including at a minimum the elusive "average citizen," legislators, and most particularly those directly affected by the decisions. Involving representatives of these groups, particularly the last one, may be difficult: the Oregon initiative has experienced some difficulty with this and has had to set Medicaid priorities with only limited input from actual Medicaid recipients.

ISSUES RAISED BY THE TOTAL ARTIFICIAL HEART

Access to Total Artificial Hearts

If the overall consideration of incomplete technologies raises issues of substantive justice, the specific case of the TAH raises issues of procedural and distributive justice such as how, ethically, to define and assure adequate access to the device. The technology is the only possible life-sustaining treatment for certain end-stage heart disease patients, and most individuals will not be able to afford it without Medicare or other third-party coverage. Because the TAH is still in development, whether such coverage will be forthcoming has not been determined and the likelihood of adequate coverage is uncertain. A critical issue is whether developing the TAH is in the public interest if a substantial portion of the insured public will not have access to it.

If access to the TAH is determined, either as a matter of national or state-level policy or through Medicare and other third-party coverage decisions, to be within the definition of adequate or basic care called for by the President's Commission (1983), another question remains: Should access to TAHs be provided to the more than 30 million citizens with no health insurance? If so, yet another question arises: Would adequate care include, for example, replacement of the device, which in initial clinical use would be needed every two to five years? Decisions on these types of questions will be made, either explicitly or indirectly, but the committee's conclusions about the allocation of NHLBI funds are not equivalent to conclusions about whether the artificial heart falls within the category of basic care.

If basic or adequate care is defined to include access to the TAH for certain individuals in need-that is, ethical access is assured within categories of clinical appropriateness-or if funding of TAH development continues for other reasons, the interim period before routine availability of the TAH should be used to improve those individuals' procedural access to health care and to facilitate more systematic and consistent third-party decision-making processes. Considerations would include equitable access and use across socioeconomic, ethnic, and racial categories for those with equivalent clinical indications for use, equitable geographic availability, and reduction of nonmonetary restraints on availability such as limited numbers of facilities and personnel able to provide such care.

The case of the artificial heart offers a significant, previously unavailable opportunity: a test case for managing the application of a health care technology. Defining and controlling appropriate access to such a technology prior to its first clinical use has never been possible. Legislators and policymakers at state and federal levels should begin, now, to decide

about equitable access to MCSSs and other technologies by establishing commissions or other broadly based groups to aid in making those decisions. If access decisions are made on a state-by-state rather than national basis, then an adequately funded organization or mechanism should be established to provide information and assistance to such state decision-making processes. With the knowledge already accumulated about the TAH, and the 15 or so years before it is generally available, the TAH becomes an unprecedented potential case study.

Criteria for Use

Ensuring appropriate access includes the identification of research subjects and patients using an equitable process. Patient use criteria are necessary for investigational clinical trials, and the Stanford University heart transplantation program has established selective criteria that may be relevant for MCSS use (Christopherson, 1982). Criteria for routine MCSS use, however, will be more exclusionary than selective for two reasons. First, MCSSs are not a limited resource, like donor hearts. Rather than choose among potential recipients, as in a clinical trial, criteria for general clinical use will exclude those patients who clearly would not benefit from MCSSs (Jonsen, 1984; Parker et al., 1990). Second, routine MCSS use will be largely determined by third-party coverage. Health insurance coverage will therefore be a critical exclusionary criterion.

Use of a strict upper age limit for determining eligibility for MCSS implantation is inappropriate unless such an age limit addresses only extreme cases; MCSS implantation in a 90-year-old patient, for instance, seems an extreme case. But on an ethical level, age should not be used to categorically define or regulate access to care. On a pragmatic level, chronological age may indicate relatively little about the potential benefits of an MCSS to an individual and may be far less significant than factors such as medical condition, comorbidities, and other available interventions. Appropriate and significant clinical benefit to the patient should be the overriding consideration in determining the appropriateness of individual MCSS use, and indications for use should be cooperatively developed by clinicians, third-party payers, and others, as discussed in Chapter 7.

If MCSSs become available for routine clinical use, third-party payers rather than individual hospitals and physicians are likely to determine whether specific patients receive them. This identification of patient eligibility will be performed through the mechanism of prior review for each case. History tells us, however, that the availability of a health care option can be quickly transformed into a right without sufficient reference to clini

cal appropriateness. This is particularly likely with the TAH, a life-saving technology of great symbolism and visibility. As noted by the President's Commission, the ethical imperative to provide adequate or basic care does not guarantee the provision of sufficient care. The committee reiterates the importance of using explicit clinical criteria to define appropriate use on an individual level, and using the goals of equitable and appropriate access and use to define overall access.

Aggregate Societal Costs

Because of its cost, the eventual levels of TAH use will be highly responsive to coverage and reimbursement decisions by Medicare and other third-party payers (see also Chapter 4). Depending on the clinical indications for use and third parties' coverage criteria, adequate coverage for VADs and TAHs could add several billions of dollars annually to national health care expenditures. Such factors are not usually considered in R&D allocation decisions because they are most appropriately addressed at the federal level by Congress, the Department of Health and Human Services, or other policymaking bodies, or at the state level by legislatures and health departments.

Another possible broad impact from the use of long-term VADs and TAHs is the potential cost to society of prolonging the lives of tens or even hundreds of thousands of individuals. This issue was reviewed by the National Heart and Lung Institute (NHLI) Artificial Heart Assessment Panel (NHLI, 1973). Consideration of the nation's unemployment and underemployment levels is beyond the committee's scope and expertise, but it must note that the prospect of MCSS recipients returning to the work force does not appear great, particularly if they were disabled by heart disease for some time before receiving the MCSS.

In concluding this section on societal concerns, a final comment: Clarity about the various goals of TAH development and use is necessary when considering the issues surrounding access and appropriate use. In his addendum to the NHLI 1973 report on the TAH, Havighurst notes that "society's humanitarian [self-]image" is often served by providing highly visible benefits to identifiable individuals in order to preserve the "myth of life's infinite value" (NHLI, 1973, pp. 243-244). This "rule of rescue," or impulse to save identified lives-which does not necessarily encompass concern about the quality of that life-will be a powerful factor in future decisions about MCSS use (Jonsen, 1986a; NHLI, 1973, pp. 231-247). The appropriateness of clinical use of the TAH to reinforce a symbolic valuation of human life should not go unquestioned in decisions about appropriate access and distributive justice.

PROTECTING THE INDIVIDUAL PATIENT

Informed Consent and Advance Directives

The issue of patient autonomy, both generally and in reference to the TAH, has been well addressed in the bioethical literature[6] and in previous reports on the TAH. Informed consent is designed to ensure, as much as possible, that patient choices about treatment are autonomous, informed, and in accordance with their personal values. Although the concept of informed consent is supported and partially defined by the law, meeting the legal definition of informed consent is a starting point, not an assurance of having conducted the consent process in an ethical and complete fashion. In both clinical trials and routine TAH use, an individual's informed consent must result from a careful, explicit, and accountable process.

Patients such as those considering a TAH are seriously ill and faced with difficult choices; their capacity for objective, considered consent will be impaired. Consent should be obtained through a series of discussions, over time, to assure adequate understanding of alternative and palliative therapies, risks and benefits, and long-term effects of treatment, as well as clarification and communication of the patient's preferences and values.

The patient's preferences about discontinuing use of the TAH should be explicitly examined and, as well, recorded in an advance directive. The specific, personal considerations associated with such a decision (including clinical condition, prognosis, and procedures to be performed) should be clear for the patient, health care providers, and a proxy or surrogate decision maker. This advance directive will ensure future treatment in accordance with the patient's preferences and will reduce emotional distress and guilt for loved ones, close friends, and the medical professionals providing care (Engelhardt and Wildes, 1991).

To further the likelihood that the patient's wishes will be carried out, each patient should also consider executing a durable power of attorney. "Durable" signifies that a trusted relative or representative is legally authorized to make treatment decisions in accordance with the patient's wishes,

[6] "The most general idea of autonomy is that of being one's own person, without constraints either by another's action or by a psychological or physical limitation.... To respect autonomous agents is to recognize with due appreciation their own considered value judgments and outlooks even when it is believed that their judgments are mistaken. To respect them in this way is to acknowledge their right to their own views and the permissibility of their actions based on such beliefs. And to grant them this right is to say that they are entitled to such autonomous determination without limitations on their liberty being imposed by others." (Beauchamp and Childress, 1979, pp. 57-58; see also Shaw, 1984)

should the patient be unable to do so.[7] Any patient, and any person acting according to the patient's wishes through a power of attorney, should be able to make explicit choices about treatment, including termination of treatment (President's Commission, 1983; Schiedermayer and Shapiro, 1989).

In the context of informed consent, prior directives, and powers of attorney, issues of patient-physician interactions must be carefully considered. As examined by Katz (1984) and by Annas (1987) in the situation of the first experimental human uses of long-term MCSSs, the hopes and understandings of physicians and patients can become intertwined in a complex manner, amounting to a situational transference brought about by the risks, fears, hopes, and mutual dependencies of both the patient and the physician.

Table 8.1 delineates, for patients, researchers, and physicians, considerations for decision making about MCSS use. Emotional transferences are always a consideration in the physician-patient dyad, particularly with the use of life-saving technologies, but they require particular scrutiny during experimental or investigational use when the researcher and the patient have somewhat divergent goals. As shown in the table, the purpose of investigational use is to evaluate the device by determining benefit under controlled conditions. This is, however, a statement of the goal shared by the researchers and patient. The patient has a prior, preemptive goal of improving survival or quality of life and is dependent on the researcher for care, continued survival, and hope. The researcher, by contrast, is dependent on the patient for continuation of the trial. The noncomplementary interdependencies of patient and researcher should be a constant consideration in the clinical trial consent process.

All the above factors diminish the patient's ability to consider consent fully. A disinterested observer should therefore be involved throughout the presumably lengthy discussions before the granting or denying of consent and determining of advance directives. In the case of clinical trials, a mechanism to ensure ethical oversight is the hospital institutional review board. Such an entity should ensure that, even as a last resort in the treatment of seriously ill patients, investigational use of a device or a technique such as xenografting is not undertaken without a legitimate foundation for research, a clear, objective anticipation of benefits, and informed consent for each event in the process of medical care.

[7] Various legal documents for creating a durable power of attorney exist; a recent collaborative effort in Massachusetts, for example, resulted in a single-sheet "health care proxy" form that meets all the requirements of Massachusetts law (Annas, 1991). Those interested in obtaining advance directive forms could consult their hospital's legal counsel or administration, which may have forms appropriate for that state or regional jurisdiction.

TABLE 8.1 Decision-Making Considerations for Patients, Physicians, and Researchers with Respect to MCSS Use

Variables	Investigational Use in Clinical Trials	Routine Use in Treatment
Purpose	To evaluate the device by determining benefit under controlled conditions.	To improve individual patients' mortality, quality of life, and morbidity.
Patient Criteria	A process of selection: Emphasis on choosing the best possible patient for the research protocol. This goal is complicated by the fact that patients cannot, ethically, be eligible for the clinical trial if an alternative treatment is likely to be more clinically beneficial (Parker et al., 1990).	A process of exclusion: Emphasis on not choosing patients for whom the balance of risks and benefits of MCSS use is unfavorable or unreasonable.
Informed Consent	Few hard data on probable outcomes are available to be provided to patients. Much attention must be paid to the entire process of informed consent throughout both the trial and use of the device, including termination of use. Oversight by institutional review boards and less directly through the mechanism of NHLBI funding.	Because benefits and risk are more clearly known, patients' personal preferences are important in determining use. Informed consent is still crucial but now approximates consent for the use of similar life-sustaining technologies.

MCSS, mechanical circulatory support system; NHLBI, National Heart, Lung, and Blood Institute.

A final form of patient protection is provided through NHLBI. Most probably, NHLBI does not consider its funding role to have any quasiregulatory components. Nevertheless, continued federal funding through NHLBI can restrict the investigative use of MCSSs to those groups with the most expertise, experience, resources, and commitment. This regulatory influence can provide added protection for patients and further reduce the possibility of MCSS misuse in clinical investigations (Jonsen, 1986b). This influence is particularly relevant for future clinical trials of VADs, as discussed further in Chapter 10.

CONCLUSIONS

For both clinical trials and general use, regard for the individual patient's autonomy and concern about equitable access to TAHs will continue to be complex, serious issues. Decisions should be made in advance of the device's availability about its relative priority compared with other health care

technologies. Based on such priorities, preparation should begin now for dealing with the procedural and substantive justice concerns that will be raised by the availability of an approved TAH.

The question of access to TAHs must be addressed by the nation's health care policymakers before TAHs become available for general use. With such planning, it may be possible to achieve appropriate levels of benefit for both individual patients and society in exchange for understood, equitable, and acceptable levels of cost and burden. Progress on the question of access to TAHs will also provide, for the first time in the United States, a case study for defining and controlling access to a health technology.

The committee was assembled to help NHLBI determine whether, and in what amounts, funds should be allocated to further development of TAHs; in the process of doing so, it became necessary to examine larger societal concerns raised by TAH development. The limited scope of this study, however, precludes recommendations on such national issues as substantive justice and national health priorities. The committee's recommendations on resource allocation for R&D should not be construed as responses to these larger national issues.

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9

Roles of Government and Industry in Medical Technology Research, Development, and Use

FROM ITS OUTSET IN 1964, the artificial heart program has differed from most of the extramural research supported by the National Institutes of Health (NIH). It has involved a three-way partnership of government, academic researchers, and for-profit developers and manufacturers; it is more clearly applied R&D than basic research; it relies on the contract mechanism to support its major R&D projects, not the grant or cooperative agreement; and it is interdisciplinary as distinct from discipline-oriented research.

As a consequence of these features, the artificial heart program has generated a number of questions. The most general of these include the following: (1) What is the proper role of the federal government in the support of applied R&D? (2) How consistent are the program's purposes with the mission of NIH and the National Heart, Lung, and Blood Institute (NHLBI)? (3) What is the proper role of the federal government in enabling the use of new technologies? Although these aspects of the artificial heart program have received little external attention over the years, the committee has examined them because they are relevant to the program's future as well as to government-sponsored biomedical research in general.

The major portion of this chapter addresses the above questions. It also reviews the most appropriate organizational approaches to interdisciplinary R&D and to industry-university relations, the optimal manner in which to accomplish the type of interdisciplinary collaborative research that the artificial heart program represents, and the possible adverse effect of industry support of academic R&D on open communication among mechanical circulatory support system (MCSS) researchers.

ROLE OF THE FEDERAL GOVERNMENT IN THE DEVELOPMENT OF MEDICAL TECHNOLOGY

The federal government plays several different roles in the development and use of medical technology such as the artificial heart. It sponsors research and development related to the technology; it regulates the investigational use of medical technology (drugs, biologicals, and medical devices) with human subjects and allows only those products that have been evaluated as safe and effective to be introduced to the commercial market; and it makes coverage and reimbursement decisions for Medicare. This section examines the first of these roles.

Rationale for Federal Support of Research and Development

Although the support of private-sector research and development by the federal government has deep historical roots, only since the end of World War II has this support become a major government function. The immediate postwar rationale was provided by the successful application of science and technology to military purposes. Consequently, national security R&D, the development of nuclear energy for power generation, exploration of outer space, and the support of medical and basic scientific research dominated federal spending in the first two postwar decades. As the scale of federal R&D grew and as its purposes embraced domestic policy concerns, a relatively clear conceptual rationale emerged for the respective roles of the public and private sectors in the support of R&D, which has implications for MCSS development.

Theoretical Considerations

Economic theory provides the clearest expression of the rationale for federal support of R&D, predicated on the theory of market failure. Basically, this theory holds that in a perfectly competitive economy the private sector will systematically underinvest in research. The reasons to expect this underinvestment, as Arrow (1962) stated them, are that research is risky; unlike other resources, research is not consumed by use but generates increasing returns from use; and access to information (the result of research) can be restricted only to a limited extent. These features hold most clearly at the basic end of the research continuum and are less and less relevant as activity moves closer to application.

Market failure illustrates one aspect of the problem of externalities. Where the production of a good generates external benefits (social rates of return greater than private rates of return) to those who do not pay for it, private firms will underinvest in its production relative to a socially optimal

level. Where the production of a good like steel generates external costs, such as air pollution for third parties who do not consume steel, private firms will produce above the socially optimal level. With research and other examples of the first case, the economic value of the external benefits cannot be incorporated by producers in the price of the good; consequently, those benefits are available to "free-rider" third parties. In the second case, the costs of production are not fully reflected in the price of the good but are passed on to third parties in the form of nuisance, environmental degradation, and adverse health consequences.

The theoretical argument regarding market failure and externalities leads to an argument for public investment in research because of its "public goods" nature. A public good is defined as one whose social rate of return exceeds the rate of return that could be realized by private firms producing the good. For example, the results of research benefit many parties across a wide range of applications, in unpredictable ways, over extended periods of time, even though such results may have no known relation to application at the time they are generated.

Practical Implications

Practically speaking, the above argument leads to three conclusions. First, a justifiable and active role for the federal government is clearest in the support of the basic research stage of the innovation process. Here, from the above discussion, we expect the private sector to underinvest and the burden of financial support to be borne by the federal government. However, no method exists for determining the optimal level of such research that the federal government should support, that being determined by the political process rather than by methods such as cost-benefit analysis (Williams et al., 1976).

Second, the least justifiable role for the federal government in the support of R&D is at those stages nearest to application. Here, usually, products are divisible and benefits from them can be restricted by the producer to those who purchase them, uncertainty is relatively low, and consequently private firms are able to capture a return on their investment. Moreover, private-sector understanding of how to combine knowledge of the market with technical knowledge is highest (and public-sector understanding of the same is lowest).

Third, between these two identifiable polarities lies an intermediate or gray zone in which judgments about the roles of the public and private sectors with respect to particular R&D programs or projects are a matter of dispute. The conceptual rationale discussed above provides little clear guidance to policymakers and other interested parties, who usually include the government, academic institutions and researchers, and private firms. Parti

sans of public-sector investment will advance a public goods argument (based on the private sector's unwillingness to support public-benefit R&D); defenders of a leading role for the private sector will argue that investment in the application of R&D is best left to the private sector.

Under the circumstances, the definition of the public interest must be left to the political process. Controversies in this area typically focus on issues such as the federal policies and procedures designed to ensure public accountability, or on the probable social benefits (health outcomes in the case of biomedical programs or projects). They may also involve, as discussed in a later section of this chapter, "industrial policy" or international-trade considerations.

Status of the Artificial Heart Program

The foregoing discussion is relevant to NHLBI's role in MCSS research in academe and private industry because, despite almost 30 years of NHLBI support, questions persist about the appropriateness of that support. The mission statements of NHLBI and NIH provide little guidance on the types of research to support (e.g., basic or applied research). Neither do they clarify the appropriate purposes of R&D efforts, or the management tools for either targeted programs to develop a product or nontargeted activities to develop new knowledge.

The NHLBI mission and thus its authority for conducting R&D programs is broad in scope, namely "to provide leadership for a national research program in diseases of the heart, blood vessels, blood, lungs, and in the uses of blood and the management of blood resources" (NIH, 1988, p. *51).* In carrying out its mission, NHLBI supports research, investigations, clinical trials, and demonstration and education projects. For example, NHLBI's Devices and Technology Branch, which includes the artificial heart program, "plans, conducts, and directs a program of development and assessment of devices, instruments, and other technology applied to the problems of cardiovascular disease . . ." (NHLBI, 1990). Although the mission statements are broad, and thus offer no clear guidance about the appropriate roles of the federal government and the private sector in the case of the artificial heart program, it is possible to identify several issues about which controversy may occur.

Management and Accountability

As described in Appendix B, NHLBI's artificial heart program began with a program office formally established in July 1964. Then as now, the program's targeted, contract-based nature was unusual in biomedical research, having been modeled after Department of Defense, National Aero

nautics and Space Administration, and other federal R&D components engaged in the procurement of technologically complex systems.

The establishment of this targeted circulatory support program within the National Heart Institute was consistent with President Johnson's declaration in 1965 that he wanted "the secrets of the laboratory" unlocked and applied at the bedside in order to stem the tide of human illness (Omenn, 1984). It was manifested as well in the Artificial Kidney/Chronic Uremia program of the National Institute of Arthritis and Metabolic Diseases, as well as in several prominent programs of the National Cancer Institute (Rettig, 1977).

The controversy over management methods also involves resource allocation. That is, the use of grants or contracts has clear implications for the kind of research supported and those likely to perform such research. In addition, the private sector is often concerned about the way that the contract mechanism, as administered by NIH, affects the innovation process.

Social (Health) Benefits

The intermediate-zone criterion that perhaps is most directly relevant to decisions about the artificial heart program is the likely social benefit of research in terms of its impact on health outcomes of the U.S. population. Unquestionably, the prevailing opinion in medicine, which is shared by Congress and the general public, is that medical research is the key to clinical progress. However, no generally acceptable criteria exist to judge the effectiveness of NIH research in terms of its contributions to national health status. The same factors that lead private firms to underinvest in basic scientific research make the calculation of the social benefits of such research problematic.

The methods for turning scientific achievements into socially relevant products and services are rarely clear, and the time frame within which economic and social relevance is to be demonstrated is highly debatable (Moskowitz et al., 1981; Omenn, 1984; Finneran, 1986; NAS, 1989). Appropriate management of this technology transfer task has been identified by one observer as "NIH's most significant problem" (Lane, 1981, p. 14). For the country, therefore, Congress closely monitors each NIH institute's attempts to balance its allocation of research funds between the development of new knowledge and its application (Shodell, 1990).

In summary, historical analysis of the application of economic theory leads to no conclusive answer about the propriety of continuing federal support, through the artificial heart program, for MCSS development. This committee, along with NHLBI decision makers each time they face funding issues, must balance the benefits and risks.

Industrial-Policy Considerations

With programs such as the artificial heart, the lack of clear criteria defining public and private roles typically evokes justifications for federal involvement in terms of industrial policy—policies regarding taxes, patents, antitrust controls, and particularly international trade—that are designed to improve the economic strength of the United States in competitive world markets. A major policy issue involves how the federal government can best stimulate innovation, applications, and commercial development of biomedical technology and, more specifically, which technologies (NAS, 1989; NRC, 1990). The relevance of industrial policy arguments for any specific R&D program can be determined only through the political process, by evaluating competing views about the appropriateness of federal government involvement in the particular aspect of the country's industrial life.

The Small Business Innovation Research (SBIR) program is one example of federal support of applied research in the private sector that is motivated by industrial-policy considerations. Through the SBIR program, federal agencies having large extramural research programs allocate at least 1.25 percent of their annual R&D expenditures to peer-reviewed applications from for-profit firms. The program imposes limits on the length and amount of awards, unlike venture capital investments. These limits can discourage firms from confronting the uncertainties of innovation, which can be costly in both time and dollars. Nevertheless, the SBIR program has responded to the medical device industry's interest and to specific needs related to the artificial heart. As of August 1990, eight of NHLBI's SBIR awards, with a total annual value of $888,000, were under the artificial heart program (NHLBI, 1990).

The SBIR program, ultimately, is based on judgments about the relative importance of small entrepreneurial firms in the innovation process and their contribution to the entire economy. The entrepreneurial role of small businesses is one argument raised in these discussions. Roberts (1988) observes that, in the medical field, young small firms provide a supportive environment for creativity but rarely have the infrastructure or financial resources needed to support and sustain innovation through the steps necessary to obtain financial return to the company. He concludes that "being technologically innovative may well be a curse rather than a benefit" (Roberts, 1988, p. 45) and believes that the situation justifies government funding for product development as well as market applications research.[1]

[1] Another federal effort to stimulate technological development for international-trade reasons is the Critical Technologies Institute in the White House Office of Science and Technology Policy. This new institute's principal task is to identify technologies "deemed especially important for international competitiveness and national security" and to provide guidance for public investment in these technologies (Hamilton, 1990).

The United States currently is considered a world leader in health technology; the positive impact of that status on the economy is not to be taken lightly (NAS, 1989). Concern exists, however, about the ability of the United States to maintain this leadership, given the competitive nature of the international health care market and the recent experience of countries such as Japan-but not yet in the health care field—in doing a better job of production and marketing (commercialization) than U.S. industries (Bylinsky, 1990; Derian, 1990; Murray and Lehner, 1990). The ability to increase U.S. economic competitiveness is perceived by many to be closely aligned to how effectively government stimulates industry in the transfer of technology to the marketplace (IOM, 1990) and to what extent the U.S. market emphasizes high-quality design and low cost in health technology (NAE/IOM, 1988).

International-trade considerations thus sometimes constitute a policy justification for particular R&D programs. Advances being made in countries such as Germany, Italy, and Japan in MCSS development are of particular relevance. The committee noted two concerns in relation to these foreign efforts: Will the United States be able to exploit the commercial opportunities provided by its research investment in the artificial heart program? Is the current U.S. lead in developing the artificial heart likely to shift to other countries because of possible future underinvesting in bioengineering research in this country (Maxwell, 1991)?

Although no hard figures are available on either the projected cost of ventricular assist devices (VADs) and total artificial hearts (TAHs) or their annual sales volumes, estimates of market size can be made from the projections discussed elsewhere. Assuming that U.S. manufacturers capture all of the domestic market for both types of devices and that, as of 2010, 25,000 VADs and 10,000 TAHs are sold annually at prices (in 1991 dollars) of $50,000 and $100,000, respectively, the total domestic market would be $2.25 billion. Assuming, again as of 2010, these same prices and total foreign sales of 5,000 VADs and 2,000 TAHs, the United States would gain $225 million in its balance of payments if it captured 50 percent of the foreign market as well as retained all of the domestic market. In contrast, if there are no U.S. manufacturers in 2010 and all MCSSs used in this country are imported, the net change in the annual balance of payments or balance of trade would be $2.5 billion. This would constitute a substantial impact, in relation to a current trade balance that typically is about $100 billion (negative) overall. It can be argued, however, that international

trade considerations should be secondary to the balancing of benefits and risks to patients from the technology under scrutiny, or to other overriding considerations that may affect the basic decision about whether the R&D investment is in the public interest.

Conclusions

On theoretical economic grounds, the artificial heart program falls between extremes at which a federal government role is clearly appropriate or clearly inappropriate. Thus the determination of the federal role in supporting R&D related to this technology must be addressed and resolved through the political process. The practical considerations that need to be assessed in arriving at a policy determination include NHLBI's role and mission, the resource implications (especially opportunity costs), health benefits, management and accountability issues, and industrial policy issues.

Actions of Congress, NHLBI, and the National Heart, Lung, and Blood Advisory Council indicate that, historically, these bodies have implicitly considered the artificial heart program to be in the public interest, although with reservations. The relatively low level of funding for the artificial heart program, within the context of both total dollars ($15.8 million in the 19891990 fiscal year) and proportion (about 1 percent) of the total NHLBI budget, is evidence, however, of the extent to which other competing R&D efforts are considered to have equal or greater public merit. A lack of clarity about the appropriateness of the roles of government and industry in MCSS research also may be a contributing factor in the relatively modest level of support that NHLBI has provided.

From an immediate-term perspective, the committee concludes that industry, for the most part, should provide the majority of financial support needed to perfect and market temporary-use VADs as well as the costs associated with clinical trials of these devices; industry has clearly moved in this direction. However, public support for the upcoming clinical trial of the Novacor long-term VAD and other time-limited efforts to develop longterm VADs should continue; see Chapter 10 for additional conclusions and recommendations concerning VADs. Public funds are also needed to carry TAH development at least through an interim period, perhaps leading eventually to marketable products, and to stimulate new approaches to MCSS development. Neither industry support nor venture capital is currently available for development of long-term MCSSs in the United States for various reasons noted in this chapter.[2] NHLBI should also continue to support scien

[2] In contrast, in foreign countries and particularly in Japan, private R&D financing sources are satisfied to recover their investments over much longer periods of time than are acceptable to U.S. firms and their financing sources.

tifically meritorious R&D involving alternative power sources and MCSS components such as valves, batteries, and biomaterials, although the committee has not reviewed this aspect of the artificial heart program in depth.

The committee does not believe that international-trade considerations should play a primary role in decisions such as these, because NHLBI's mission is not to address the nation's balance-of-trade deficit. While the potential exists for this R&D to yield substantial international-trade benefits, the committee believes that potential benefits to patients should be the primary justification for NHLBI to continue to support MCSS development.

ROLE OF GOVERNMENT IN THE USE OF MEDICAL TECHNOLOGY

One analyst of the impact of public policies on medical device innovation has coined the term polyintervention to describe the policy environment created by numerous government actions (Foote, 1991). Foote states that although similarities exist in the innovation processes for drugs, devices, and procedures, they each have distinct public policy environments, and the device environment is perceived as being the most complex. This section examines this environment into which MCSSs will be introduced.

Almost two decades ago, Lewis Thomas (1972) pointed out that, although economics plays a critical role in the United States in most aspects of technology, the nation has paid little attention to the economics of health care technology. The financing structure for health care, heavily reliant on third-party payers, has resulted in disengagement of the patient from the economics of health care. Medical devices, for example, are rarely purchased directly by consumers; physicians and hospitals are the major decision makers regarding the purchasing or adoption of a particular medical technology and, until recently, their economic incentives were pro-technology.

The current emphasis on health care technology assessment, accompanied by almost nationwide private and public cost-containment efforts in health care, indicates a major policy trend relating to the economics of health care. The financial and regulatory climates in which developers of VADs and TAHs will seek marketing approvals from the Food and Drug Administration (FDA) and third-party coverage and payment decisions are stringent.

Uncertainties related to the regulation of new technologies through FDA, or by the Medicare program and other third-party payers, are one of the most important factors in the private sector's reluctance to support MCSS research. The length of time required for payback of the typical R&D investment is another factor, and it is related to the first because of the time required to obtain those regulatory approvals. Hence, potential problems with the various regulatory mechanisms must be examined.

Food and Drug Administration

Because MCSSs are life-support devices, FDA considers them in Class III, the most strictly regulated group of devices. Investigators or sponsors must receive an investigational device exemption (IDE) from FDA before undertaking MCSS clinical trials. Upon completion of the clinical trials, sponsors also must obtain premarket approval (PMA) from FDA prior to general marketing. In the area of obstacles and problems with obtaining IDEs and PMAs, particularly relevant to MCSSs is the gap between the level of information (qualitatively and quantitatively) desired by FDA before making decisions on requests for IDEs and PMAs and the level perceived to be realistic by researchers in the MCSS field.

Problems that are peculiar to MCSSs may potentially arise in two areas. First, bench and animal testing of these devices does not fully simulate use in humans. Neither blood nor some devices' bioprosthetic (animal tissue) valves can be used in long-term bench testing, and mechanical valves undergo stresses that differ, also, between use in animals and in humans. Further, different device configurations are needed, particularly in testing TAHs, because of anatomical differences between the animals that are used and humans.

Second, the number of implants that is typical in NHLBI-supported clinical trials of these devices (20, for instance, in the forthcoming Novacor VAD trial) is unlikely to produce reliability-testing results with the high confidence level that FDA wants. In developing the protocol for the Novacor trial, FDA personnel are meeting with the investigators and NHLBI representatives in the hope of avoiding such problems. The results of these joint efforts will not be known until late 1991 at the earliest.

Medicare and Other Third-Party Payers

The success of marketing endeavors depends greatly on third-party payment policies, including decisions about coverage policies and payment rates. Long-term MCSSs present new challenges to the payment policies of Medicare, state Medicaid programs, and private insurers. This technology will undergo close scrutiny because of its relatively poor costeffectiveness and because it will be among the most costly ever developed, on a per-patient basis. Medicare, in particular, can be expected to scrutinize it closely, because many potential candidates for both TAHs and VADs will be Medicare beneficiaries; the Medicare program is likely to be required to pay for more MCSSs than any other third-party payer, if it decides to cover broad MCSS applications.

Perspectives vary about the impact of third-party payment decisions on industry's willingness to invest resources in manufacturing, marketing, and

distributing new technologies. Some analysts believe that historically the health care coverage and reimbursement policies in the United States have been a major positive incentive for progress such as that already made in developing MCSSs; these incentives have enough momentum to overcome barriers. Supporters of this view maintain that the United States is a prohealth technology society exerting influence on the delivery of health care worldwide (Foote, 1991).

Particularly since the implementation of the Medicare prospective payment system, others consider that the payment policies of the U.S. health care system have become a major barrier, specifically to industry support for MCSSs. Issues raised by those with this view include (1) the reluctance of insurers to consider trade-offs in costs that reflect all aspects of care, not just the services covered by the insurer, when assessing a new technology's cost-effectiveness; (2) the likelihood that Medicare will, as in previous instances, assign MCSSs to an existing diagnosis-related group (DRG) with a payment rate that inadequately covers the cost of the device and its implantation; and (3) the inability of some hospitals to absorb the unrecovered costs in MCSS cases because of an overall climate of austerity that provides little financial flexibility.

As an example of problems currently being encountered, the most costly implanted device now in routine use is the automatic implantable cardioverter defibrillator (AICD), for which a hospital's purchase price is about $20,000 including the necessary leads. The Prospective Payment Assessment Commission recommended the establishment of a temporary, device-specific DRG for AICDs that would have allowed adequate payments. The Health Care Financing Administration (HCFA) refused to follow the recommendation, instead assigning AICD implantations to two existing DRGs with rates that do not fully cover the cost of the device and its implantation. A study by the Medical Technology and Practice Patterns Institute (MTPPI, 1989) found that, as a result, hospitals providing AICDs to Medicare patients in 1987 lost a total of $3.8 million on those cases. The average direct costs of $31,829 (not including any allocated indirect costs) were substantially greater than the DRG payment rates of $20,522 and $26,112.

Yet another example can be found in Medicare payment decisions about cochlear implants. The decision to include implantation of this costly device in a DRG with a rate substantially below the total cost led first to underdiffusion of the technology and subsequently to a loss of interest on the part of manufacturers in pursuing development of a second-generation device (Kane and Manoukian, 1989).

In contrast, percutaneous transluminal coronary angioplasty was originally assigned by Medicare to a DRG with a payment rate substantially greater than the procedure's cost. This led to rapid diffusion of the technol

ogy, along with other cardiovascular technologies such as coronary angiography that were seen by hospitals as similarly profitable.

To consider a technology closely related to MCSS, the circumstances affecting the diffusion of heart transplantation differ somewhat but it provides another example of diffusion of a cardiovascular technology. Although heart transplantation has been documented to generate financial losses in at least some hospitals (MTPPI, 1988), hospitals may undertake transplantation services because of the marketing and other competitive advantages inherent in offering such high-technology services, even if costs are not fully recovered. Because MCSS implantation offers similar competition-related incentives, use of this technology may also grow even if losses are expected with some patients.

Conclusions About Regulatory Constraints

Clinicians and others concerned about the appropriate use of long-term MCSSs have a unique opportunity during the 1990s to develop clinical practice guidelines for the use of these devices. Researchers and the devices' developers can also be expected to undertake technology assessments (including cost-effectiveness analyses) that will incorporate forthcoming clinical-trial results and eliminate some of the uncertainty that confronted this committee's efforts. Such developments as these will be very useful to the Medicare program and other third-party payers, possibly making the regulatory hurdles to be overcome by newly approved VADs and TAHs somewhat less daunting than they would otherwise be.

Because of the truly interdisciplinary nature of MCSSs, FDA, the Medicare program and the Office of Health Technology Assessment that advises it, and other third-party payers could put the same opportunity to even better use by developing new approaches to their upcoming reviews of MCSS-related applications. They could be involved both prospectively and collaboratively, along with NHLBI personnel, in an integrated, contemporaneous evaluation of each particular model of MCSS, contributing their knowledge to one another, instead of waiting for the separate, sequential reviews that traditionally occur. Such a collaborative, interdisciplinary review of regulatory decisions concerning MCSSs would be highly appropriate because of the characteristics of the technology itself, and would also serve as a model for future consideration of similar technologies. Restrictions on access to proprietary data (e.g., in a manufacturer's PMA application) might hinder such an effort, but the manufacturer's interest in early decisions by each of the agencies might lead to waivers of those restrictions in at least some instances.

HCFA might even play a direct role in the decisions NHLBI must make in the 1990s about continuing to fund MCSS development, if NHLBI were

to consult it either formally or informally before making those decisions. HCFA's views on the likelihood that it would approve Medicare coverage, or the range of clinical indications it sees as acceptable, have the potential to be important influences on the future use of this technology. The question might best be presented to HCFA in the form of alternate scenarios that include details as to projected clinical effectiveness and cost.

Finally, once a third-party payer has approved coverage of MCSS use for patients with particular clinical characteristics, a payment rate should be established that adequately compensates providers for the costs of implanting the device.[3] In the committee's view, below-cost payment rates are not an acceptable means of limiting technology use.

ENCOURAGING INTERDISCIPLINARY AND INDUSTRY-ACADEME COLLABORATION

Several factors deter industry support for development of mechanical circulatory support devices, in the context of analyzing the current technological potential and costs of MCSS R&D. This section explores possible structures and mechanisms to overcome factors that deter collaborative, interdisciplinary MCSS research, whether by way of government support of industry, industry support of academic research, or collaboration among academic scientists, engineers, and physicians.

As the committee understands the organizational processes of NHLBI and other institutes of NIH devoted to disease-or organ-specific research, those processes do not promote and may even hinder collaboration among physicians, engineers, and life scientists. Additionally, the composition of NIH study sections works against the success of collaborative proposals involving physical scientists or engineers, as virtually all members of these peer-review groups are either life scientists or physicians.

Thomas (1988) suggests that government support for the development of new technologies and devices should be through interdisciplinary structures combining biochemical and biomedical engineering. He argues further that such efforts should be sensitive to the costs and benefits associated with the product's introduction. He cautions against using traditional funding of university laboratories for biomedical engineering research, particularly if the goal is procurement of a product needed by government.

[3] Because of uncertainty about costs during early MCSS use, one possible payment mechanism would be an interim rate for the "learning curve" period when only a few institutions are involved and a different rate or basis for payment when use becomes more widespread. Such an approach has been advocated for the early diffusion phase of technologies generally (Perry and Pillar, 1990).

The implications and breadth of the issues involved in the governmentindustry research interface are exemplified by Congress's enactment of the Omnibus Trade and Competitiveness Act of 1988, which includes a request that the National Academies of Sciences (NAS) and Engineering (NAE) and the Institute of Medicine (IOM) examine the effectiveness of existing programs in fostering R&D in civilian technology. A study panel housed in these organizations' Committee on Science, Engineering, and Public Policy is currently examining public-private R&D ventures, collaborative R&D efforts overseas, foreign government policies to promote technology development, and the role of federal agencies in technology transfer; a report is due in late 1991.

Role of Biomedical Engineering Research

Another aspect of the artificial heart program that is unusual, in its context at NHLBI, is one of its goals: The program was one of the first within NIH to adopt the goal of developing an industrial capacity in biomedical engineering (Maxwell et al., 1986). Because of the interrelatedness of many issues relating to research collaboration and to the field of biomedical engineering, an overview of biomedical engineering research may be useful.[4]

Biomedical engineering is an interdisciplinary field that joins numerous engineering fields with medicine and other life sciences. It involves the use of engineering science and technology to advance understanding of life sciences as well as the development of devices and systems for prevention, diagnosis, monitoring, treatment, and rehabilitation of medical problems (Gelijns, 1990). Another closely related term is biomedical technology, which encompasses all disciplines, not only those involving the engineering sciences (Moskowitz et al., 1981).

Biomedical engineering has made important contributions to advances in biomedical measurement, analysis, and instrumentation. Examples are the use of engineering mechanics to measure myocardial contractility and the use of signal analysis to understand better how the inner ear processes auditory signals. Such research contributes not only to cardiac physiology, neuroscience, and other health sciences, but also to the development of improved health technologies. Although there is no widely accepted taxonomy of biomedical engineering, some of the major clusters of interest have been in cardiovascular devices, biosensors and signal processing, hospital facilities, medical informatics, medical imaging, neurologic and sen

[4] This section is based, in part, on material prepared by Clifford S. Goodman, former director of the IOM Council on Health Care Technology, and Karl Yordy, director of the Division of Health Care Services, IOM.

sory technologies, patient monitoring (e.g., in anesthesiology), and rehabilitation. Compared with other, longer-standing disciplines, biomedical engineering has less clearly defined educational programs, professional certification criteria, roles in academic and health care delivery organizations, and dedicated funding sources. It is, perhaps, at approximately the same point as was the field of computer science some 15 years ago, before it became a clearly defined discipline with separate departments in universities.

Support for biomedical engineering research currently comes from NIH, the National Science Foundation (NSF), other government agencies, industry, and private foundations. Biomedical engineering has a focus at NSF following a 1989 program reorganization, although the funding available for new projects is not great. Currently, this NSF division has three R&D programs: biochemical engineering, biotechnology, and biomedical engineering; the last-named has a total annual budget of about $3.5 million (Katonah, 1990). The Department of Veterans Affairs, the Department of Energy, the Department of Defense, the Department of Education, and the National Institute of Standards and Technology of the Department of Commerce also support and conduct certain efforts related to biomedical engineering.

Several major U.S. corporations have substantial programs in biomedical engineering research. However, most medical device companies are one-or few-product enterprises whose activity in biomedical engineering is directed exclusively to development or refinement of particular products. Even among the larger companies, support for biomedical engineering research may be limited to short-term, product-directed efforts rather than to more basic research and development that could lead to advances over the longer term in such technologies as implantable devices and components, biosensors, biocompatible synthetic materials, and vascular grafts. Foundation support for biomedical engineering research is quite limited.

Several barriers to the satisfactory development of this field have been identified by studies conducted by the National Research Council (NRC, 1987; NRC, 1990). They include inadequate coordination among supporting agencies, the need for appropriately trained researchers, and inadequate financial support. The concern about lack of adequate funding mechanisms may be derived in part from the respective missions of key federal agencies such as NIH and NSF; their diverse missions impede interdisciplinary collaborative extramural research (NRC, 1990).

U.S. public policy has tended to support biomedical technology innovation through the academic environment. Some analysts see such policies as resulting in a less-than-adequate cadre of biomedical engineers in the commercial or industrial setting (Goodman, 1981; Roberts, 1988; Murray and Lehner, 1990), and this in turn slows the production and marketing phases of technology.

Current Collaborative Structures

Although no existing model of management structure within NIH adequately addresses broad concerns about collaborative extramural research in a comprehensive manner, some current examples elsewhere in government have potential as models. One structural example that may be useful is NSF's collaborative efforts with state governments, industry, and venture capital firms for developing interdisciplinary coalitions sharing common science, technology, and economic goals. Another example is NSF's Engineering Research Centers program, which is designed to foster interdisciplinary collaboration of academic and industry researchers in specific areas (see Office of Technology Assessment, 1990). One engineering research center, at Duke University, is in the biomedical engineering field.

Examples of industry-academe collaboration—not involving government support—include the Monsanto Corporation's relationships with Harvard University and Washington University. Although controversial at the time, these relationships broke new ground in industry-university collaboration, launched Monsanto into the modern biotechnology era, and have since been emulated by Exxon and others. The joint industry collaborations in the computer, semiconductor, and manufacturing technology fields (e.g., MCC, SEMATECH) offer another model, particularly considering that NSF and the Department of Defense are major financial supporters of many of these activities.

A recently implemented example of joint government-industry support for innovative R&D is the new Advanced Technology Program (ATP) of the National Institute of Standards and Technology (U.S. Department of Commerce, 1990). This program announced 11 awards in March 1991 for private-sector basic research in computer hardware and software, electronics, and similar advanced technology fields (U.S. Department of Commerce, 1991). Costs are to be shared approximately equally between the government and industry; the initial 11 federal awards total $9 million in their first year. Additionally, a number of state governments support technology R&D through various structures (Osborne, 1989).

NHLBI and other NIH components have established detailed policies and procedures governing cooperative relationships with all types of private sector organizations (NHLBI, 1985). These NHLBI guidelines specifically allow joint federal-private support of both intramural research and extramural R&D conducted by industry.

An arrangement by which NHLBI provides only partial support for an industry project, such as the ATP program just described, is not precluded by these guidelines. It would, however, be required to comply with the customary review process through an ad hoc peer-review group (NHLBI, 1985). Any proposal for jointly supported NHLBI-industry activity thus

would, except for basic research, very likely encounter the same type of peer-review disfavor as would a straightforward academic proposal for such research. Furthermore, the guidelines are not clear about when competition must be sought through a publicized request for proposals (RFP), in lieu of a sole-source contract. Absent either an RFP or congressional sanction to omit that step, it seems unlikely that NHLBI could enter into an agreement for jointly funded industry research involving a substantial federal commitment without offering other firms the same opportunity. Additionally, accomplishing such a joint activity on an open, competitive basis would seem to introduce a degree of complexity that would likely make the activity very difficult, if not impossible. Cooperative agreements between NHLBI and industry are another possible mechanism to be considered.

Conclusions About Collaborative Research

Federal support of contractual, targeted R&D by industry may be seen to be more appropriate as a research mechanism when the government is perceived to be the major purchaser or user of the end product than when, as with MCSSs, it is not directly a purchaser. The committee seconds the conclusion reached by an earlier IOM committee (IOM, 1990) about the need for constructive policies to integrate the efforts of government and private-sector sponsors of biomedical research.

It is not clear to the committee whether the relatively slow pace of the artificial heart program's achievements since 1964 can be attributed to the constraints imposed by its placement in an organizational structure oriented to basic research, to the limited funding it has received, to other unidentified factors, or to all of these. If similar efforts are to be mounted in biomedical research, further study of the program in these particular respects is warranted.

The committee suggests that the artificial heart program, as well as similar efforts that may be undertaken in the future, may be more successful in stimulating interdisciplinary collaborative research, cost-sharing with industry, and other innovative R&D-sponsorship mechanisms if NHLBI specifically addresses ways in which such flexibility of approaches can be best achieved. Integration within overall NHLBI processes is necessary, but a better "fit" will aid the artificial heart program in achieving its goals. This may well be true of other NIH programs involving interdisciplinary R&D, but the committee's scope has precluded its reviewing others.

In particular, the committee is concerned that the typical makeup of study sections, oriented as their members are to basic research, may be a less-than-ideal means of peer review for technology development applications involving biomedical engineering and other disciplines outside the life sciences. In order for adequate peer review of proposals concerning

MCSSs and other complex technologies to occur, biomedical engineers and others with specialized technological knowledge must play an important role. If a review group's priority scoring process is dominated by basic researchers with a lack of expertise in fields involved with the particular proposal, the value of the peer-review process suffers.

NHLBI might also consider sponsoring a formal collaborative arrangement that encompasses both public-and private-sector interests in biomedical engineering, in order to achieve maximum advantage from the artificial heart program's available funds. Organizations such as SEMATECH may be useful models (Congressional Budget Office, 1990).

Lessons can perhaps also be learned—a topic beyond the scope of this study—from the experience of NSF and other government agencies that have successfully sponsored collaborative research involving both industry and academe. Experimenting with allowing the artificial heart program greater operational flexibility might be useful to NHLBI, NIH, and the Department of Health and Human Services as a model for similar efforts in the future.

While considering means for improving interdisciplinary collaboration in artificial heart R&D, appropriate mechanisms could also be sought for partially achieving desired goals, such as general oversight and encouragement of this type of cooperative effort. Two options might be considered: (1) establishing a subcommittee for health sciences of the Federal Coordinating Council for Science, Engineering, and Technology (FCCSET) in the Office of Science and Technology Policy, or (2) creating a forum such as the NAS/NAE/IOM Government-University-Industry Research Roundtable; both were recently recommended by the IOM Committee on Policies for Allocating Health Sciences Research Funds (IOM, 1990). At a level more directly relevant to the MCSS, the committee endorses the recommendation made by the Bioengineering Research Panel of the National Research Council (NRC, 1987) that an interagency entity be given responsibility for coordinating biomedical engineering research. This entity also might be a subcommittee of the FCCSET, thereby providing the opportunity for interdepartmental participation and linkage to industry.

EFFECT OF INDUSTRY SUPPORT ON COMMUNICATION AMONG RESEARCHERS

The subject of communication and cooperation among MCSS researchers was discussed in the 1989 IOM planning committee report and included in NHLBI's charge for this study. According to the experts who appeared at the committee's public meeting and workshop, however, this is not a major issue or problem. All U.S. researchers in the field, as well as a number of overseas ones, meet regularly twice each year, once at the annual confer

ence of the American Society of Artificial Internal Organs and again at the Conference on Cardiovascular Science and Technology held each year in Louisville, Kentucky.

Nevertheless, the possible "chilling" effect on communication from increased private-sector involvement is a concern to the committee and one that warrants open discussion by those directly involved. Three points need to be considered:

- The committee heard that, as academic researchers become involved with firms interested in marketing the results of their research, industry representatives express concern about the extent to which the academicians discuss their R&D activities with colleagues in the field.
- At the December 1990 annual conference of MCSS developers in Louisville, prominent researchers expressed strong concern about the serious decrease in collegial information exchange, after several early-stage researchers refused to describe their achievements or to answer questions, at the behest of those funding them, because patent applications had not yet been submitted.
- A study in the biotechnology field (Blumenthal et al., 1986) found that 25 percent of industrially supported university faculty reported that they had conducted research that belonged to the sponsor and could not be published without prior consent; 40 percent of the same group said their collaboration resulted in unreasonable delays in publishing.

Industry involvement in academic research may raise legal issues such as property rights in patentable disclosures that result from the sponsored research. The committee recognizes, however, that increased industry involvement with academic MCSS researchers is likely as these devices approach approved status and, indeed, encourages such involvement. Concern remains about the possible deleterious effect of these relationships on the traditional collegial communication among researchers that has been so valuable in the MCSS arena. The committee suggests that the MCSS research community discuss this specific issue at a forthcoming professional conference and urges that industry representatives and academic MCSS developers, alike, avoid arrangements that impede collegial communications. Further, universities should develop and implement policies consistent with this concern. Additional specifics are discussed in a recent IOM report that studied potential conflicts of interest in the activities of patient outcome research teams that receive both government and industry support (IOM, 1991).

Conclusions

On the topic of communication and cooperation among researchers, the committee concludes that current mechanisms are generally adequate.

Nevertheless, those involved will need to take concrete steps to ensure that the growing industry involvement in academic MCSS research does not adversely affect collegial communication among researchers.

SUMMARY AND CONCLUSIONS

The three-way partnership among NHLBI, academic researchers, and industry that has long been a prominent feature of the artificial heart program is unusual in biomedical R&D. As discussed further in Chapter 10, NHLBI's continuing support of applied research, development work, and clinical trials in this field is warranted by the potential benefits to patients that this R&D appears likely to yield, given the committee's conclusion that private sector support for these activities will not be forthcoming at least until the first long-term VAD has been approved for general use. Moreover, policy changes by NHLBI could provide greater flexibility in the funding approaches and mechanisms used in this continuing R&D support, which in turn may prove to be useful to government support of other types of collaborative biomedical research involving academe, industry, or both.

Specific conclusions discussed at the end of each section of this chapter are summarized in Chapter 10, in conjunction with the committee's recommendations on these topics.

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10

Conclusions and Recommendations

AS THE PRECEDING CHAPTERS HAVE RELATED, the artificial heart program of the National Heart, Lung, and Blood Institute (NHLBI) is nearing one of its goals, that of developing a fully implantable device that offers indefinite maintenance of cardiac function to individuals suffering from end-stage heart disease. Surgeons will soon implant the first long-term ventricular assist device (VAD) that needs no skin-penetrating air hose or wire. It is therefore time, despite many uncertainties, to begin examining how appropriately these devices will be used in health care. Because of their life-or-death implications and high cost, their use poses profound economic, ethical, and clinical questions.

At the request of NHLBI, an Institute of Medicine (IOM) study committee examined the agency's artificial heart program and the devices being developed for long-term use.[1] This document is the committee's report.

Nine questions set forth below, formulated in 1989 by another IOM committee, have guided this evaluation. A number of closely related issues have also been addressed, including government and private-sector roles in research and in the development of new technologies.

To succeed in improving patient care, the goals of the NHLBI artificial heart program and the outputs of its R&D efforts must be compatible with the U.S. health care system, particularly because:

[1] This discussion and the report as a whole do not consider devices that are intended only for temporary cardiac support, as they were not a focus of the study.

- on a per-patient basis, the mechanical circulatory support systems (MCSSs) being developed will be among the most costly therapeutic devices to date;
- MCSSs may be coming into general use as the health care system is under growing scrutiny for the quality and cost of care and patients' access to it; and
- the heart, an organ that has special cultural symbolism and life-sustaining importance, is involved.

FOCUS OF THIS STUDY

A 1989 IOM planning committee formulated nine questions to be addressed in this evaluation although, as seen in the preceding chapters, the committee's deliberations went beyond answering the questions. The committee's responses to the questions are very briefly summarized here.

1. *What are the nature and magnitude of the target populations for which MCSSs may be applied?* Once a fully implantable MCSS is established to be clinically useful for long-term cardiac support, many more patients will receive one than the current annual volume of 2,000 heart transplant recipients. The number of potential MCSS candidates in the primary group (those most urgently in need of cardiac support) is between 35,000 and 70,000 annually, but practical limits on the growth of this technology's use will hold patient volumes below this range, for perhaps 10 years. In the 2010-2020 period, if device and transplantation outcomes are then similar, potential use may grow substantially beyond this range.

   Most of the devices implanted during the first decade of MCSS use will be VADs. As many as 10,000 to 20,000 of each year's primary group of patients have impairment of both of the heart's ventricles, however, and will be candidates to receive a total artificial heart (TAH) after these devices become available, likely between 2005 and 2010.
2. *What are the alternative technologies for preventing and treating end-stage heart disease that may affect the need for MCSSs?* For the foreseeable future, transplantation will remain the treatment of choice for end-stage heart disease. Current forms of treatment other than transplantation offer most patients only limited benefits, such as relieving symptoms but not significantly prolonging life. Early in the next century, advances in drug therapy may at least be able to delay the onset of end-stage disease for some patients, and perhaps prevent it.
3. *What is the potential for MCSSs to prevent and treat end-stage heart disease, and what are the current technological and other barriers to their development?* Almost three decades of research and development have overcome many technological barriers to developing a fully implantable

long-term device and have identified areas susceptible to solution by further technological development. Forthcoming clinical trials may clarify the relative importance of those areas needing additional research. Areas that have already been identified for further R&D include potential thromboembolic problems, through-the-skin power transmission, valves, and biomaterials.

4. *What is the clinical effectiveness of MCSSs?* The experience to date with temporary-use devices provides reasonable assurance that one or more long-term MCSSs can be proven clinically effective for specific patient groups, probably before the turn of the century. As R&D efforts yield more technological advances, device performance and effectiveness levels (e.g., survival probability) are likely to improve steadily.
5. *What are the projected costs of research and development of MCSSs?* NHLBI currently spends about $7 million each year through the contracts that provide most of the support for MCSS development and trials. Another $8 million is spent annually for investigator-initiated grants related to cardiovascular technology. The level of past funding of MCSS contracts has been constraining for MCSS developers; the annual total may need to be slightly greater if NHLBI accepts the committee's recommendations to continue R&D with TAHs, as well as with more than one model of VAD, for an interim period. Not including the costs of the Novacor VAD trial, for which funds are already committed, approximately $2 million per year will be needed for additional VAD development for at least the next two fiscal years, and thereafter a possible additional amount to support further clinical trials. For TAH development, the total amount needed will depend upon findings during the recommended extensions of current contracts. The extensions themselves will likely cost a total of $3 to $6 million per year for a 2- or 3-year period, perhaps to be followed by a total cost of $30 to $90 million (over 10 years) for the two final stages of R&D, as discussed further in Chapter 6. (All of the foregoing amounts are expressed in 1991 dollars.) A number of NHLBI decisions in future years will have a substantial impact on these funding requirements.

   The devices themselves will, in the initial phase of use, cost about $50,000 for a VAD and $100,000 for a TAH, expressed in 1991 dollars. The hospital and physician care required to implant either type will cost about $100,000 in addition. Later costs will depend heavily on the extent to which care is required for complications or for repair or replacement of the device.
6. *What is the cost-effectiveness or cost-benefit of research and development of the various MCSSs, and how does this compare with what is known about the cost-effectiveness or cost-benefit of the research and development of alternative technologies for preventing and treating end-stage heart disease?* The cost-effectiveness of long-term TAH use depends on the extent to which a device benefits patients, in particular the quality-adjusted life years (QALYs) gained in comparison with outcomes of conventional medi

cal treatment. The TAH's estimated incremental cost-effectiveness, $105,000 per added QALY (in 1991 dollars), is substantially less favorable than for heart transplantation and most other forms of heart disease treatment. If technological developments lead to improved TAHs with life-year gains that approach those of transplantation, cost-effectiveness will improve.

7. *What should the roles of government and industry be with respect to research and development of MCSSs?* The NHLBI artificial heart program is unusual among health care R&D in the extent of its government support, in that the government has funded virtually all work to date, including the device development and testing costs usually borne by industry for similar technologies. As discussed later in this chapter and in Chapter 9, existing circumstances warrant continued NHLBI funding of both VAD and TAH research for at least a two-to three-year period. Further, NHLBI may wish to pursue formal cost-sharing arrangements with industry for some future efforts.
8. *Should decisions concerning further investment in the artificial heart program depend on whether the current cost-effectiveness or cost-benefit findings indicate the technology is acceptable or unacceptable, or are there additional factors that should be taken into account?* Cost-effectiveness is one of several factors relevant to the committee's recommendations to NHLBI concerning the artificial heart program. Other factors argue for NHLBI to continue its involvement, at least for an interim period. NHLBI's participation, for instance, may influence the manner in which clinical trials are conducted; also important is studying the quality of life of patients during clinical trials, which might well not occur without NHLBI support. Further, it is important that NHLBI participate in activities such as developing clinical practice guidelines for MCSSs and monitoring posttrial device performance.
9. *How can these findings be used to support decisions on allocation of research funds for artificial heart technologies?* All of the topics considered by the committee are relevant to the decisions that NHLBI must make. Because of the risk of unforeseen technological problems, if clinical trials are conducted with only one VAD model, NHLBI funding of other scientifically meritorious VAD development efforts should continue for a period of at least two to three years. NHLBI support for the development of TAHs should also continue for the same interim period until the early results of long-term VAD trials are available, because of the potential future benefit to patients from TAHs, and because information from those trials will help in future decisions about TAH development. NHLBI decisions about allocating R&D funds should be aided by the use of cost-effectiveness analysis (CEA) and other explicit criteria, as described in Chapters 3 and 6.

Other topics. The committee has also reviewed a number of other areas related to MCSS development and use. The recommendations in this chap

ter cover such topics as promoting the appropriateness of MCSS use, deciding about patient access to this technology, and avoiding a possible adverse impact of industry support for academic R&D on open, collegial communication among researchers.

PROMOTING APPROPRIATE USE OF MECHANICAL CIRCULATORY SUPPORT DEVICES

The committee is very concerned about possible inappropriate MCSS use, similar to concerns expressed over the years about other new technologies. The proper response is not to terminate federal support for R&D in this area. Rather, the decade or more that will be needed to complete MCSS development offers an unusual opportunity for all interested parties to deal positively with this concern.

Substantial variations in rates of use of many technologies, as well as in other physician practice patterns, indicate that either overuse or underuse occurs regularly; both possibilities raise questions about the effects of such patterns on the quality of patient care. Further, the overuse of technology continues to be blamed for much of the steady increase in the cost of health care. Many regulatory and educational measures that once seemed promising as means of achieving appropriate technology diffusion and use have proven insufficient for the task. *With MCSSs, crucial activities can occur before these devices go into general use, to improve the likelihood that they will be applied appropriately.*

The 1990s provide an opportunity to improve the prospects for appropriate MCSS use, once their development and clinical trials are completed, and activities with that goal should be undertaken. The committee recommends continued federal support for MCSS development, based on an assumption that this will be done. Among the relevant activities that can begin immediately are the development of provisional clinical practice guidelines (indications for use)[2] and of guidelines for the institutional resources and staff expertise necessary for appropriate MCSS use, as well as the initiation of selective coverage programs (e.g., third-party payers approving coverage for MCSS use only when the device is implanted at designated institutions).

Participants in developing and implementing measures to enhance the appropriateness of MCSS use should include: the researchers developing

[2] In this report, the term "clinical practice guidelines" should be construed as including the closely analogous medical review criteria that will be developed from such guidelines and used by third-party payers in acting on preauthorization and payment requests, as well as in posttreatment reviews of care such as those performed by peer review organizations.

these devices; cardiothoracic surgeons, cardiologists, and other physicians; allied health professionals; representatives of the Medicare program and other third-party payers; and others such as health services researchers, economists, and ethicists. Advice and consultation should be sought from patients who have experienced MCSS use and from family members and others who have cared for them. Further, because of their in-depth knowledge of this technology, NHLBI personnel should be intimately involved in these activities, in particular to design evaluative studies of MCSS use.

Efforts to enhance the appropriateness of MCSS use will fit well with current trends to develop clinical practice guidelines and to tighten the granting of practitioner privileges to use particular technologies. Additional studies of these devices' long-term outcomes will be an important basis for the efforts to enhance appropriateness of use that should continue indefinitely. Because of this technology's cost and visibility and because clinical studies and technology assessments of MCSS use will be important in these and other efforts, the Public Health Service's Agency for Health Care Policy and Research (AHCPR) might give such studies a special priority. Considering the foregoing, the committee recommends the following:

- **MCSS developers, physicians, and others should work together during the 1990s to establish clinical practice guidelines and other measures to promote the likelihood of appropriate MCSS use.**
- **Recognizing the cost of this technology, adequate federal and private research funds should be devoted to clinical studies and technology assessments of MCSS use.**
- **Staff of the NHLBI artificial heart program should participate in these appropriateness-enhancing activities and work with AHCPR to develop support for the needed studies.**

ACCESS BY ALL TO CIRCULATORY SUPPORT DEVICES?

The health care community and state and federal governments may or may not take action in the years ahead to assure equitable access, either to health care generally or to specific forms of treatment, for the 30 million or more people in the United States who have no insurance or are inadequately insured. The committee has not considered itself charged to break new ground on the issue of access to health care; see discussions of access to care such as that of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (1983). The committee would, however, be reluctant to recommend continued federal support for MCSS development, if it believed these devices would

be available only to those with personal resources or adequate insurance coverage.

It is also beyond the scope of this committee's charge to decide, or even to recommend, whether an MCSS should be part of a basic level of health care that is applicable nationwide, or whether the federal government or states should provide universal access to MCSSs or to an overall basic level of care. Nonetheless, as with the appropriateness issue, the nation's health care policymakers could and should use the emergence of this new technology during the 1990s as an opportunity to face the access issue squarely and examine it in depth before MCSSs come into general use. *The time is ripe for the United States to make clear decisions about access to health care, including costly new technologies.* A conscious policy decision about MCSS access would also minimize future claims that products of government sponsored research should automatically become a public entitlement.

Access via Third-Party Payers

As an alternative to universal access either to MCSSs for a clinically defined population or to a basic level of services, partial but more uniform access could be achieved via third-party payers. Many state legislatures have mandated specific benefits to be provided by all private health insurers in their states; such measures, although sometimes controversial, have proven to be more feasible at the state than the federal level.

If no legislative mandate for MCSS coverage exists, third-party payers have a strong incentive to deny coverage under even the most generous benefit packages, because the high per-patient cost will result in a very high aggregate cost if all those who need MCSSs are able to obtain them. Medicare and state Medicaid programs are likely to be more reluctant, even, than private insurers to approve MCSS coverage.

The nature of the health care gains provided by an MCSS presents a strong counter-argument. If these devices are proven clinically effective, it will be difficult for either private or public third-party payers to assert that they are properly a "second tier" technology that can be denied to identified patients. There remains, however, a possibility that long-term MCSSs will, in fact, become available only to those who are able to pay for them through special insurance coverage or with private funds.

Clinically Limited Access

At least in the early stages of MCSS diffusion, it will be imperative to limit access on clinical grounds, much as the number of heart transplantation candidates is limited by stringent approval criteria for placement on the transplant waiting list. If provisional indications for long-term MCSS use

can appropriately be restricted on specific clinical grounds to a relatively small group of candidates, third-party payers may be more comfortable in approving such a limited degree of MCSS coverage and payment.

This approach must recognize, however, that narrow indications for use are likely to be temporary, considering the evolution of indications for technologies such as percutaneous transluminal coronary angioplasty, as additional clinical experience was gained. Limited access to heart transplantation is warranted by the small number of available donors; with a manufactured device, no such curbs will occur on the supply side. Furthermore, those developing any restrictive indications for use and the clinicians who apply them to individual patients must take great care that they do not favor a particular demographic group (e.g., middle-class white males) disproportionately to disease incidence.

Limiting Access by Inadequate Payments

As discussed in Chapter 9, the Medicare program, in particular, sometimes approves coverage of a new technology but then establishes a payment rate for its use that is substantially below the cost of providing the service. *Paying 50 or 75 percent of costs is an unacceptable way to ration access to technology.*

Medicare and other third-party payers should determine coverage policies on clinical and cost-effectiveness grounds. If coverage is approved for a particular clinically defined group of patients, a payment rate should be established that adequately compensates providers for the costs of the service, both direct and indirect.

As discussed more fully in Chapter 8, the committee has four recommendations concerning access:

- **Long-term MCSSs should become an example of a specific technology that, once it qualifies clinically, must be explicitly included or excluded from basic health care coverage as defined for particular insurance programs.**
- **Legislators and policymakers at state and federal levels should begin now to decide about equitable access to MCSSs and other technologies, establishing commissions or other broadly based groups to aid in making those decisions.**
- **Below-cost payment rates should not be used to restrict access.**
- **If access decisions are made on a state-by-state rather than national basis, an adequately funded organization or mechanism should be established to provide information and assistance to such state decision-making processes.**

CLINICAL AND COST-EFFECTIVENESS

It is clear to the committee that the years of substantial federal commitments to artificial heart R&D will soon lead to clinically useful long-term devices that are adequate to prolong life and restore function for thousands of end-stage heart disease patients, as discussed more fully in Chapter 2. Clinical trials will first establish whether these devices are efficacious. Later clinical use and patient follow-up studies will be needed to identify more details of their effectiveness, as these terms are differentiated (see Chapter 3).

Given the health care environment that now exists and will continue for the foreseeable future, scrutiny of the care that is delivered will become increasingly stringent. Attention to the assessment and assurance of quality in the provision of care is at an all-time high. Costs are receiving an equal degree of review but, in its consideration of the future role of MCSSs, *the committee is particularly concerned that increases in aggregate health care costs resulting from MCSS use are matched by patient-care gains.*

Clinical Effectiveness

It is premature to judge precisely when a clinically effective long-term VAD will be approved for general marketing, but such an approval appears likely to occur before the end of the century. A fully implantable TAH will likely follow about 10 years later, depending on future NHLBI decisions about funding of TAH development.

The review mechanisms of NHLBI and the Food and Drug Administration (FDA), coupled with the efforts of those developing the devices and conducting their clinical trials, will provide reasonable assurance that devices coming into general use are efficacious, based on evidence from the clinical trials. Data will need to be obtained from a registry and from follow-up studies to establish their long-term clinical effectiveness. Continuing attention to assessing patient gains from implanting these devices will be important as their volume of use grows.

Quality of Life

No comprehensive assessment of a technology's clinical effectiveness can be complete without carefully examining its impact on patients' quality of life, because therapeutic interventions may have similar physiological effectiveness but still differ in terms of quality-of-life outcomes of patients. Quality-of-life measures can be especially important in assessing the outcomes of patients receiving therapies that carry high risks of negative consequences.

NHLBI is, perhaps, preeminent among others of the National Institutes of Health (NIH) in focusing attention on this essential component of patient outcomes; the committee is gratified to note NHLBI's broad quality-of-life initiative, not only in the artificial heart program but in other aspects of its research. Assessment of patients' postimplantation quality of life is a component of the current NHLBI-sponsored VAD clinical trial.

Irrespective of the degree and direction of change in any one or more quality-of-life domains (e.g., social functioning might improve and self-care might deteriorate for a patient, over time), three general health state outcomes are possible from a treatment. The determination of whether improvement, deterioration, or "no change" has occurred in health status is subjective, depending on the weights and values that are assigned by the individual making the trade-offs among the various states described. The results or products of trade-offs can be converted to quantitative values, namely preference weights (utilities), for particular health states; in the committee's cost-effectiveness analysis (CEA), these weights form the basis for calculating quality-adjusted life years (QALYs). All NHLBI sponsored research and clinical trials that include cost-benefit analyses or CEAs should include preference-weighted or utility measures.

Further work is needed in quality-of-life instrument development and validation to determine which domains are important to particular patient populations and, within domains, which components are sensitive to burdens perceived by patients. In addition to the more traditional core set of domains used in assessing health states, the study committee identified three health-related quality-of-life domains of potential significance to patients considering or having received an MCSS—machine dependence and societal reaction, the meaning and purpose of life, and spiritual well-being.

To the extent that policymakers judge it to be in the public interest to use public resources to develop MCSSs, those decisions should include commitments to support comprehensive assessments of health-related quality of life in patients receiving MCSSs during clinical trials and even thereafter. A core set of quality-of-life domains, similar to those used for this study's utility measures, should be assessed in all MCSS clinical trials. More research is needed to identify and understand support systems and selected other determinants of health-related quality of life that might be helpful in identifying those patients, among the groups meeting certain clinical conditions, who are more likely to benefit from an MCSS.

Cost-Effectiveness

The cost of health care and its clinical effectiveness, including quality-of-life gains, can be related to one another and assessed in various ways;

the most highly quantified are CEA and cost-benefit analysis. As described in Chapter 6, the committee has used CEA methods to examine both TAH clinical effectiveness and the funding of TAH development. In clinical studies, CEA yields a cost-effectiveness (C/E) ratio that expresses the incremental cost of each QALY gained from using the technology studied, compared with one or more alternate forms of treatment.

The committee's CEA examined the projected cost-effectiveness of TAH use and heart transplantation, comparing both with conventional medical treatment for end-stage heart disease as of 2010, the earliest that TAHs are likely to be in routine use. This required making a number of estimates of such aspects of TAH use as device failure rates and the probability of various TAH-related clinical complications, as well as lengths of hospital stays and outcomes of such events. The estimates developed for the CEA may well be more conservative than occurs when a current technology is examined, because of uncertainty about the outcome of use of these devices 20 years in the future.

From the committee's analysis, the estimated relative cost-effectiveness of using a TAH instead of medical treatment is about $105,000 per added QALY (in 1991 dollars), a C/E ratio that is considerably less favorable than those for other generally acceptable forms of heart disease treatment, such as $32,000 per QALY for heart transplantation and $34,000 per QALY for coronary artery bypass surgery for two-vessel disease with severe angina. The C/E ratio for TAH use is also less favorable than C/E ratios for other costly interventions (e.g., renal dialysis).

The committee's CEA examined only TAH use, the primary focus of the study. Because of the lower device cost and the fact that VAD failures may cause death less often than do TAH failures, the C/E ratio for long-term VADs may be somewhat more favorable than for TAHs. Further, results of the Novacor VAD clinical trial, other VAD use during the 1990s, and continuing technological gains will likely, over time, form a basis for improved C/E ratios for both types of MCSS.

Cost-Effectiveness in Research and Development Decisions

Cost-effectiveness analysis can also be applied to the consideration of research and development options. The committee used CEA to examine alternative levels of R&D investment during the next phase of TAH development. Based on assumptions of the impact of increased funding on the length of time required to complete R&D and on the future selling price of TAHs, this CEA reveals that increased R&D funding may be beneficial, assuming that the basic $105,000-per-QALY C/E ratio of TAH use is considered acceptable. If performed with care, CEA can make a useful contribution to decision making about R&D activities.

MAKING IMPORTANT DECISIONS

The committee has reviewed the ways in which NHLBI decides about the allocation of extramural research funds. It has also examined how decisions in the regulatory environment influence the entry of new technologies into the health care system. The committee believes there is room for improvement in both of these areas.

Allocation of Research Funds

The traditional peer-review process, as applied by study sections in their review of research grant applications, remains the best means of assessing the relative scientific merit of specific R&D proposals. Peer review through such mechanisms as the NHLBI Cardiology Advisory Committee can also assist in making some allocation-of-funds decisions.

For many other types of decisions about the allocation of funds among R&D program alternatives, peer review is less useful. In making these decisions, NHLBI essentially uses subjective professional judgment by its executive and administrative personnel. In this respect, it is no different from many other government and private-sector organizations that support academic and industrial research.

The committee has suggested in Chapters 3 and 6 several approaches that can serve as aids to decision making about the allocation of R&D funds at various levels within NHLBI and other organizations. Two of them involve cost-effectiveness analysis; the committee also developed 18 specific criteria, ranked as to their importance in R&D allocation decisions, that NHLBI can use as a starting point in developing explicit criteria for particular allocation decisions.

The committee recommends that, in addition to its appropriate reliance on the peer-review process, NHLBI consider adopting explicit criteria and more systematic methods such as cost-effectiveness analysis to aid it in allocating research funds among and within R&D programs at various levels.

Regulatory Decisions About Technologies

Several agencies and organizations must consider and approve new medical devices, drugs, and sometimes surgical procedures before they can be widely used. These actions by FDA, the Medicare program, and numerous other third-party payers are the regulatory counterparts to the development of clinical practice guidelines and other measures that help to improve the appropriateness of technology use.

Food and Drug Administration

One important proposition is that FDA, in making decisions about VAD and TAH clinical trials and posttrial applications, apply principles that are consistent with those applied by NHLBI in formulating the particular R&D program, as discussed in Chapter 9. The current level of cooperation between these two agencies of the Public Health Service is gratifying, and experience is likely to improve the consistency of their actions.

The committee recommends that NHLBI and FDA work together to assure that the design and conduct of MCSS clinical trials reflect agreed-upon principles that ensure safe and effective patient care and that facilitate the product approval process.

Third-Party Payers

The high visibility and cost of implanting MCSSs are likely to lead to individual coverage and payment decisions by a number of third-party payers. Additionally, as mentioned in the preceding discussion of access, this technology's high cost (both individually and in the aggregate) may predispose third parties toward denying coverage or establishing payment rates at below-cost levels in order to discourage MCSS use.

Relatively few third-party payers have explicit criteria or standards for their coverage decisions, particularly ones that can be applied to an emerging technology for which data are limited. Clinical practice guidelines may eventually be able to guide third parties in their actions concerning MCSSs, both in developing coverage and payment policies and in acting on pretreatment authorization requests. Indeed, these are likely to be important applications of clinical practice guidelines that are developed for use of these devices.

The committee recommends that third-party payers take into account the clinical evidence derived from MCSS trials and these devices' cost-effectiveness when establishing coverage policies that recognize both the technology's cost and clinical benefit to patients on a provisional basis, subject to later review and modification.

Consistent with the recommendation concerning institutional qualifications for MCSS implantations, the committee encourages third-party payers to consider implementing selective coverage programs as a part of their coverage decisions. In this manner, procedures will be performed only by surgeons and at hospitals that can demonstrate the necessary skills, experience, resources, and record of favorable outcomes. To the extent possible,

such programs might be undertaken on a cooperative basis or, as a minimum, using consistent criteria.

CONTINUING DEVELOPMENT OF TOTAL ARTIFICIAL HEARTS

The committee's principal charge is to advise NHLBI about continuing to fund TAH development. Considerations favoring the continuation of this support include:

- the substantial progress achieved over the artificial heart program's 27 years;
- the number of end-stage heart disease patients-probably at least 10,000 annually-for whom no other form of treatment appears able to prevent disability and death; and
- the likelihood, as explained elsewhere, that this development effort will not move forward without government support.

Offsetting these arguments is the current great uncertainty about virtually every aspect of this technology's likely status early in the next century. We have no hard information about either the clinical effectiveness of these devices or their cost. It is premature, with so little information, to move-with a new five-year phase of R&D-in the direction of routine use of a technology with the potential to add billions of dollars to the nation's health care costs.

Clinically effective performance, including an adequate patient quality of life, will be the principal factor in establishing clinical indications for the use of both TAHs and VADs. Further, clinical effectiveness and cost will be the principal factors in decisions by third-party payers and government policymakers about MCSS access; decisions about indications for use, third-party coverage, and access to MCSSs will combine to determine how many patients receive a device each year.

Based on reasonable but possibly conservative estimates of TAH performance, clinical effectiveness, and costs as of 2010, the committee's analysis found the TAH's C/E ratio to be $105,000 per QALY gained, in 1991 dollars, when compared with conventional medical treatment of end-stage heart disease. This ratio is substantially less favorable than that for heart transplantation and other generally accepted forms of treatment for heart disease, as well as for other catastrophic diseases.

A C/E ratio of this magnitude could be interpreted as reason to suspend or terminate all work on MCSS development, on the theory that the health care system cannot afford such a costly technology regardless of its potential to prevent death and disability for many thousands of patients each year. The committee considered this question carefully and is *not* recom

mending blindly moving ahead with a major commitment to the next five-year phase of TAH development.

The committee believes, instead, that the TAH's currently estimated C/E ratio is a reason to exercise great caution in making further commitments. At this stage of development, considerable uncertainty exists about these devices' eventual clinical effectiveness, some of which may be resolved in the next two to five years as results of the Novacor VAD trial and additional temporary MCSS use become available. The committee thus recommends that NHLBI continue its support of TAH development for a two-to three-year period only, with funding thereafter to depend on information developed during the next few years.

In addition to the financial commitment already made to the Novacor VAD trial, the committee estimates that it would cost between $5 and $10 million per year between 1993 and 1995 to continue development of TAHs as well as development of at least one additional approach to VAD design, a subject discussed further in the next section. (The precise figure would depend on peer-review evaluation of the developers' proposals to continue R&D and on NHLBI administrative decisions about the funding needed under each contract.) Such a level of expenditure is consistent with the current level of spending on targeted, contractual MCSS development and, in the committee's view, could be achieved with little or no effect on other R&D such as the investigator-initiated (R01) grants also supported by the artificial heart program.

Another consideration in the recommendation to continue R&D support for an interim period is the strong likelihood that, if TAH funding is suspended when the current contracts expire, at least some of the four developers will not be able to obtain private financing to continue their R&D work and the development teams will disband. If findings from VAD clinical trials during the 1990s yield revised performance estimates substantially better than those we can make at present but development teams have been disbanded, it would take years to resume TAH development and regain the current momentum.

NHLBI and other organizations regularly commit funds to R&D ventures with varying certainties of outcome; no reason exists to demand guaranteed success from the artificial heart program. Uncertainty admittedly exists about the ultimate TAH C/E ratio and its consequences, but moving ahead cautiously with additional TAH development during 1993-1995 offers the possibility of substantial benefits to patients who might otherwise die if TAH development is delayed by a suspension of funding. Because the needed $5 to $10 million per year is a relatively small amount, the committee believes the possible gain in future patient benefits outweighs the opposing uncertainty.

A final consideration relates directly to the TAH's C/E ratio. It is a

reason for exercising caution in making long-term R&D commitments but should not be viewed as an immediate, absolute reason to suspend this R&D support. Society may well be willing to pay $105,000 per added QALY for life-sustaining therapy. If it is, spending a relatively modest amount in the next few years is worthwhile to provide options for patients who may need TAHs early in the next century. The committee itself has no basis on which to place a maximum value on extending life and no authoritative entity exists to answer such questions. If some such entity were to decide that even $60,000 or $70,000 per QALY is too great a cost, then it would be reasonable to suspend both TAH development and R&D on new approaches to VADs until the current VAD development efforts yield MCSS clinical effectiveness data that are sufficiently improved to reduce the C/E ratio below $60,000.

The committee thus concludes that continuing NHLBI support of TAH development, for a limited period of two to three years beyond the current contracts' expiration in September 1993, is in the public interest because of its possible future benefit to patients and the additional information to be developed during that time. The developers whose work is to receive continued funding should be chosen through peer review of the scientific merit of progress to date and their proposed continuing efforts.

Between now and the end of the interim period of R&D funding, the developers should also be requested to specifically study and report to NHLBI on the possible impact of various levels of future support on (1) the duration of the preclinical or device readiness testing phase and thus device availability, and (2) the ultimate selling price of the device, once it goes into manufacture. The committee understands that somewhat larger contract budgets than have been customary could have an impact in both of these respects; the CEA it performed to test the effects of such scenarios established that more funding for certain stages of R&D might be a beneficial investment.

During this same period, NHLBI and the various interested sectors of the health care community also should begin to take action on this committee's general recommendations about appropriateness of use and access to care. It is important that this work, which is generic to both TAHs and VADs, proceed immediately, because the development of long-term VADs is likely to be completed several years sooner than that of TAHs.

Considerations for the Next Decision Point

Based on the information developed between 1991 and 1995, NHLBI will then have to make a decision about the next phase of TAH development. Information from long-term VAD clinical trials and continuing use of temporary MCSSs will be critical in confirming or revising the various

estimates used in our CEA. Clinical findings about a single VAD's ability to sustain cardiac function despite biventricular failure also will be helpful in determining the extent of the need for long-term TAH use; the need may be small enough to be met by transplantation, within the available supply of donor organs. As additional preparation for the next decision point on TAH development, NHLBI also should examine systematically the likely impact on future MCSS demand of several of the alternative forms of treatment discussed in this report. What are the prospects, and timetable, for the development of drugs that effectively prevent or delay end-stage disease? To what extent are cardiomyoplasty or other less drastic alternative forms of long-term cardiac support likely to reduce the need for costly implantable devices? What are the prospects for immunologic gains making human xenografts (heterografts) of animal hearts possible, and how will this affect the need for MCSSs? All are relevant questions.

Another possible consideration for NHLBI involves international activity concerning MCSS development. Decisions about continuing to develop TAHs or VADs may have international-trade or balance-of-payments implications, but the extent to which NHLBI should consider such implications in its decisions about R&D programs is debatable. The committee believes that potential benefits to patients should be the primary basis for federal support of health care R&D, with MCSSs or other technologies. If successful development of MCSSs leads to substantial exporting of these devices and thus a balance-of-trade gain, so much the better.

By assessing all of this information against explicit criteria such as those recommended in Chapter 3, NHLBI will be able to expand on this committee's work and make a sound decision about the next full-scale stage of TAH development. If the decision is made to proceed, the information reported by TAH developers about the impact of increased R&D funding can be used to fix the funding level that is most appropriate and, as well, can be reflected in contractual provisions for the next phase of R&D so as to provide incentives for the developers to accomplish those objectives.

Both the committee's recommendations and any NHLBI action consistent with them should be understood by everyone involved not to imply a long-term commitment to TAH development. If clinical performance estimates do not improve based on information developed during the interim period, NHLBI's proper course in 1994 or 1995 may well be to suspend all support for TAH development until further VAD experience has been gained. A much broader range of sensitivity analyses than this study's resources allowed will also be helpful in testing the impact of the estimates developed for NHLBI's next decision.

The committee concludes that NHLBI should continue to support scientifically meritorious TAH development for a two-to three-year period until preliminary results of the Novacor VAD trial (and perhaps other trials)

are known. Based on the important assumption that the broader concerns previously discussed-appropriate use and access-are being addressed concurrently, the committee has a three-part recommendation:

- **NHLBI should continue to support the four current TAH developers, to the extent warranted by the scientific merit of their work, for a two-to three-year period following the current contract expirations in September 1993 and at a level sufficient to ensure that research teams are not disbanded.**
- **TAH R&D should be reconsidered in 1994 or 1995, taking into account the VAD experience and information about other potential long-term TAH benefits generated in the interim.**
- **NHLBI should decide at that time whether to move ahead with funding for the next phase of TAH development, after further peer review and a decision-making process that takes into account a then-current cost-effectiveness projection and other relevant criteria.**

By proceeding in this manner, it may be possible to devote some funds to other uses in the intervening years, additional potential long-term savings and gains can be explored in detail, and the TAH designs that ultimately result can reflect lessons learned from early use of long-term VADs. The committee's cost-effectiveness example, analyzing the impact of increased levels of R&D funding, will be useful to NHLBI in its 1994-1995 TAH decision, as will be the explicit decision-making criteria suggested in Chapter 3.

OTHER RECOMMENDATIONS

The preceding recommendations and discussions fulfill the committee's principal obligation to NHLBI, responding to the nine questions set forth in the 1989 report of the IOM planning committee and making recommendations concerning future TAH development. The committee believes that several additional conclusions and recommendations about aspects of MCSS development are also appropriate.

Future Development of Ventricular Assist Devices

The need for a fully implantable, long-term VAD is substantial, and at least one long-term VAD appears reasonably certain to be approved for routine clinical use during the 1990s. Although it will be perhaps 2010 before the technology's use will diffuse sufficiently to meet the need, an annual primary pool of between 35,000 and 70,000 candidates to receive either a VAD or TAH now exists. If continuing development efforts result

in a device whose performance approaches transplantation outcomes (now about a 70 percent 5-year survival rate), the size of the candidate pool will increase by perhaps another 200,000 per year, as of about 2020.

Taking full advantage of the potential of VADs is thus a vital goal. In this regard, the committee is concerned about the possibility that development of long-term VADs other than Novacor's may not continue. If NHLBI ends its contractual funding of other VAD developers, the economic uncertainties might preclude private funding of their R&D work and they may suspend it. Therefore, a risk exists in relying on a single approach to VAD development. Further, lower device prices may also result, if more than one VAD is available. (This discussion specifically does not refer to VAD development under investigator-initiated [R01] grants; consideration and funding of such grants should continue via the usual peer-review process, under any circumstances.)

All current models of VADs were essentially designed in the late 1970s; they do not reflect either more recent R&D results or possible new approaches to VAD design that have not yet reached the prototype stage. Knowledge and a range of approaches gained during the 1980s, but not yet applied, may prevent unnecessary delays in developing a clinically useful VAD, particularly if the Novacor VAD encounters unanticipated problems during the forthcoming trial. An end to federal R&D support may also adversely affect the continuity of research by causing the loss of key research personnel to other fields.

Yet another reason for continuing NHLBI involvement in additional VAD research is that it enables the agency to ensure that clinical trials are properly designed and conducted. FDA review of a developer's investigational device exemption application is theoretically sufficient to ensure that all aspects of a trial are properly designed and conducted, including periodic postimplantation assessments of patients' physiologic status and health-related quality of life. In practice, however, the committee recalls the criticisms of past artificial heart trials at Salt Lake City, Louisville, Phoenix, and other locations as having important shortcomings; by continuing its R&D involvement NHLBI can exert strong influence over all aspects of VAD trials.

Finally, because of the relatively large potential volume of long-term VAD use, private-sector interest in this technology will likely increase after one VAD has gone into general use and has received third-party coverage approvals. Commitment of substantial private resources to long-term VADs at their current stage of R&D appears unlikely, however, because of the length of time consumed in the development and regulatory processes and the uncertainty about when regulatory approvals will be granted and general use begin.

The committee therefore believes that ending contractual support for all

but one VAD developer carries substantial risks that NHLBI may wish to avoid and concludes that continued support of other scientifically meritorious VAD development is desirable, for at least a two-to three-year period. This could be done either by implementing a new peer-reviewed initiative such as a request for proposals to design a state-of-the-art implantable VAD or by continuing to support, at least temporarily, one or more VAD developers whose approaches differ from the current Novacor model.

After preliminary postdischarge follow-up results for the early patients in the forthcoming VAD trial are available, perhaps in 1993, NHLBI will be able to decide with greater certainty about the need for continuing support of VAD development.

The committee therefore recommends that, in addition to the Novacor clinical trial, NHLBI consider the continuation of targeted R&D support for other VAD development for at least a period ending in late 1993 or 1994, with further support to be considered at that time.

Clinical Trials and Patient Follow-up

The committee has several concerns in the area of MCSS clinical trials and ongoing patient follow-up.

Clinical Trials

In order to determine the continuing role of MCSSs, three types of data should be routinely collected in clinical trials: (1) physiologic data (e.g., cardiovascular, renal, neurologic, hematologic), obtained periodically throughout the trial period; (2) health-related quality-of-life data, using core sets of test questions that tap both generic and condition-or treatment specific domains; and (3) data about the clinical outcome and cost of treatment so that reports of the trial can include cost-effectiveness analysis. Funding of all trials, including that of the Novacor VAD, should be adequate to ensure that all aspects of device use, and their implications, can be addressed by those conducting the trial. Trial design and implementation should also ensure that study populations include adequate representation of women and minority populations.

It is important that MCSS trials, whether supported by public or private funds, make provision for each patient to provide a fully informed consent, an advance directive concerning termination of treatment, and legal designation of a proxy; see the review of these ethical safeguards in Chapter 8.

The committee thus recommends that all NHLBI-supported and private MCSS clinical trials include adequate funding for the

collection of physiologic, health-related quality-of-life, and costeffectiveness data and, as well, include provisions protecting patients' ethical rights, such as a requirement for written advance directives and, if allowed by state law, designation of a proxy decision maker. Trial protocols should ensure adequate representation of women and minorities and should provide for comparability with other studies by using, for instance, a standard core set of quality-of-life domains and assessment methods.

Postmarketing Surveillance

All patients receiving a long-term MCSS should be followed for the remainder of their lives, at least to the extent of obtaining rudimentary survival information on a periodic basis. An MCSS implantation is not a simple, time-limited treatment episode. This type of lifetime follow-up can best be accomplished through a registry that receives information from clinicians who implant devices and patients who receive them. If public and quasi-public funds, the latter provided via health insurers, are to support the development and use of this costly technology, special measures are warranted to oversee its long-term clinical effectiveness.

The committee recommends that long-term MCSS patients and their physicians provide lifelong follow-up information to a registry, and that hospitals, stimulated by requirements of third-party payers and their payments for this component of care, fund such a registry as an integral part of providing the care.

Posttrial Follow-up

The two-year follow-up period that is typical of clinical trials of implanted devices is not long enough to reveal all problems that may occur with MCSS use. In addition to any registry that is established, an adequate sample of patients receiving MCSSs during clinical trials should be followed periodically after the trial period ends, to ascertain and study details of posttrial patient management and outcomes. This could be accomplished by various means. For subjects in clinical trials sponsored by NHLBI, that agency should fund follow-up studies of either all patients or a sample. If such a study is to be undertaken by a device developer, such as to fulfill FDA postmarketing surveillance requirements, provisions should be included to ensure that results of the study will be published promptly, regardless of outcome.

For patients receiving an MCSS after it is FDA-approved, AHCPR should fund one or more long-term follow-up studies of an adequate sample of

patients, to be performed by academic or independent researchers. In all instances, funding should be sufficient for the study to gather and report data about patients' physiologic status, health-related quality of life, and treatment costs.

The committee therefore recommends that NHLBI and AHCPR support long-term follow-up studies of an adequate sample of all patients receiving MCSSs and fund such studies adequately.

Fostering Collaborative Interdisciplinary Research

As previously mentioned, the artificial heart program, with its targeted, largely developmental R&D effort, is unusual not only within NHLBI but also in NIH as a whole. The policies and mechanisms by which the artificial heart program operates were originally developed to review, approve, and manage traditional investigator-initiated, nontargeted research by basic scientists, not the development of complex devices and support of their extensive technical evaluation, redesign, preclinical testing, and clinical trials.

Additionally, although traditional scientific peer review is as important to MCSS research as it is to any other field, considering artificial heart program proposals in the existing peer-review committees puts this truly interdisciplinary research involving biomedical engineers, clinicians, and others at a serious competitive disadvantage, as discussed in Chapter 9. Adequate peer review of MCSS R&D requires the involvement of biomedical engineers and professionals with other relevant expertise (e.g., quality-of-life assessment, cost-effectiveness analysis).

The committee recommends that all proposed grants and contracts for MCSS development be peer-reviewed by a group or groups including appropriate numbers of biomedical engineers, clinicians, and professionals from other relevant disciplines.

The organizational structure within which the artificial heart program operates, designed as it is to administer grants to individual investigators, is not as flexible as would be ideal to make collaborative grants that involve both academe and industry. The committee believes that collaborative multidisciplinary research, structured to encourage industry to share in the R&D costs, is an important aspect of government support of private-sector research, consistent with the examples of R&D support by other government agencies (e.g., Department of Defense, National Science Foundation).

The committee recommends that NHLBI amplify its attention to alternative policies and structures for programs such as the

artificial heart program that allow greater flexibility in operating modes and that might serve as models for future efforts to encourage collaborative R&D on a cost-sharing basis, considering the successful experience of other agencies.

Patients' Quality of Life and Treatment Preferences

In many sectors of health care, patients' health-related quality of life has not received adequate attention. For a device such as an MCSS, which patients and their families must learn to live with for an indefinite period, as discussed in Chapter 5,

the committee recommends that physicians and hospitals involved in implanting long-term MCSSs develop support programs to enhance the quality of life of MCSS patients and their families during the period of hospitalization and after discharge.

Attention to explicit patient preferences is a growing aspect of medical care. Fully informed patient preferences, or those of a properly designated surrogate decision maker, should be accorded great weight in treatment decisions about implanting an MCSS in the first place as well as withdrawing support at a later time. Thus, as recommended above, protocols for MCSS clinical trials should provide for advance directives and the naming of surrogate decision makers by prospective patients.

Research Needs

Heart Failure Research

Whatever NHLBI's decisions about continuing to support MCSS development, that support should not be at the expense of basic and clinical research concerning medical treatment of end-stage heart disease. The borderline cost-effectiveness of TAH use, as well as the costliness and other logistical problems of transplantation, support giving a high priority to research that may ultimately prevent heart failure or delay its onset. The committee therefore concludes that NHLBI should not use the development of MCSSs as a reason to reduce its level of funding of basic heart disease research. Instead,

the committee recommends that NHLBI continue to support, at an adequate level, scientifically meritorious research into the mechanisms of heart failure and approaches to the prevention and medical treatment of end-stage heart disease.

Epidemiological Research

The committee's projections of MCSS use required reliance on numerous sources of epidemiological data about end-stage heart disease, none of which was completely satisfactory. Little is known from an epidemiological perspective about the course of this disease, as discussed in Chapter 4. Better basic data will make future projections of MCSS use more accurate. The committee therefore applauds NHLBI for supporting the longitudinal studies recently begun; further,

the committee recommends that, in addition to current longitudinal studies of heart disease in persons over age 65, NHLBI undertake as a high priority, and possibly with the involvement of the National Center for Health Statistics, the development of additional epidemiological data about the natural history of end-stage heart disease in patients of all ages, with special attention to the inclusion of women and minority populations.

Communication Among MCSS Researchers

Medical device manufacturers and other private sources of financing are increasingly becoming involved in the support of academic MCSS research and development. The committee encourages this, but it is also concerned that such involvement may have an adverse effect on the open, collegial communication among researchers that has been a valuable aspect of MCSS development to date.

The committee recommends that, when undertaking relationships with the private sector, academic researchers work cooperatively to minimize restrictions on their freedom of communication with other researchers, and that their universities develop policies consistent with this goal. It further recommends that this topic be explicitly and thoroughly discussed at a meeting involving all researchers and developers in the field.

HOW THIS REPORT SHOULD BE USED

This study, following six panels that conducted similar evaluations over the past 22 years, has posed a special challenge for the committee: namely, to review all aspects of a relatively small, but nonetheless important and highly visible, segment of federal support of biomedical research and to make projections and recommendations about the future of this unique technology. Faced with the absence of key data in numerous areas, the committee has made estimates that it considers reasonable based on the current evidence.

This study has been able to add to the knowledge base of previous NHLBI studies of the artificial heart program because the technologies involved are so much nearer to clinical use than they were in earlier years. It has also reviewed some aspects of the NHLBI research funding process, a topic not discussed in previous studies.

Most important, any one of the comprehensive studies of the artificial heart that have been performed could serve as a model of the type of study that should become an integral part of the U.S. health care system. Technologies have gone into widespread use with little understanding of their clinical, quality-of-life, ethical, and economic prospects. By and large, patients have been fortunate; most new technologies prove to have clinical value.

Yet technology continues to be blamed for much of the steady rise in health care costs. Comprehensive studies—whether to assess new technologies, guide their diffusion, or measure their impact on costs—have been few in number. It is neither simple nor inexpensive to study complex new technologies, let alone to develop measures that assess and improve the appropriateness of their use.

The committee expresses the hope that leaders in key components of the U.S. health care system, as well as policymakers in the administration, Congress, and state capitals, will consider the recommendations of this study, particularly those that are broadly applicable. The research, development, and diffusion of future technologies require attention to methods and oversight mechanisms that reflect the full range of considerations discussed here. These conclusions and recommendations can, if applied both to MCSSs and to other new technologies, improve the ways in which the nation's health care providers and regulators deal with them, as well as the ways in which those who support health care R&D manage the innovative research that yields so many health care gains.

REFERENCE

President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. 1983. *Securing Access to Care. Vol. 1. Report on the Ethical Implications of Differences in the Availability of Health Services.* Washington, D.C.: U.S. Government Printing Office.

Appendixes

A

History and Methods of This Evaluation*

IN OCTOBER 1988, the director of the National Heart, Lung, and Blood Institute (NHLBI) requested that the Institute of Medicine (IOM) evaluate the NHLBI artificial heart program. NHLBI's request was made in light of a growing consensus among many groups, including the National Institutes of Health, Congress, federally funded researchers, and private industry associated with artificial heart research and development, that a new evaluation of the priorities of the NHLBI artificial heart program was needed to help chart the program's future.

The issue was raised in part by a decision by NHLBI in May 1988 to cancel, in the first year of funding, four five-year contracts for developing and integrating systems for a total artificial heart. Expressing concern about the feasibility of developing a safe, effective implantable total artificial heart, and citing budgetary concerns, NHLBI decided to place greater emphasis on programs that supported research and development of left ventricular assist devices. The agency reasoned that progress in developing ventricular assist devices could be applied to future work on the total artificial heart, because both devices share many of the same technological and scientific barriers to development.

NHLBI's decision to cancel the four projects was not well received by the contractors and certain professional and industry organizations, and

* Sections of this description of the Institute of Medicine studies and their methods are adapted from *The Artificial Heart Program of NHLBI. Plan for Evaluation,* published by the Institute of Medicine. Washington, D.C.: National Academy Press, 1989 (reprinted in *Artificial Organs* 1990; 14:227-242).

when members of Congress objected, the decision was subsequently rescinded. As of this writing, the four total artificial heart projects are proceeding according to contractors' original plans and with funding committed through September 30, 1993. See Appendix B for a chronology of the NHLBI artificial heart program and related events.

Because of the breadth and complexity of issues involved in evaluating a program like the NHLBI artificial heart program, IOM and NHLBI agreed to a two-stage approach: a 5-month planning study and subsequent 15-month evaluation study. The purpose of the planning study was to identify the scope and particular tasks of the evaluation. Accordingly, in May 1989, the IOM established a committee to undertake the five-month planning study. The planning committee focused on the following question: on what bases can rational decisions regarding allocation of artificial heart research and development funds be made? It then identified nine evaluation questions for use in answering this central question, and drafted a work plan for the subsequent study committee. These nine questions were incorporated into the charge of the second study committee, along with a tenth question addressing communication and cooperation in mechanical circulatory support system research. The questions are listed in Chapter 1, Table 1.3.

The second IOM committee comprised 17 members with expertise in the fields of cardiothoracic surgery, bioengineering, cardiovascular and internal medicine, epidemiology and decision analysis, program planning and evaluation, ethics, health policy, economics, law, social sciences, and third-party payment. In the course of the study, the committee met four times, sponsored a public meeting, and held two workshops in conjunction with its second and third meetings. The list of those making presentations at the public meeting follows at the end of this appendix. The committee also commissioned five background papers from outside experts as resource materials for the workshops, and as background for sections of the committee's report. The committee reviewed a considerable body of medical, scientific, and health policy literature, including earlier reports on the artificial heart from expert groups established by NHLBI, journal articles, and other documents on artificial heart technologies. The committee solicited, in addition to public meeting presentations, the views of more than 75 individuals who could offer insight into issues pertaining to the study. The committee's deliberations covered a total of nine days, including numerous small-group discussions of specific topics and conference-call discussions.

The second IOM committee's report, which forms the main portion of this book, was reviewed twice by all committee members. Consistent with the procedures of IOM and the National Academy of Sciences, the final report was also evaluated through the report review process established by the National Research Council, by a group of anonymous experts possess

ing relevant expertise. The report was published by the National Academy Press in the fall of 1991.

ADDENDUM

Presenters at the Public Meeting on July 13, 1990

George J. Annas, J.D., M.P.H., Professor of Health Law and Director, Law, Medicine and Ethics Program, Boston University School of Public Health

Kenneth L. Baughman, M.D., Cardiovascular Division, Johns Hopkins School of Medicine

Harvey S. Borovetz, Ph.D., Department of Surgery, University of Pittsburgh

Stanley A. Briller, M.D., Department of Surgery, Allegheny General Hospital, Pittsburgh

Kenneth C. Butler, Director, Engineering, Nimbus, Inc., Rancho Cordova, California

Jack G. Copeland, M.D., Department of Surgery, University of Arizona Health Sciences Center, Tucson (for the Society of Thoracic Surgeons)

O. Howard Frazier, M.D., Chief, Transplant Service, and Co-Director, Cullen Cardiovascular Research Laboratories, Texas Heart Institute, Houston

William A. Gay, Jr., M.D., Professor and Chairman, Department of Surgery, University of Utah School of Medicine, Salt Lake City

Leonard A.R. Golding, M.D., Acting Chairman, Department of Artificial Organs, Cleveland Clinic

Bartley P. Griffith, M.D., Department of Surgery, University of Pittsburgh

J. Donald Hill, M.D., Chairman, Department of Cardiovascular Surgery, Presbyterian Hospital-Pacific Medical Center, San Francisco

Robert K. Jarvik, M.D., Jarvik Research, New York, New York

Thomas E. Kottke, M.D., Cardiovascular Diseases and Internal Medicine, Mayo Clinic, Rochester, Minnesota

George J. Magovern, M.D., Chairman, Department of Surgery, Allegheny General Hospital, Pittsburgh

Alan Millner, Ph.D., Principal Scientist, ABIOMED, Inc., Danvers, Massachusetts

John C. Norman, M.D., Humana Heart Institute International, Louisville, Kentucky

Yukohiko Nosé, M.D., Department of Surgery, Baylor College of Medicine, Houston

Donald B. Olsen, D.V.M., Director, Institute for Biomedical Engineering, University of Utah, Salt Lake City

D. Glenn Pennington, M.D., Department of Surgery, St. Louis University Medical Center (for the American Society for Artificial Internal Organs)

William S. Pierce, M.D., Evan Pugh and Jane A. Fetter Professor of Surgery and Chief, Division of Artificial Organs, Pennsylvania State University College of Medicine, Hershey

Victor L. Poirier, President, Thermo Cardiosystems Inc., Woburn, Massachusetts

Peer M. Portner, Ph.D., President, Novacor Division, Baxter Healthcare Corporation, Oakland, California

Robert L. Whalen, President, Whalen Biomedical Inc., Cambridge, Massachusetts

B

A Chronology of the National Heart, Lung, and Blood Institute Artificial Heart Program and Related Events*

1963	Prominent medical and other scientific researchers testify before Congress that it would be possible to develop an artificial heart if more funds, particularly for bioengineering, were available.
	The National Heart Advisory Council recommends a long-range program of research to develop a permanently implantable artificial heart that could be used to replace a failing natural heart.
1964	The director of the National Heart Institute (NHI) convenes an ad hoc advisory group that includes leading investigators in the artificial heart field. The group urges the institute to expedite the development of the artificial heart and to use contracts for research and development.
	NHI establishes the artificial heart program with special congressional approval and an appropriation of $581,000. The intent is to develop a totally implantable mechanical heart. Six contracts are awarded to support comprehensive analyses of technical development issues and of needs for the artificial heart.
	NHI establishes the Artificial Heart Program Office when congressional funds are made available.
	The National Advisory Heart Council endorses the proposal that the artificial heart program be approached on a systems development basis because it perceives the problems of development to be

* Terms used in the chronology are consistent with those used at the times noted. They differ in some cases from the terms used in the Institute of Medicine committee's report. Italics indicate related events.

	largely engineering in nature, and thus amenable to the same general approach as that being concurrently used in the space program.
	The President's Commission on Heart Disease, Cancer, and Stroke recommends development of the artificial heart.
1965	Congress invites the National Institutes of Health (NIH) to state for the record how much money in addition to its current budget it would require to start a planning program to develop the artificial heart. NIH requests $40 million for fiscal years 1965-1968.
1966	NIH Director James Shannon, who has stated that a full-scale effort to develop an artificial heart is premature, writes to the Surgeon General and the Secretary of the Department of Health, Education, and Welfare stating that he does not think that total cardiac replacement is feasible at the current time and that concentration of money and effort toward this end would curtail development of alternative strategies to reduce end-stage heart disease mortality and morbidity.
1967	Director Shannon persuades Congress that the artificial heart can be developed for less money than currently appropriated (i.e., $10 million per year). He renames the program "The Artificial HeartMyocardial Infarction Program" and allocates $8.5 million to research contracts, of which $2.9 million is used to support research on electrical, nuclear, and other power sources.
	In South Africa, Christiaan Barnard performs the first human heart transplant.
1969	*Denton Cooley of the Texas Heart Institute performs a human artificial heart implant to keep a patient who had postoperative complications alive until a donor heart could be found and transplanted. The patient survives 64 hours on the device, but dies 32 hours after the transplant.*
	Emphasis in the artificial heart program shifts from separate development of each component to integrating existing components to produce a fully implantable cardiac assist device for testing in animals.
	The proceedings of the first Artificial Heart Conference, sponsored by NHI's artificial heart program, are published. The proceedings note that the philosophy of the artificial heart program is to stress rehabilitation rather than mere prolongation of life.
	The NHI-sponsored Ad Hoc Task Force on Cardiac Replacement, consisting of 10 members, 9 of whom are drawn from the medical community, publishes a report, *Cardiac Replacement: Medical, Ethical, Psychological, and Economic Implications.* The task force concludes that the most serious technical problem confronting the

	artificial heart program is the development of materials entirely compatible with human blood. In addition, it notes in the body of the report that there is currently no way to use external wires or hoses (for air or fluid) without exposing patients to risk of potentially lethal infections. The prospect of a totally implantable power source is deemed to be years away. The task force in its recommendations states that ventricular assist devices (VADs), specifically a left ventricular assist device (LVAD) that would augment the ability of the heart's left ventricle to pump blood into the aorta, are considered to be a promising area of research.
1973	The National Heart and Lung Institute (NHLI)-sponsored Artificial Heart Assessment Panel, composed of members primarily from outside the biomedical research field, issues a report, *The Totally Implantable Artificial Heart: Legal, Social, Ethical, Medical, Economic, Psychological Implications,* that focuses on the implications beyond the scientific and technical aspects of the artificial heart program. The panel's charge is limited to an assessment of problems that would be expected to arise from introduction and diffusion of a clinically effective artificial heart. Although the panel is not asked to review technical issues or to consider whether a total artificial heart (TAH) is feasible, it strongly advises against use of nuclear-driven energy converters. This convinces the Atomic Energy Commission to terminate support in this area. The panel also urges NIH to establish a permanent, interdisciplinary, and representative group of public members to monitor and to help formulate guidelines for the artificial heart program. NHLI sponsors a workshop on the left ventricular assist pump. The resulting document, *Report on Left Ventricular Assist Device Teco-Models VII & X,* concludes that a basic materials problem exists that must be resolved before clinical use of the device is warranted; it also recommends that continued research on the LVAD should progress in an orderly and stepwise fashion, i.e., through bench testing and animal testing, before clinical use of the device can be warranted.
1974	The artificial heart program is moved into the NHLI Division of Heart and Vascular Diseases to improve administrative and programmatic functions. Emphasis in the program continues to be on VADs. Research on nuclear power sources is halted.
1975	Authorization is given to begin clinical trials of an LVAD for temporary use in patients who are unable to resume cardiac function after open heart surgery.

1977	The National Heart, Lung, and Blood Institute (NHLBI) Cardiology Advisory Committee publishes the report *Mechanically Assisted Circulation: The Status of the NHLBI Program and Recommendations for the Future.* The committee recommends that highest priority be given to the NHLBI LVAD program, starting with short-term devices and progressing through intermediate to long-term circulatory support as progress warrants. It also concludes that the most pressing demand is for cardiac assistance in the immediate postoperative period for weaning patients from cardiopulmonary bypass.
1978	*Phillip Oyer of Stanford University performs the first bridge to transplant with an electrically powered assist device; several days later, Jack Norman of the Texas Heart Institute performs the first bridge to transplant with an air-driven device. In both cases, the patients are successfully transplanted.*
1980	NHLBI sponsors an evaluation of its artificial heart program. The resulting report, *Mechanically Assisted Circulation: Report of the NHLBI Advisory Council Working Group on Circulatory Assistance* and the Artificial Heart, concludes that the program has been productive and is adequately funded and administered. It stresses continued research of ventricular assist system technology.
1981	Researchers Willem Kolff, William DeVries, and Robert Jarvik at the University of Utah apply to the Food and Drug Administration (FDA) for an investigational device exemption to allow implantation of a TAH into a human. Their request is approved. In light of the Utah research, NHLBI sponsors a working group to evaluate the technical, social, ethical, and economic issues surrounding the TAH. In its report, *Report of the Artificial Heart Working Group,* the working group recommends continued research on temporary and permanent VADs and the TAH. It concludes that use of total heart replacement can be justified only when massive and irreversible heart damage has occurred. The working group further recommends that the following ethical issues be addressed before clinical testing is initiated: the procedure for obtaining informed consent, the potential influence on decision making and possible emotional trauma resulting from extensive publicity, the quality of life to be anticipated following insertion of the device, and the uncertainty, at the current stage of development, of the long-term future of the patient. *To sustain a patient who has suffered a myocardial infarction during a triple bypass procedure, Denton Cooley uses an artificial*

	heart until a suitable human heart becomes available. The patient survives 54 hours before receiving a donor heart.
1982	*William DeVries implants the Jarvik-7 artificial heart into Barney Clark, a patient with end-stage cardiomyopathy, under an investigational device exemption granted by FDA that permits use of the artificial heart in patients unable to come off a heart-lung machine or in patients with chronic degenerative heart disease. Barney Clark lives 112 days.*
1984/1985	*The Jarvik-7 heart is implanted in four more patients, including one in Sweden.*
1985	The NHLBI-sponsored Working Group on Mechanical Circulatory Support of the NHLBI publishes a report, *Artificial Heart and Assist Devices: Directions, Needs, Costs, Societal and Ethical Issues.* The working group endorses continued governmental support of the development of circulatory support devices, and urges NIH to resume funding to develop a totally implantable permanent heart.
1988	In January, largely on the 1985 recommendation of the working group, NHLBI awards contracts worth more than $22 million to four research groups[1] to continue research and development of the TAH. *In February, responding to requests from the scientific community and others, William DeVries and colleagues publish several articles in the Journal of the American Medical Association (JAMA) that detail the medical history of each of the four total artificial heart implants that he performed.* In May, NHLBI announces that institute support for developing and integrating systems for a TAH will be suspended as of September. NHLBI Director Claude Lenfant states that the decisive factors behind the suspension of funding are that implantable LVADs are nearly ready for human testing and that NHLBI does not have sufficient funding to support both human testing of LVADs and continued development of the TAH. Dr. Lenfant notes that he was also influenced by DeVries' JAMA articles and by other reports of complications suffered by bridge patients who remained on the Jarvik-7 for longer than a few weeks.

[1] The four groups awarded contracts were ABIOMED, Inc., Danvers, Massachusetts; Nimbus Company, Rancho Cordova, California; Pennsylvania State University Medical Center, Hershey, Pennsylvania; and the University of Utah Institute of Biomedical Engineering, Salt Lake City, Utah.

	Dr. Lenfant's announcement of the funding suspension is not well received by four TAH contractors. Senator Orrin Hatch (RUT), ranking Republican on the Senate committee that authorizes the NIH, and Senator Edward Kennedy (D-MA), chairman of that committee, take the lead in pressuring NIH to restore funding to the TAH systems development. Senator Hatch, with the backing of Senator Kennedy, drafts legislation that would require NIH to fulfill existing contracts like those supporting the TAH development before starting any new programs and prohibits the agency from cutting existing programs by more than 10 percent. In support of their action, the senators note that the NHLBI Advisory Council that ratified NHLBI's decision had appealed for more funding to continue the artificial heart program. NIH subsequently restores funding to the TAH contractors.
1989	NHLBI asks the Institute of Medicine (IOM), through its Council on Health Care Technology, to undertake an evaluation of NHLBI's artificial heart program. Given the breadth of the proposed study, the IOM and NHLBI agree that it should be conducted in two phases. The first is to be a five-month planning phase involving a committee to define the scope of study and the specific tasks to be accomplished. The second is the evaluation itself, which will be a more lengthy evaluation by another committee to be appointed by the IOM. *By April, the Jarvik-7 total artificial heart has been used in 92 patients as a potential bridge before transplantation: 63 received new donor hearts and 35 survived.* In May, IOM is awarded a contract to conduct the planning study. In August, NHLBI releases a request for proposal for a Clinical Evaluation of Implantable Ventricular Assist Systems for Human Subjects with Chronic Refractory Heart Failure, and funds a contract to produce 30 medical-grade totally implantable LVADs for use in patients with end-stage heart disease.
1990	In March, IOM is awarded a contract to conduct the evaluation proposed in the 1989 IOM planning committee's report, *The Artificial Heart Program of NHLBI: Plan for Evaluation;* in mid-year, the NHLBI funds contracts with St. Louis University and the University of Pittsburgh for a joint clinical trial of 20 Novacor LVADs.
1991	In mid-year, IOM completes its evaluation for NHLBI and issues its report, *The Artificial Heart: Prototypes, Policies, and Patients.*

C

Technological Opportunities and Barriers in the Development of Mechanical Circulatory Support Systems

GERSON ROSENBERG

THE CONCEPT OF MECHANICAL CIRCULATORY SUPPORT was first postulated by LeGallois in 1812 (LeGallois, 1813). Much later, in 1934, DeBakey proposed a simple continuous flow blood transfusion instrument that was a simple roller pump (DeBakey, 1934). In 1961, Dennis and colleagues performed left heart bypass by inserting cannulae into the left atrium and returning blood through the femoral artery (Dennis, 1979). In 1961, Kolff and Moulopoulos developed the first intra-aortic balloon pump (Moulopoulos et al., 1962). In 1963, Liota performed the first clinical implantation of a pulsatile left ventricular assist device (Liota et al., 1963). In 1969, the first implant of a total artificial heart was performed by Denton Cooley (Cooley et al., 1969). Mechanical circulatory support has been used in over 1,300 patients since 1985. There have been implants of approximately 186 total artificial hearts, 600 left ventricular assist devices, and 112 right ventricular assist devices along with 409 biventricular assist devices. Of these 1,300 patients, over 600 have been weaned and approximately 365 have been discharged from the hospital (Joyce et al., 1988; Pae and Miller, 1990).

Progress in the use of ventricular assist devices and artificial hearts has been excellent. In the 1970s, animal survival with the total artificial heart

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was averaging approximately two weeks; animal survivals today are approaching one year, and patients have survived for almost 600 days with artificial hearts. The use of temporary ventricular assist devices is becoming more routine, and the development of permanent left ventricular assist devices and total artificial hearts is well under way. Yet with all the progress that has been made, there are currently several complications associated with the permanent application of left ventricular assist devices and total artificial hearts. These can be broken down into durability and biocompatibility (including bleeding, thrombosis, sepsis, calcification, and hemolysis). These factors appear in various degrees in all of the devices and will be discussed, but they do not appear to be insurmountable problems; in fact, several appear to be close to solution.

CURRENT STATE OF THE TECHNOLOGY IN MECHANICAL CIRCULATORY SUPPORT SYSTEMS

Artificial hearts and circulatory assist devices are currently under development in the United States, Korea, Russia, Canada, Switzerland, Japan, Germany, Czechoslovakia, Italy, France, Australia, China, and other countries. A detailed description of all of these devices is beyond the scope of this document, and only those with significant design features or devices sufficiently developed to be nearing clinical trials will be discussed.

The most frequent clinically used mechanical circulatory support systems (MCSSs) are those currently manufactured in the United States (Pae and Miller, 1990). The animal survival times with pneumatically powered devices are essentially the same in the United States and abroad, indicating approximately the same technology level (Total Artificial Heart, 1985; Total Artificial Heart, 1987). Electric motor-driven circulatory assist and artificial heart devices are, at the present time, more advanced in the United States than in any other country, although devices in Japan (Total Artificial Heart, 1985) and Switzerland (Odermatt, 1989) are advancing rapidly.

All of these MCSSs have met with similar difficulties in development and application. These difficulties include device durability and biocompatibility. Various solutions have been implemented for these problems and have allowed devices to function for over a year in vivo and greater than two years in vitro.

Short-Term-Use Devices (fewer than 180 days)

Both total artificial hearts and univentricular or biventricular assist devices can be utilized temporarily for mechanical circulatory support. All of the total artificial hearts that have been utilized clinically have been pneumatically powered devices. The ventricular assist devices that have been

utilized clinically include pneumatically or electrically powered pulsatile devices and nonpulsatile devices.

Total Artificial Heart

For the purposes of discussion, total artificial hearts will be considered those devices that are orthotopically placed with the removal of the native heart, thus distinguishing these devices from biventricular assist devices.

Animal and Clinical Results

Over the past decade, several short-term pneumatic artificial hearts have received significant development. These devices include the pneumatic artificial hearts of The Pennsylvania State University (Penn State) and the Free University of Berlin, the Jarvik or Symbion artificial heart originally developed at the University of Utah, the Cleveland Clinic Foundation heart, and the heart of the University of Perkinje in Bruno, Czechoslovakia. Other hearts are being developed in Tokyo, Japan (Pierce, 1986; Total Artificial Heart, 1989). The longest survival with a pneumatic artificial heart in a calf or sheep is 353 days, accomplished by the Penn State group (Aufiero et al., 1987). A sheep at the University of Utah lived for 297 days and a goat with a pneumatic artificial heart lived for 344 days at the University of Tokyo. The Tokyo heart was not orthotopically placed, but was located outside the animal's thoracic cavity. Thus, it is accurate to say that a small percentage of the artificial heart animals have been able to survive for slightly less than one year. Several factors contribute to this one-year time limit. In the growing animal such as the calf, the animals have the potential to outgrow their cardiac output. Typically, pneumatic artificial hearts are capable of pumping a maximum of 12 liters per minute. Normal healthy calves will gain as much as 1 kilogram per day. Starting with a 100kilogram animal gaining just 1 kilogram a day, the calf will outgrow the heart in less than one year based upon a minimum cardiac output of 70 milliliters per minute per kilogram. Calcification has also been a problem in the growing animal, causing device failure through rupture of the polymeric sac. Sepsis and, to some degree, thrombosis have been present in the long-term animals.

The experience at Penn State for 21 consecutive pneumatic artificial heart animals indicates that 3 died from pannus formation, a proliferation of unwanted tissue in the inlet of the artificial hearts. (This problem has been remedied and has not occurred for four years.) Of the 21 animals, only 1 died from a thromboembolic event. Technical error caused five of the animals to die. One animal died of anticoagulant-related bleeding, and two of the longest-surviving animals, living 275 and 353 days, respec

tively, died of cardiac cachexia. These animals basically outgrew their artificial hearts. Mechanical failures were responsible for 9 of the 21 animal deaths (43 percent). Blood sac or diaphragm perforations occurred in six of the nine animals that died as a result of mechanical failure, which was related to stress and/or calcification of the flexing polymer. Since Penn State instituted medical therapy with warfarin sodium and etidronate disodium to retard calcification, along with design changes to reduce the stress experienced with the flexing surfaces, there has not been any failure from these causes in pneumatically driven pumps. Although not a cause of death, sepsis was present in many of these animals (Pae et al., 1987). It should be noted that valve failure and drive system failure have not been a cause of death in these animals.

Clinical results with pneumatic short-term artificial hearts are limited almost exclusively to the results with the Jarvik 100-cubic centimeter (cc) and 70-cc stroke volume devices and may not be indicative of other devices. As of 1990, there have been 186 applications of pneumatic total artificial hearts; 127 of those patients were weaned, and 62 were transplanted and discharged. As previously stated, the largest percentage of those patients received the Jarvik/Symbion-type artificial heart. Of the 186 patients to receive pneumatic total artificial hearts, the major complication was bleeding and reoperation in 28 percent of the patients. Renal failure occurred in 19 percent of the patients. Hemolysis occurred in 7 percent of the patients, respiratory failure occurred in 13 percent, thrombosis in the system occurred in 4 percent, and embolus occurred in 9 percent, for a total of 13 percent for thromboembolic complications. Infection occurred in 21 percent of the patients (Pae and Miller, 1990).

Technological Development of Pneumatic Total Artificial Hearts

Durability. Pneumatic artificial hearts have functioned in animals for approximately one year, and there have been devices that have functioned on the mock circulatory system, at various institutions, for periods in excess of two years. Insufficient studies have been done to accurately predict the reliability of these devices. The clinical registry data indicate that mechanical failure was present in 1 percent of the patients who received the total artificial heart. Similar sac-type blood pumps utilized for left ventricular assist devices have demonstrated a two year reliability in vitro (Jaszawalla et al., 1988). Thus, the durability for short-term application of total artificial hearts appears to be quite adequate, with approximately 1 percent mechanical failures in 186 clinical applications. It is interesting to note that the device that received the most widespread clinical use, the Symbion device, was withdrawn from the market by the Food and Drug Administration. The Food and Drug Administration discontinued the

device's trials owing to the inadequacy of the methods, facilities, and controls used for the manufacturing, processing, and installation of the device and the inadequacy of the monitoring and review of the investigation. The investigational device exemption (IDE) was also withdrawn because Symbion did not provide assurance that the integrity of the device had been maintained by adhering to the original design specifications and manufacturing controls and that the clinical studies being performed were adhering to the clinical protocols approved in the original IDE. Thus, the device was withdrawn not because of poor performance but rather because of inadequate manufacturing and application of the device.

Control. Throughout the development of the artificial heart, there have been various control schemes proposed for the artificial heart. The majority of artificial hearts are controlled in a Starling-like manner or fill-limited mode. Thus the device will pump blood that is returned to it within a particular range of cardiac outputs. One of the problems with this type of control system is that the gain is somewhat limited. Thus, it requires large changes in filling pressure to effect physiologic changes in cardiac output. The Penn State group has utilized an electronic automatic control system to control the devices for not only cardiac output but also actively balancing the left and right pumps. This cardiac output control system is sensitive to pump afterload, and balancing is accomplished by indirect sensing of left atrial pressure (Snyder et al., 1986). Other systems have been proposed and tested, such as systems measuring the P-wave from the remnant atrium or using various ChemFETS or other devices to measure blood chemistry values. It does not appear that animal survival has been limited by the various control schemes, since the major groups differ in control method but have essentially the same survival times. Various control schemes may require continuous monitoring and adjustment to maintain balance or cardiac output, while others perform this task automatically. It appears that as long as the control system can maintain a physiologic left atrial pressure, provide a resting cardiac output in the range of 70 milliliters per minute per kilogram, and allow for changes in cardiac output as required, the animals survive normally. In most cases, as the calf continues to grow and survive for longer periods of time, elevated central venous pressures become apparent. These central venous pressures range from 10 to 20 millimeters mercury. The etiology of the increased central venous pressure is unknown. Studies involving the measurement of atrial natriuretic peptide (ANP) have indicated that there is a disruption in the normal ANP control mechanism, and perhaps this is a contributing factor. Studies of ANP levels in these animals will prove very valuable basic knowledge about this not-wellunderstood physiology. It is also possible that the various control schemes that are utilized, although providing grossly adequate cardiac output, may

affect the long-term regulation of central venous pressure (Mabuchi et al., 1988). Even with elevated central venous pressure, however, it does not appear that control systems and control strategies are a limiting factor in the utilization of temporary or long-term artificial hearts.

Biocompatibility. Thrombosis. In clinical applications, thrombosis or embolus occurred in 14 percent of the 186 applications of the pneumatic artificial heart. It is important to point out here, again, that this was the Symbion-type artificial heart, which may not be indicative of all pneumatic artificial hearts (Gaykowski et al., 1988). Of the three patients who received the Penn State artificial heart, the longest-surviving patient, who lived for 390 days, had one thromboembolic event 10 weeks after implantation. This patient's anticoagulant therapy was modified, and no further thromboembolic complications occurred. Based upon existing data, it would be reasonable to predict that 14 percent of the patients to receive a short-term artificial heart would have a thrombotic event with the Jarviktype artificial heart. It is not possible to predict the thromboembolic complications with devices of other designs. Thromboembolism is a function of the material that is used in the blood pump, the cleanliness and surface characteristics of that material, the actual geometry within the blood pump (which can affect regions of stasis and blood flow), the presence of cracks or crevices, and the careful matching of materials within the blood pump, including heart valves and associated adjoining hardware. Thrombosis is very design-and manufacturing-sensitive. The only device currently available for clinical application of a total artificial heart is the Penn State device. Very careful attention has been paid to the geometry and surface characteristics, as well as careful design and choice of materials in this device, to avoid thrombosis. Other groups also have designs that are potentially superior to the Symbion/Jarvik-7 system. As previously stated, at Penn State with a pneumatic total artificial heart, 1 animal of 21-approximately 5 percent-that received the device suffered a thromboembolic event causing death. Yet evidence of thrombotic complications and organ infarction was noted in 13 of 24 calves, indicating that thrombosis is still a major complication with total artificial heart devices in animals (Al-Mondhiry et al., 1989). Similar results have been seen by other artificial heart research groups (Nojiri et al., 1989).

Sepsis. In the clinical applications of artificial hearts, sepsis was present in 21 percent of the 186 patients undergoing implantation of the artificial heart (Pae and Miller, 1990). Septic complications have also been noted in the early patients receiving the Jarvik-type artificial heart (DeVries, 1988; Gristina et al., 1988; Kunin et al., 1988). In a series of 24 calves at Penn State, septic complications were documented in 10 animals, thus indicating

that sepsis is a major complication with the pneumatic total artificial heart with percutaneous leads.

Hemolysis. In reports from the clinical registry for the application of total artificial hearts, hemolysis was listed as a complication in 7 percent of the patients. Experience at Penn State with pneumatic artificial hearts in calves shows that compared with baseline levels, the hemoglobin was significantly lower and the plasma hemoglobin and serum lactate dehydrogenase levels significantly higher throughout the follow-up period. The platelet count decreased during the first 10 to 30 weeks, but returned to preoperative levels by week 35. Platelet survival levels in these animals in stable condition were normal and within normal limits (Al-Mondhiry et al., 1989). Similar findings have been presented by other groups (Nojiri et al., 1989). The hemolysis levels do not seem unreasonable considering there are four prosthetic heart valves within these devices as well as a large amount of prosthetic materials. The hemolysis levels, although clinically significant, are not unmanageable.

Calcification. All groups utilizing calves and sheep have reported some degree of calcification within their devices (Pierce et al., 1980). Calcification within devices employed in growing animals such as calves has been very severe and a limiting factor in many of the experiments, causing stiffening and perforation of the diaphragm. This calcification does not appear to be as severe in the sheep and goat models (Portner, 1987). The calcification also appears to be a function of the material's surface characteristics and stress on the material. Results with the clinical application of these devices, for over 600 days, indicate that calcification is not a limiting factor for a two-year device life at the present time. Certainly, in applications of these devices for short-term use, calcification is not significant.

All the current short-term total artificial heart devices appear to have three significant complications in common: bleeding, thrombosis, and sepsis. In the clinical application of these devices, the most frequent complication is bleeding and reoperation in 28 percent of the patients. The next most common complication is infection, occurring in 21 percent of the patients. Thrombosis occurs in approximately 14 percent of the patients, while hemolysis occurs in only 7 percent and is easily managed in most.

Univentricular or Biventricular Assist Devices

Pulsatile Devices (Sac/Diaphragm)

Currently four pulsatile assist devices are available for clinical application in the United States: the ABIOMED BVS System 5000, the Novacor

left ventricular assist device, the Pierce-Donachy device presently manufactured by Thoratec Laboratories and Sarns, and the Thermedics (Thermo Cardiosystems) Heartmate device (McGee et al., 1989; Macoviak et al., 1990). There are other ventricular assist devices under development such as the device at the Cleveland Clinic Foundation, the device under development by ABIOMED Corporation, and the device under development by Electrocath Corporation. Ventricular assist devices are also under development in Japan (Atsumi et al., 1989). The Symbion ventricular assist device, which is no longer available, had undergone clinical trials. The most widely used device is the Pierce-Donachy ventricular assist device manufactured by Thoratec Laboratories.

Animal and clinical results. In a multicenter study of 29 patients utilizing heterotopic Thoratec prosthetic ventricles as a bridge to cardiac transplantation, 21 received heart transplants and 20 were discharged from the hospital after a median 31 days. Of the 29 patients, 6 were reported to have had infections during their circulatory support period, but in only 2 did infection cause death; 11 of the 29 patients had severe bleeding complications. Two neurologic events were reported in two patients who were later discharged. In one of the patients who sustained a neurologic event, the drive console was off for 20 minutes the night before transplantation, resulting in insufficient blood flow. In both of these patients, thrombus was found in the explanted pump (Farrar et al., 1988).

The ABIOMED BVS 5000 has been used on more than 170 patients in clinical centers throughout the world. It is currently in clinical trials in the United States in 11 centers. The mean patient age is 46 years, ranging between 7 and 74 years. The mean duration of support is 4 days, with the longest support duration being 30 days. The predominant support mode has been biventricular in 67 percent of the cases. In postcardiotomy support, which is the primary intended use of the system, 45 percent of the patients were weaned with 51 percent of these patients surviving. These numbers are comparable to the registry values (postcardiotomy) of 43 percent and 54 percent, respectively. Complications encountered are quite similar to the overall registry results.

The key features of the BVS 5000 are its low cost and simplicity of use. A primary reason for its low cost is the use of trileaflet polyetherurethane valves. These valves were originally developed under the sponsorship of the National Heart, Lung, and Blood Institute. This technology grew out of the mechanical circulatory support program and is an important element in our efforts to expand the clinical utility of this temporary cardiac support system.

The results from the clinical registry of mechanical ventricular assistance show that bleeding and reoperation are still the major complicating factors in all pneumatic mechanical ventricular assist devices, with an incidence of

approximately 30 percent. Renal failure was second with 25 percent, infection was third with 17 percent, biventricular failure occurred in 16 percent of the patients, and respiratory failure occurred in 16. Thrombosis in the system occurred in 5 percent of the patients, and embolus occurred in 7 percent. Thus, it is apparent that the problems that occur in the short-term artificial heart also occur in short-term univentricular or biventricular assist devices when all the devices are considered as a group. Some devices do much better than others.

Technological development. Durability. Durability of these devices for their intended period of application has been very good. Mechanical failure has only occurred in 1.45 percent of those cases reported to the registry (Pae and Miller, 1990).

Control. Devices have been run synchronously and asynchronously both partially full and full-to-empty. There have been no definitive clinical studies showing the relative advantages of one modality over the other. There are theoretical considerations, but there are no data indicating improved survival with one technique over the other.

Biocompatibility. As previously stated, thrombosis, sepsis, and to some degree hemolysis are complications associated with the application of short-term univentricular and biventricular assist devices. Of the pulsatile ventricular assist devices, several designs and materials have been utilized. The Novacor, Symbion, and Thoratec devices all use a smooth segmented polyurethane surface. The device developed by Thermedics (Heartmate) utilizes a textured surface to facilitate the formation and adhesion of a biologic lining. The Heartmate pump diaphragm is fabricated of integrally textured polyurethane, and the metallic surfaces of the pump are textured by using powdered metallurgy techniques. There has been no clinical evidence of thromboembolism in any of the 17 patients for whom the device has been used, nor was there any evidence of thromboembolism in patients who came to necropsy (Graham et al., 1989). It has also been reported that in these patients, plasma hemoglobin levels remained acceptable throughout support. Blood chemistry and hematologic values returned to normal in most cases. One of the patients with this device was supported for 132 days (Nakatani et al., 1989). Thus, with the Heartmate device there is an indication of improvement in the area of thrombosis.

Steady-Flow Devices

Animal and clinical results. There are currently several systems available for clinical application that are of the steady-flow type. These include

the Biopump manufactured by Biomedicus, the Centrimed System manufactured by Dolphen, Incorporated, and the Hemopump manufactured by Nimbus, Incorporated. There are also several other devices under development. These include devices such as the spindle pump and the axial flow pump described by Schistek and others (Schistek, 1989). A review of the clinical experience with steady-flow or centrifugal devices shows that there is a slightly higher incidence of bleeding and reoperation with centrifugal devices versus pneumatic devices: 46 percent of the patients had bleeding and reoperation with the centrifugal devices, whereas only 30 percent had bleeding as a complication with the pneumatic devices. There were other slight differences in hemolysis and sepsis, and only a very slight difference in thrombosis and embolus with the two types of devices. If one looks at the outcome of mechanical circulatory support for postcardiotomy cardiogenic shock based upon ventricular assist pump type, 24 percent of the patients with the centrifugal pump were discharged after use of the device and 21 percent of the patients with pneumatic devices were discharged. There does not appear to be a major difference. Careful analysis of all the data within the clinical registry shows that there are some slight differences between devices, but they may be related to the indications for use, i.e., postcardiotomy cardiogenic shock versus staged cardiac transplantation. Yet a review of all of the short-term devices, total artificial heart, biventricular, and univentricular devices, pulsatile and nonpulsatile devices, indicates that bleeding, infection, thrombosis, and to a lesser degree hemolysis all are problems. Other complications such as renal failure and respiratory failure are most likely associated with the poor condition of the patient at the time of surgery. In fact, many of these patients have improved renal and respiratory function with initiation of pumping. If one examines the overall outcome of staged heart transplantation based on all types of ventricular assist devices, 72 percent of the patients with pneumatic devices, 67 percent of those with centrifugal devices, and 86 percent of those with electric devices are discharged. The electric device, in this case the Novacor device, appears to have improved results, but the device is used only for bridge to transplantation.

Summary

When considered as a group, short-term and long-term pneumatic and centrifugal unilateral and bilateral assist devices and total artificial hearts have complications of thrombosis, sepsis, bleeding, and hemolysis, and it is not entirely clear which will be the limiting factor in the longevity of these devices. It is apparent that for short-term use, durability is not a limiting factor and devices appear to be satisfactory for use up to 180 days. Control systems do not appear, on the surface, to have a significant impact on the

outcome of the use of these devices. The hemolysis levels associated with the short-term devices, in general, are not life-threatening. Bleeding may not be directly attributable to the device, but due to anticoagulant therapy or prolonged cardiopulmonary bypass. Careful anticoagulant therapy and better patient selection may affect the bleeding and reoperation rate.

Although these complications exist, there are no fundamental physical laws or reasons that limit solutions to the problems of thrombosis, sepsis, and bleeding. Improved materials, as well as improved hemodynamic designs of these devices, can lower not only thrombosis but bleeding, since improved devices will require less anticoagulation therapy. Totally implanted devices as well as new techniques for encapsulating these devices will reduce infection.

Permanent or Long-Term-Use Mechanical Circulatory Support Systems (more than 180 days)

Unilateral Assist Devices

In Vitro and In Vivo Test Results

Several groups in the United States and abroad are now working on permanent electric motor-or thermal-powered ventricular assist devices. These include Nimbus in Rancho Cordova, California, Novacor Division of Baxter Healthcare Corporation in Oakland, California, Penn State in Hershey, Pennsylvania, Thermedics in Waltham, Massachusetts, and various groups in Europe and Japan. Currently, the most advanced device is the ventricular assist device developed by Novacor. The totally implantable left ventricular assist system has demonstrated a two year life in vitro with an 80 percent reliability. Implants in sheep of up to 279 days for the ventricular assist device have been accomplished, and this device has received clinical application for short-term use in patients.

In its use as a temporary assist device, bleeding and reoperation occurred in 42 percent of the patients, infection occurred in 18 percent, and thrombosis and embolism occurred in 16 percent. The outcome of staged heart transplantation with the Novacor system in 41 patients that were implanted is that 22 or 54 percent were transplanted. Of the 22, 80 percent were discharged. Since this device, with a transcutaneous energy transmission system (TETS), will be utilized for long-term support, a prediction of the associated complications can be approximated based upon the short-term use. Infection rates may be improved by the elimination of percutaneous leads.

Permanent Total Artificial Hearts

Currently four groups are under contract to the National Heart, Lung, and Blood Institute for the development of permanent electric motordriven total artificial hearts. Other systems being developed utilize thermal engines to provide energy for blood pumping (Emoto et al., 1988; Butler et al. 1989). At the present time, the thermal systems are several years behind the current electric motor-driven devices. The four groups supported by the National Institutes of Health for development of implantable electric motor-driven artificial hearts are the University of Utah, Nimbus/ Cleveland Clinic, ABIOMED/Texas Heart, and Penn State. There are several non-U.S. systems being developed and they will be briefly described in a later section.

University of Utah System

The University of Utah totally implantable artificial heart system consists of two blood pumps that are similar in design to the pneumatic Utah 100 artificial heart (Khanwilkar et al., 1989). Located between these two pumps is an axial flow pump that will pump a working fluid from one blood pump to the other. This working fluid then displaces blood within the blood pump itself. The axial flow pump alternately pumps in one direction, stops and reverses, then pumps in the other direction to provide systole for both the left and right blood pumps. In the past, this system has had two major drawbacks. One is that an axial flow pump can only be optimized for flow in one direction. That is, the pump efficiency can be good in one direction and but poor in the other, or mediocre in both directions. The second drawback of this system, in the past, has been the ability to balance the output of the left and right pumps. An attempt will be made to overcome the second drawback, balancing of the two blood pumps, by placing a shunt between the left and right atria. The University of Utah system will use a TETS that transmits energy across the intact skin by radiofrequency coupling. The system to be employed will be similar to that developed by Thermedics. Thus far, only the blood pump portion and energy converter have undergone in vivo testing. At the present time, the material used in this blood pump is the segmented polyurethane (Biomer) manufactured by Ethicon, Incorporated, Somerville, New Jersey. Animal results with pumps of this type have shown evidence of thrombosis, sepsis, and calcification (Khanwilkar et al., 1989).

Nimbus/Cleveland Clinic System

The Nimbus/Cleveland Clinic system is based upon the E4T electrohydraulic total artificial heart design. This design is the culmination of many

years of research performed by the Cleveland Clinic Foundation and Nimbus. The design uses an electrohydraulic energy converter. The blood pumps utilize pusher plates and flexible diaphragms and all blood contacting surfaces are covered with a seamless biocompatible coating through the biolization process that has been developed at the Cleveland Clinic (Harasaki et al., 1979). Human dura mater tissue valves are used in these devices. The pusher plates are actuated by an electrohydraulic energy converter, the fourth in a series of implantable energy converters developed at Nimbus. The pumping unit is located intrathoracically, consisting of the left and right blood pumps and energy converter. The TETS secondary coil is located subcutaneously over the left thorax. This TETS system, developed by Thermedics, utilizes 160-kilohertz radiofrequency to transmit energy across the intact skin (Sherman et al., 1984). Efforts to date on the development of this system have been focused primarily on the pumping unit (Himley et al., 1990). An electronic controller powers a brushless direct-current (DC) motor which turns a gear pump. The gear pump provides hydraulic power to a hydraulic circuit, alternately actuating a piston from one end to the other. The piston indirectly drives pusher plates which are magnetically coupled to the piston. Blood pumps are alternately actuated. Since the follower is not directly coupled to either pusher plate while one blood pump is being ejected, the other blood pump is free to fill. Hall effect sensors detect the pusher plate stroke position and hydraulic main spool position. These signals provide the fill and eject rates of the left blood pump which are used in the left master control algorithm. The control mode is based on matching the actuator eject rate to the left blood pump fill rate by altering motor speed. It is claimed that the resulting operation provides a simulated Frank Starling behavior. Various components of this system have been fabricated, but the system has not been tested, fully assembled, in vivo. In vivo testing is scheduled for late 1990.

ABIOMED/Texas Heart System

The ABIOMED total artificial heart consists of a thoracic element fitted orthotopically in the thoracic cavity, an abdominally placed battery package, a transcutaneous skin transformer, and an external battery vest. The distinguishing characteristics of the ABIOMED total artificial heart are as follows.

- Hydraulic power generated by an electrically operated centrifugal pump energizes the blood pumps (Millner et al., 1990). The electrohydraulic approach allows a flexible configuration for optimized blood flow and membrane life.
- Flow compensation for left-right imbalance utilizes blood as a compli

ance volume, thus eliminating the use of gas compliance chambers. The left and right sides are alternately pumped while the filling of one side occurs simultaneously with ejection from the other side.

- Trileaflet valves and seamless blood pumps fabricated from Angioflex, a polyetherurethane, provide long life and smooth thromboresistant surfaces at affordable cost. The blood pump is toroidal in shape and may reduce flexing stresses, thus contributing to a high reliability.

The use of blood as a volume compensation medium for left-right flow imbalance is unique (Kung et al., 1989). The volume compensation chamber is hydraulically in communication with the right hydraulic chamber, while the flexing membrane, which ordinarily is in contact with tissue, in the ABIOMED system is placed in contact with left atrial blood.

The degree of compensation is regulated by the hydraulic fluid flow path resistance, by a design parameter, and by the left atrial pressure. The imbalance flow and resulting left atrial pressure are self-regulating. Higher left atrial pressure results in more fluid displaced from the compensation chamber during right diastole. This means more fluid flowing into the compensation chamber during the following right systole, and so a smaller effective stroke volume from the right ventricle. The lower right-side flow reduces the blood volume in the lungs, reducing the left atrial pressure.

The new geometry integrates well with the energy converter, allowing placement of the pump and valve in the hole in the toroid for efficient use of space. The unidirectional operation of the pump, made possible by the use of a rotary valve to reverse fluid flow, is well matched to the centrifugal pump as well. Efficiencies of 40 percent have been demonstrated. An integrated energy converter has demonstrated the functionality of the new valve in combination with a centrifugal pump.

A new design atrial cuff has been detailed, built, and is about to be tested in vivo. The cuff is rough Dacron on the inside to promote growth of pseudointima, and coated with silicone rubber on the outside to prevent leakage and avoid a need for preclotting. The connector has a smooth Angioflex-coated cannula projecting into the cuff, creating a flow pattern which is expected to avoid pannus overgrowth. The interface between the two mating parts of the connector is the interface between rough and smooth surfaces, and so any initial surface thrombus forming here is expected to attach to the rough surface and avoid embolization. This concept will be tested.

The sensor and electronics have been designed, selected, and individually fabricated for component testing. Critical parameters such as pressure sensor drift are being tested in vitro in a long-term life test. The control algorithm, which makes pump motor speed responsive to filling pressure and beat rate responsive to stroke volume, has been thoroughly tested.

The ABIOMED program has advanced from the design phase to the current hardware integration and testing phase. During the next year, activities will be concentrated on device evaluation in chronic studies and in vitro testing.

Pennsylvania State University System

The Penn State implantable electric motor-driven total artificial heart system utilizes a brushless DC motor to turn a roller screw mechanism. This mechanism imparts rectilinear motion to pusher plates attached to the ends of the roller screw. Blood pumps are attached to the motor housing. The motor turns six revolutions, turning the roller screw and moving the pusher plate for its complete ejection phase, then the motor stops and counter-rotates, moving the screw and pusher plates through the diastolic phase. Blood pumps are alternately actuated through this mechanism. Energy is transferred through the intact skin by using radiofrequency waves. This system also uses a highly modified Thermedics type of TETS. Both the number of turns per coil and coil configuration have been modified along with a completely redesigned TETS electronics. This system has proven extremely reliable both in vitro and during in vivo experiments (Weiss et al., 1990). An intrathoracic compliance chamber is utilized to provide volume for balancing of the left and right outputs. An automatic electronic control system is employed to balance both the left and right blood pumps (Rosenberg et al., 1984).

The Penn State total artificial heart system utilizes extremely smooth, seam-free blood contacting surfaces currently manufactured from either Biomer provided by Ethicon, or the segmented polyurethane Hemothane, provided by 3M Corporation, St. Paul, Minnesota. Currently, an advanced segmented polyurethane is being developed by DuPont Corporation, Wilmington, Delaware, and will be evaluated by the Penn State group. The shape and design of the blood pump are based upon extensive hemodynamic studies utilizing pulsed Doppler ultrasound, laser Doppler anemometry, and hot film anemometry techniques to determine the velocity field within the blood pump (Baldwin et al., 1988). Particular care is taken in the selection of mating materials and in minimizing regions of stasis where thrombus formation may be initiated. The blood pump and mechanical mechanism for this device in its 100-cc stroke volume design have run for over one year on the mock circulatory system. Animal experiments with this device utilizing only the electric motor and blood pump portion with a sealed compliance chamber have run for 222 days (Rosenberg et al., 1984), and another experiment has lasted for 205 days. Neither of these animals had thrombus or thromboembolic events, nor was sepsis present, a very promising result. In both cases, the electronics have been located outside

the animal and connected via a percutaneous lead. More recently, in mid1990, a complete system has been implanted in two animals. This system consists of completely implanted blood pump, electronics, and TETS. This system currently requires no percutaneous lead, thus eliminating a major nidus for infection. Both of the animals died in less than two weeks, of pulmonary complications; system performance has been very encouraging.

Non-U.S. Systems

A system similar to the Penn State roller screw system is being developed in Japan. It utilizes a drum cam which is similar to the early Penn State device. This Japanese system has undergone some initial in vivo testing (Fukumaga et al., 1989). A system very similar to the Penn State roller screw system is being developed in Geneva, Switzerland. The system utilizes the same roller screw mechanism and very similar blood pump design. Both of these systems are approximately one year behind the U.S. systems in development. Also, more recently Daimler Benz AG has agreed to support the development of a German totally implanted total artificial heart. The design features of its system have not been released.

Summary

In summary, the four U.S. groups undertaking development of permanent total artificial hearts have several common design features. They use radiofrequency TETS, which have been employed in animals by the Thermedics group in left ventricular assist animals and in the Penn State left ventricular assist and total artificial heart animals. The systems have functioned quite satisfactorily, indicating no limiting factors in terms of tissue response to the radiofrequency energy reference.

The University of Utah, ABIOMED, and Penn State devices all utilize segmented polyurethane. Various forms of segmented polyurethane have been tried and are currently under development. The most widely used segmented polyurethane is Biomer, manufactured by Ethicon. This material, initially utilized by Pierce in 1967, is a very old material but still the most widely used material in blood pumps. The Penn State group is working with both 3M and DuPont to develop improved blood contacting material based upon this polyurethane chemistry.

All of the four groups employ electric motor drives to power their artificial hearts. Three of the groups utilize electrohydraulic energy converters, while the Penn State group uses a purely mechanical converter. A two-year reliability has not been demonstrated for these energy converters thus far, but utilizing standard techniques, a life in excess of five years can be predicted for energy converter systems. Blood pump reliability studies

have not yet been undertaken, but there is evidence from the Novacor left ventricular assist device that achieving a two-year reliability is quite possible.

All of the groups have identified the need for a control system to balance the left and right blood pump outputs as well as control the overall cardiac output. The Penn State group has demonstrated control of these devices with animal survivals in excess of seven months. The other groups have also demonstrated success in controlling the left-right balance of the blood pumps. At present, it appears that all of the groups working on electric motor-driven total artificial hearts are essentially on schedule with their program plans. The Penn State group has had two in vivo experiments of a completely implanted system. This group has also had two animals with electric hearts survive over six months without thrombotic complications or significant sepsis.

At the present time, non-U.S. systems, those of Japan and Europe, appear to lag slightly behind in development. The group in Geneva, Switzerland, has performed some in vivo experiments with their roller screw system. These experiments were conducted without implanted electronics.

CURRENT TECHNOLOGICAL BARRIERS TO DEVELOPMENT OF A SUCCESSFUL MECHANICAL CIRCULATORY SUPPORT SYSTEM

What Is a Successful MCSS?

Determining the criteria for a successful MCSS is not trivial. Value judgments about cost, quality of life, and overall length of patient survival are all major considerations.

Short-Term Devices (fewer than 180 days)

There has been extensive use of short-term MCSSs, with well over 1,000 applications. When used as a bridge to transplant, these devices have successfully bridged over 50 percent of the patients (Miller et al., 1990). The outcomes of these staged cardiac transplantations are not substantially different than for nonbridged transplantations. A review of the clinical registry, as previously mentioned, outlines the complications associated with these devices. With all types of these devices, there have been fewer than 5 percent mechanical failures in all of the applications.

Although these devices work well when used as a bridge to transplant with survival in over half of the patients, further research is required to reduce the complications associated with these devices. The Food and Drug Administration is currently monitoring several systems under IDEs. When

these devices receive their premarket approval, can one say that they are successful? If one compares the current results with today's MCSSs with the results of the early use of mechanical heart valves, or for that matter early pacemakers, it can be appreciated that devices of these types improve with time. The early pacemakers needed to be pushed around on carts. Patients with these devices were not able to leave the hospital. Today, these devices have progressed to very small, essentially forgettable, systems. Artificial heart valves initially had quite high mortality rates. Even today, patients more than 65 years of age undergoing aortic valve replacement can have as high as a 30 percent mortality at 5 years (Mitchell et al., 1988). It is also important to remember that other cardiovascular devices such as prosthetic blood vessels and heart valves have risks of mortality associated with them that are most significant. Determining the risk of thromboembolism following valvular replacement is an extremely difficult task (McGoon, 1984). The risk varies with valve type, position, age of the patient, and other preexisting disease or condition. The fact that a short-term circulatory assist device uses valves and involves prosthetic materials similar to those utilized in heart valves and vascular grafts would, at the present time, make it seem unreasonable that these devices should provide superior performance to current heart valves and vascular grafts. At the present time, the goal should be to make these devices as safe as existing devices such as heart valves and vascular grafts. It should be noted that both short-and long-term devices, left ventricular assist devices and total artificial hearts, may have considerably more surface area and as many as four artificial valves associated with them.

It is this author's opinion that the performance of short-term mechanical circulatory assist devices in their current stage of development is comparable to that of heart valves in their early stage of development; thus, it is not unreasonable to state that these devices are currently successful but require additional development, as do current heart valves and other cardiovascular devices, to eliminate or minimize all associated complications.

Long-Term Devices (more than 180 days)

Defining a successful long-term MCSS is a somewhat more difficult task than defining a successful short-term device. Fortunately, one way to determine the success of a device such as this is to compare it with existing technology. Currently, the alternative for a patient with end-stage heart disease is cardiac transplantation. Actuarial statistics now show that approximately 50 percent of the patients who receive cardiac transplantation are alive after five years (Kriett and Kaye, 1990). Of the patients who received cardiac transplantation five years ago, less than half are currently alive, so that the actual survival is less than 50 percent at five years for

patients receiving a heart transplant (this figure may be as low as 35 percent). Thus, at the current time, it would not be unreasonable to have as a design goal for long-term MCSSs that approximately 40 to 50 percent of the patients receiving these devices survive for five years.

Performance and Reliability

Energy Sources

Currently, all long-term MCSSs utilize electrical energy as a source of power. This may be direct electrical energy for electric motor-and solenoid-driven devices or electric energy converted to heat for thermal systems. At the present time, the most advanced systems are those that are solenoid-or electric motor-driven. The thermal systems under development by Nimbus and the University of Washington are a few years behind in development compared with the electric motor-driven systems. The most practical form of energy source for the long-term devices is external or implanted batteries. External batteries can be used to transmit electrical energy across the intact skin by using a TETS (Rosenberg et al., 1985).

Batteries

Today, the most practical form of batteries for external or implanted usage is the nickel cadmium type. Although silver zinc batteries offer higher energy densities, their cost, potential need for venting, and limited number of recharge cycles make them somewhat impractical for use with these devices. Lead acid or gel cell batteries offer some advantages for external batteries in that their cost is considerably lower than for nickel cadmium, although they are heavier. They also have the added advantage of a voltage which is proportional to the energy in the battery system. Currently, all long-term MCSSs that are being powered by batteries utilize nickel cadmium cells. There is promising new technology with lithium systems that will significantly increase the energy density and reliability of batteries. Honeywell Corporation has manufactured test cells and will be providing prototype cells to Penn State for testing in early 1991.

Transcutaneous Energy Transmission System

In the early 1960s, Dr. Schuder (Schuder et al., 1971) began development of a TETS utilizing radiofrequency energy transmission across intact skin. Later, Thermedics continued development of this system for application with their permanent left ventricular assist device (Sherman et al., 1983). There have been other such systems proposed that utilize different

coil configurations, such as the system developed by Novacor. Thermedics, Novacor, and Penn State have all conducted in vivo animal experiments with the TETS. The results of these tests show that there is some inflammation and foreign body reaction in the area of the coil. These systems must transmit 10 to 20 watts continuously across the intact skin and have been able to do this satisfactorily. This same method of transcutaneous energy transmission has also been utilized by manufacturers of cochlear implants to transmit the necessary power to operate these devices successfully. These systems have received Food and Drug Administration approval for use.

Energy Converters

Electric Motor-Driven Converters

At the present time, the long-term MCSSs are driven by electric motors or solenoid motors. Motor-driven devices either turn a mechanical linkage arrangement consisting of a cam or roller screw mechanism or, in the electrohydraulic system, power a pumping system that pumps an intermediate fluid to actuate the device. These systems range from low-speed, high-torque systems to very high-speed, low-torque systems. Some of these systems operate at speeds up to 20,000 revolutions per minute, stop and counter-rotate, and accelerate to that speed again. Some of these systems have fewer moving parts than others and range in complexity.

One thing that all of these systems have in common, in terms of electric motor, mechanical linkage, and bearings, is that well-established, sound, fundamental engineering principles can be used to design them. These principles allow the designer to predict the correct motor, mechanical linkage, bearings, and materials for the devices to function satisfactorily for the intended period of use. At the present time, the longest-running system documented is the Novacor solenoid-type electric ventricular assist device. That system has demonstrated an 80 percent reliability for two years (Jaszawalla et al., 1988). Other systems at Nimbus, Penn State, and Thermedics have run in excess of one year, but none has formally been qualified as the Novacor system has.

All of the systems under development currently utilize electronic microprocessor control systems. Ten years ago, these systems were not available and totally implanted artificial heart and circulatory assist devices were only dreams of designers. With the advent of microprocessor systems, very large scale integrated circuits, and hybrid electronics, these systems have become a reality. All of the groups in the United States working on permanent ventricular assist devices have developed miniaturized electronics and in some instances tested them in vitro and in vivo. At Penn State, a completely implanted electric motor-driven total artificial heart has

been tested in vitro and in two in vivo experiments involving calves. These were completely implanted systems with automatic electronic control systems and implanted batteries.

The technology in the mechanical systems and in the electronic components is such that it is reasonable to expect 80 percent or more of the electric motors, energy converters, and electronics to function satisfactorily for two years, utilizing current technology. With further development and testing, this could be extended to five years. At the present time, there does not appear to be any technological barrier to developing a battery system, miniaturized electronics, electric motor, and energy converter that will function satisfactorily for five years in 80 percent of the systems run, based upon current engineering predictions.

At the present time, all the systems under development utilize a polymeric material that is in contact with the blood. This polymer may be in contact with the blood in the blood sac or in contact with blood and body tissue through the compliance chamber. All of these elastomeric materials have some degree of permeability. Several groups have been working on laminating low-permeability materials in the blood sac. These have reduced the permeability of the blood sacs and compliance chambers. None of the polymeric materials can provide a truly hermetic seal. Thus, the systems must be capable of operating in an environment that can be losing or gaining mass (CO_2, O_2, N_2, H_2O plus others). Although this loss or gain in mass is undesirable, it can be overcome by utilizing an infusion port to make up for lost mass. The systems can be designed from materials that are not affected by moisture. Further development in barrier elastomers may provide for much reduced permeability.

Thus, in summary, for the current energy converters, which include the electric motor, mechanical linkage and hydraulic pump, and the associated electronics and batteries, there do not appear to be any technological barriers that would keep these devices from functioning satisfactorily for two years with current technology; with further research and development, these times could be expanded to provide a high reliability device for five years.

Thermal Heat-Cycle Energy Converters

At present, two systems utilize thermal heat cycles to power mechanical circulatory support systems. Both of these systems are based upon a Stirling thermodynamic cycle. These systems have the potential advantage of being able to run on an implanted heated lithium fluoride-lithium chloride salt mixture providing longer times between recharge than nickel cadmium batteries. These systems in general are more complicated than the mechanical systems, requiring sophisticated insulation to maintain surface tempera

tures on the device within physiologically acceptable limits. At the present time, these devices are several years behind electrically powered devices in development.

Blood Pumps

It is somewhat difficult to predict the long-term performance of blood pump sacs or diaphragms, but methods do exist. The prediction of the reliability of mechanical heart valves is more straightforward and easier to accomplish.

Sac/Diaphragm

Currently, all pulsatile long-term MCSSs use a blood pump that consists of a polymeric membrane, forming either a sac or diaphragm. Prediction of the fatigue life of elastomeric materials is difficult. Conventional methods of testing and developing a stress versus cycle diagram are not always fruitful or practical. More recently, investigators are examining these elastomeric materials to determine if they have a threshold tear energy (Capecchi et al., 1989). There is some evidence indicating that the polyurethanes exhibit this type of threshold energy. If they do, it is theoretically possible to design a device that has mechanical stresses such that the system never is exposed to energies above the threshold energy that causes crack propagation. Thus, even though the material may have inherent flaws, these will not propagate due to the low energies. At the present time, it is difficult to predict the stresses in these elastomeric membranes. Calculation of these stresses requires extremely sophisticated computation codes and supercomputers for solutions. These solutions will enable the designer to design a more reliable pump.

As previously stated, the Novacor permanent MCSS has demonstrated a complete system reliability for two years. Pneumatic devices have run at various institutions in excess of two years. Based upon these results, a two year durability for blood pumps is quite reasonable. There is also no reason to believe that careful analysis and redesign of these pumps could not provide for stresses which do not induce crack propagation, thus extending the life of the devices.

Valves

Permanent MCSSs under development use both mechanical and tissuetype valves. Although these valves are all exposed to stresses that are higher than would be encountered when implanted in the natural heart, there

are means for predicting the life of these devices. Currently valve manufacturers do accelerated testing which provides information on relative valve durability. Also, finite element analysis can be performed on the valves to determine the stresses imposed on the valve and predict the life. Many of these valves are now reused in animal experiments, and valves have run in excess of two years in these in vivo experiments at Penn State. The durability of these valves appears to be acceptable for a two-year period and may show a durability of five years with additional testing and no further development.

In summary, energy sources, energy converters, and blood pumps including sacs and diaphragms can provide for a two-year durability, and it does not seem unreasonable to predict that a five-year life may be possible with current technology and no further development. Continued testing of the devices must be done in order to accurately determine the reliability of existing systems.

Thrombosis

It is difficult to review all investigators' data relative to thromboembolic events in in vivo animal experiments. A review of the Clinical Registry shows that thrombosis in the system or embolus occurs in roughly 12 percent of patients receiving mechanical circulatory support for all indications. At the present time, none of the long-term MCSSs has undergone rigorous in vivo experiments for preclinical testing. The most advanced system, the Novacor system, has yet to generate sufficient in vivo data to be able to accurately predict the thromboembolic complications of that device. Work at Penn State with implanted electric motor-driven total artificial hearts shows that in eight animals receiving these artificial hearts for durations up to 222 days, two had a thromboembolic event. Thus, thrombosis still poses a significant complication for the use of permanent MCSSs. However, there does not appear to be a technological barrier to solving the problem of thrombosis. Thrombosis is related to the material composition, the surface characteristics of the material, and the fluid mechanics surrounding the material. It can also be activated pharmacologically. The incidence of thrombus complications is much less today than it was 10 years ago. New polymeric materials are now being developed by 3M, DuPont and others. Also under examination is the fluid dynamics within the blood pump. Laser Doppler anemometry studies as well as numerical analysis are being conducted to determine the role of fluid mechanics in thrombosis (Baldwin et al., 1989). There have also been indications from the data of Thermedics that their flocked surface may provide a much reduced thromboembolic rate (Lamson et al., 1988).

Sepsis

Infection has occurred in as many as 20 percent of the patients listed in the registry. Thus far, all patients and animals run for any significant period (more than two weeks) have utilized a percutaneous lead to provide the driving energy for the device. With the recent use of transcutaneous energy transmission and implanted electronics, the percutaneous lead has been eliminated and there is reason to believe that this will significantly lower the rate of complications due to infection. But clearly, with the sheer amount of prosthetic material implanted, sepsis will always be a serious complication if it involves the device.

Hemolysis

In short-term applications of MCSSs, hemolysis has not been shown to be a significant problem. Although patients may require occasional transfusions, the hemolysis is not usually clinically significant. Animal experiments with long-term MCSSs have also shown results indicating that, with satisfactory heart valves and proper pump function, hemolysis is not a significant complication associated with these devices and does not require transfusion. Improved heart valves and improved pump designs should be able to reduce further the levels of hemolysis.

Calcification

Although calcification has appeared to be a significant complication in growing animals, it is present to a much lesser extent in mature animals. Calves undergoing total artificial heart implantation have more calcification than do mature adult sheep. Very few blood pumps have been run in vivo for over one year. Patients implanted with the Jarvik artificial heart and the Penn State artificial heart survived for more than one year. Calcification was not the cause of failure in either of these devices. Improved materials and/or pump manufacturing combined with reduction of stresses in the blood pumps should reduce calcification. There appears to be no technological barrier to reducing calcification to a level that will not cause device failure in a two year period.

Materials

Various materials are used in the manufacturing of blood pumps. These include various stainless steels, titanium, alloy steel such as Vitalium, polymeric materials such as Delrin, Teflon, polycarbonate, and polysulfone, and elastomers such as polyurethane, Hexin rubber, silicone rubber, and Da

cron. With the exception of those components that are in direct contact with the blood intravascularly, the materials used for the MCSSs function with very minimal complications at the present time. Improvements in these materials through either pharmacological treatment or structural changes may impart antiseptic properties to the materials. At the present time it does not appear that there is any identifiable technological barrier to either changing or modifying these materials to improve biocompatibility.

Controls and Electronics

Current long-term MCSSs all take advantage of the latest developments in power and microelectronics. Systems developed to commutate and control these devices have performed satisfactorily both in vitro and in vivo. There does not appear to be any technological barrier that would limit the satisfactory performance of electronics for periods up to and exceeding five years. It is important to note that many similar systems utilized in automobiles and aircraft have performed their mission satisfactorily for comparable periods of time.

Bleeding

Bleeding has been shown to be the most prevalent complication in the application of short-term MCSSs listed in the registry. The bleeding that is associated with the application of these devices is not necessarily unique to these devices. It will occur in patients undergoing long cardiopulmonary bypass times or patients normally hemodiluted or in compromised physical condition. In animal experiments at Penn State utilizing permanent MCSSs, bleeding is still a complication. Bleeding occurs in approximately 25 percent of animals undergoing implantation of ventricular assist or artificial heart devices. In the artificial heart devices, there are longer suture lines and thus bleeding becomes more probable. Improved techniques and surgical procedures have reduced the incidence of bleeding in animal experiments over the past decade. Although the incidence of bleeding as a major complication has been decreased, there does not appear to be any fundamental technological reason why it cannot be further reduced. It is extremely doubtful that it will ever be eliminated, any more than it is eliminated as a complication in any major surgery (5 percent of open heart surgery cases return to the operating room for bleeding), particularly for those requiring cardiopulmonary bypass.

EFFECTS OF NEW OR EMERGING TECHNOLOGIES ON IMPROVEMENT IN MECHANICAL CIRCULATORY SUPPORT SYSTEMS

Several new or emerging technologies will have a positive impact on development of MCSSs. These include materials development, electronics development, magnetic materials development, and supercomputers.

Materials Development

New Plastics and Polymers

One of the most widely used polymers in mechanical circulatory support systems is polyurethane, specifically Biomer, manufactured by Ethicon. This material, first developed by DuPont, is now some 20 years old. At the present time, 3M is developing a polyurethane similar to Biomer in a joint effort with Penn State. Most recently, DuPont has made a decision to begin development of improved biomaterials, specifically an improved Lycra-or Biomer-like polyurethane. Both of these companies have highly capable individuals to perform the necessary development. The interest of these companies in developing new biomedical elastomers for blood contact is very exciting. These new elastomers will have design goals of being more biocompatible and more fatigue resistant, along with ease of fabrication. Potentially, there are thousands of polymeric materials yet to be developed. The improvement in existing polymers and the development of new polymers through research and development should have a positive effect on development of MCSSs. Elastomers can also be modified by texturing the surface or chemically altering the surface.

Surface Modifications

Surface modification of existing and new polymers is another method of improving biocompatibility. Bonding of a heparin-like substance to the surface of the material can improve the thrombogenicity of polymeric materials. Ion implantation can be performed on these materials to change their surface structure to improve mechanical properties as well as biocompatibility. Companies such as Spire Corporation have been leaders in the area of ion implantation in metal and polymeric materials. Surfaces may also be coated with LTI pyrolytic carbon. Surface charge and surface energy may play a role in thrombogenicity and also may be altered through surface modification.

New plastics which have recently become available for implant such as polysulfone have had a positive impact on MCSSs. Penn State has replaced

its devices' polycarbonate components with polysulfone, which has improved durability without changing biocompatibility. Plastics can also be used to form composites with substances such as carbon fiber, boron fiber, Kevlar fiber, and others. These composites have excellent strength-to-weight ratios and can also be manufactured of compatible biomaterials.

Improved Metals, Ceramics, and Composites

Improved Metals

Various ferrous and nonferrous metals are utilized in the energy converters and blood pumps of MCSSs. These include traditional metals such as the stainless steels and titanium alloys as well as some of the less traditional superalloys.

A relatively new class of metals, amorphous metals, is a new family of engineering materials. Amorphous metals are produced by cooling molten metals so quickly that they do not form regular crystalline structures but rather are frozen in random atomic patterns similar to those found in glass. These materials can improve motor performance. These amorphous metals or metallic glasses are being developed by Allied Corporation in the United States and other companies in Japan and Europe. Already these amorphous metals have begun to compete with the metallic strips and large ferrite cores in magnetic devices operating from 100 to 200 kilohertz. They are also being used in magnetic components for switching power supplies, in transducers for phonograph cartridges, and in magnetic shields for blocking electromagnetic interference. This new technology may also impact positively on the motors and solenoids in electrically powered MCSSs.

Surface Treatments

Surface treatments and coatings have been recently applied to various metals. Ion implantation is one method of changing the physical and chemical properties of material surfaces. Today ion implantation is used to selectively increase corrosion resistance, hardness, wear resistance, and other surface sensitive properties of metal parts without affecting dimensions.

There are also thermally sprayed coatings. Thermal spraying has become much more than a process for rebuilding worn metal surfaces. Thanks to sophisticated equipment, precision control can now be factored into the design process. Materials can be combined to produce the required surface quality such as wear resistance, solderability, or thermal barrier characteristics. Union Carbide Corporation has a new D-gun coating process as well as the traditional plasma coating process. These processes can be used to deposit material such as tungsten carbide, chromium carbide, tungsten tita

nium carbide, aluminum oxide plus titanium dioxide, chromium oxide, nickel, nickel chromium, cobalt-based alloys with aluminum dispersion, plus others. Companies such as Perkin Elmer and Norton Industrial Ceramics are developing new coating techniques.

Surface treatments can also be used to form various imperfections or irregularities on the surfaces of metals or ceramics to promote such phenomena as improved heat transfer of boiling or condensation. These would have application for devices such as a two-phase fluid compliance chamber. This is a compliance chamber designed to operate at a constant pressure utilizing a material that goes from saturated liquid to saturated vapor at constant temperature and pressure. This then is a volume change under constant pressure and can be utilized to compensate for changes in blood volume within the device (Lamson et a!., 1988).

New Ceramics

New ceramics made of materials such as alumina, aluminum silicate, carbon/graphite, silicone nitride, titanium diboride, boron nitride, Macor from Corning Glass, partially stabilized zirconia, and others all have promising applications for mechanical components in MCSSs.

One of the newest applications for these ceramics involves what are referred to as hybrid bearings. These bearings utilize conventional steels for the races such as carbon steel 52100 and stainless steel 440C, but utilize ceramic balls made of materials such as silicone nitride. These hybrid bearings have improved life.

New Composites

Literally thousands of composite material combinations are possible today (Schwartz, 1983). These composites are a matrix consisting of at least two distinct components, one the binder that contains the major structural elements of the fibers. Most composites to date have used a relatively soft matrix, a thermosetting plastic of a polyester or epoxy type. These composites can offer advantages in manufacturability of both rigid and flexing members of the devices. It may be possible to use fiber reinforcement in a flexing diaphragm to improve fatigue resistance. The binders can be reinforced with various fibers such as aluminum, steel, E-glass, S-glass, HT graphite, boron, various grades of Kevlar, and other materials. These composite materials are being used extensively in the aerospace industry, and further developments in this area will undoubtedly help to improve durability of MCSSs.

Most recently, ceramic metal composites have been developed. At present, this new family of hard, lightweight, and tough ceramic metals was devel-ofma

oped for military armor (Ashley, 1990). It consists of aluminum and boron carbide. This material would have application in cases or housings for mechanical circulatory support systems.

Electronics Development

New Power Devices

Over the past two decades there have been dramatic developments in electronics components. New power devices that switch much more rapidly and have much lower on-resistance have been developed. There will be new, even faster switching, lower on-resistance power switching devices becoming available within the next year. These will improve the efficiency and reliability of MCSSs.

New Microprocessors

Larger and faster microprocessors are becoming available almost yearly and will greatly simplify the current systems.

Hall Effect Devices

Improved Hall effect devices have been manufactured by various companies such as Honeywell. Their Hall effect sensors have gotten smaller and more reliable with improved performance specifications. New and improved devices will be forthcoming in the near future.

Room-Temperature Superconductors

Major strides have been made in approaching room-temperature superconductors, and work on them continues. Even if just an order of magnitude change is accomplished in existing conductors, this will have a very significant impact on MCSSs. Major losses occur in these devices due to the I^2R losses in the motors and leads. In summary, electronics development should have a major positive impact on MCSSs in the very near future, in terms of increased reliability, reduced size, and less power utilization.

Magnetic Materials

In the 1970s, Alnico was the magnetic material of choice for brush-type DC motors. Late in the 1970s, brushless DC motors were developed but still utilized Alnico metals. In the late 1970s, improved magnetic materials

were developed that utilized rare earth materials such as samarium cobalt. Energy products approaching 30,000,000 Gauss Oersted were obtained with this material. More recently, neodymium iron magnets have been developed that produce an energy product in excess of 30,000,000 Gauss Oersted. These improved magnetic materials mean smaller and lighter motors and better magnetic coupling in solenoid devices. Research continues for improved magnetic materials. Any improved magnetic materials would have a positive impact on MCSSs. They would reduce the size and weight of the device, and might also improve overall performance.

Supercomputers

Computational Fluid Dynamics

Supercomputers such as the Cray system have had and will, in the near future, have a significant impact on the development of MCSSs. These systems can be used to solve extremely complicated, nonlinear partial differential equations that may describe stresses in the materials or fluid mechanics. These are extremely important studies in terms of (1) understanding the fluid mechanics within the blood pump and (2) determining the stresses in the various components of the system. At the present time, it is not possible to solve a three dimensional unsteady, non-Newtonian turbulent flow within these blood pumps. Thus, it is extremely difficult to know and understand the fluid mechanics that are occurring in the device and the contribution to thrombosis, hemolysis, and the mechanical stresses within these devices. Through the use of new codes and supercomputers, solutions of this problem will yield basic information related to fluid mechanics and thrombosis.

Numerical Analysis Techniques

The ultimate longevity of the elastomeric diaphragms and other mechanical components in these blood pumps relies on an accurate prediction of the stresses imposed on the device during operation. The determination of these stresses involves the solution of difficult differential equations. New supercomputers and new codes can be utilized to solve these differential equations. These solutions can then be used to do optimization of the size and shape of the blood pump to provide for minimum stresses and minimum hemolysis and thrombosis related to the mechanical motion and fluid mechanics of the device.

Summary

Developments in new materials, electronic components, magnetic materials, and supercomputers should all have a positive impact on MCSSs. Not

only will the new materials and electronic components provide for smaller and more efficient and reliable devices, but the advent of new polymeric materials or surface-improved materials should also yield reduced thrombosis. New mathematical models solved on supercomputers will give a better basic understanding of the role of mechanical stresses and fluid mechanics in thrombosis, hemolysis, and mechanical component failure. This basic knowledge can be utilized to design and optimize improved devices.

SPIN-OFF TECHNOLOGIES

Materials and Design

Research on mechanical circulatory support has generated a pool of individuals with unique expertise in the area of artificial organs. The expertise of these individuals can be utilized in the development of other devices such as grafts, valves, new biomaterials, biosensors, and implantable battery technology.

Grafts

The technology related to materials and blood flow within MCSSs can be applied to the design of new and improved vascular grafts. New biomaterials, manufacturing processes, or surface modification techniques can be used for these grafts.

Valves

Researchers working on the development of mechanical circulatory support systems are working on manufacturing polymeric trileaflet heart valves. ABIOMED currently uses a polymeric trileaflet valve that their personnel have designed and constructed for their short-term MCSS. Researchers at the University of Utah and Penn State have also manufactured polymeric heart valves (Wisman et al., 1982). As these valves are further developed, they may find clinical application as prosthetic heart valves. They potentially could offer improved biocompatibility over mechanical and tissue valves at a reduced cost.

Biomaterials

Certainly, any biomaterial developed for MCSSs could be utilized in other implant applications. There have really been no new major biomaterials developed in the past 10 years. Increased emphasis should be placed on the development of new biomaterials that would be applicable to mechanical circulatory assist devices and other biomedical applications.

Biosensors

Researchers associated with mechanical circulatory support systems are developing biosensors that can be used to control devices such as the artificial heart. These biosensors will sense quantities such as pH, carbon dioxide, carbon monoxide, and oxygen tensions within the body. These biosensors will have uses in artificial organs such as liver, kidney, and lung. They would also have application for incorporation into catheters that can be used for monitoring of hospital patients in intensive care units.

Battery Technology

The Honeywell Energy Systems Division has identified the biomedical market as one they would like to develop a battery for. Honeywell has previously developed a lithium technology primary battery that is utilized in the implantable defibrillator. Honeywell Energy Systems is currently working on the development of new lithium rechargeable technology for use with MCSSs. This battery technology, if developed, would be used for other high-energy, high-reliability applications such as in aerospace and other medical areas.

Drug Actions

Artificial heart animals and patients provide excellent models for testing the actions of various drugs. The effects of these drugs on the vascular system can be studied while the heart is controlled by the researcher. This model can then be utilized to understand more clearly the cardiac and vascular component actions of the drugs.

Development of Transcutaneous Energy Transmission Systems

Development of transcutaneous energy transmission has already been spun off into use into the cochlear implant, as previously described. This technology would have application for other implanted artificial organs that require high energy levels.

Much of the technology that is developed for MCSSs can be used for other artificial organs or biomedical applications. Also, developments in battery technology, biomaterials, and biosensors will have uses in other high reliability situations such as aerospace applications.

SUMMARY

Current Status of Mechanical Circulatory Support Systems

Short-Term Devices

Several short-term ventricular assist devices are now available to clinicians under IDEs. These include the Thoratec pump, the Thermedics pump, the ABIOMED system, the Novacor system, the Sarns Centrimed system, and the Biomedicus pump. Usage of these short-term ventricular assist devices has been outlined elsewhere and is covered extensively in the Combined Registry for the Clinical Use of Mechanical Ventricular Assist Pumps and the Total Artificial Heart. It should be noted that complications associated with this class of devices, in general, include bleeding, infection, thrombosis, and to a lesser extent hemolysis. It is also quite important to note that some of the devices have much better results in certain areas than others. For example, the Thermedics device has been utilized in 17 patients without thrombosis or thromboembolic events. Although this is a small number of patients, the results appear encouraging. Also, a careful look at the registry data shows that a particular device may do better than the general population of devices. The success rate for these devices continues to improve with time, and there appears to be great interest in getting more of these devices into use.

At the present time, the only short-term total artificial heart approved by the Food and Drug Administration is the Penn State heart. This device has been utilized in three patients, the longest of whom survived for 390 days. The clinical indications for the use of a short-term total artificial heart have not been well established. It appears that in most instances, biventricular support or univentricular support is adequate for short-term bridge to transplant applications. With biventricular and left ventricular assist devices as successful as they are, it is doubtful that there will be an increased use of the short-term total artificial heart.

Long-Term Mechanical Circulatory Support Devices

Long-term or permanent ventricular assist devices are coming quite close to clinical application. The system developed by Novacor has demonstrated a two-year life with an 80 percent reliability in vitro. Preclinical testing in vivo will begin shortly, and clinical trials under an IDE will also be beginning in the next one to two years. The Novacor system has been utilized as a short-term device clinically with results essentially similar to the average registry results. Other research groups, such as ABIOMED, Penn State, Thermedics, and the University of Washington, are all pursuing development of long-term ventricular assist devices. Devices from Nimbus, Penn

State, and Thermedics have undergone limited in vitro testing and have all been utilized in vivo. Experiments at Penn State have been conducted utilizing transcutaneous energy transmission with a completely sealed system in the calf.

Long-Term Implantable Total Artificial Hearts

Four groups in the United States are now working under contract on long-term electric motor-driven total artificial heart devices: ABIOMED, Nimbus, Penn State, and the University of Utah. ABIOMED, Nimbus, and University of Utah have completed initial designs and have begun in vitro testing of various components of their systems. Penn State has manufactured a complete electric motor-driven total artificial heart system that transmits energy across the intact skin by inductive coupling. The system is completely sealed and totally implantable, has undergone in vitro testing, and has been utilized in two calf experiments. This system is currently in a state of development that is equivalent to the development of long-term ventricular assist devices, with the exception of the Novacor system, which is the most advanced. All of these systems have their relative advantages and disadvantages in terms of size, efficiency, and reliability, and further testing is required to determine the best system.

Prospects for the Future of Mechanical Circulatory Support Systems

Prediction of future prospects for MCSSs can be done with a certain degree of confidence for the next three to five years. When predicting for the next 5 to 10 years, one needs to be more cautious; in predicting the prospects for the next 10 to 30 years, one must be extremely cautious. Looking back at medical device and device-related technology in the early 1950s, it is doubtful that many would have predicted then the great usage of heart valves, pacemakers, implantable defibrillators, and vascular prostheses available today. In the 1950s, the first pacemaker had to be pushed around on a cart by the patient. Twenty years ago, patients were still changing or charging batteries in their pacemakers. Then new higher-energy-density primary cells and lower-energy-requiring C-MOS electronics made charging and changing batteries a thing of the past. Today there are smaller, lighter, programmable adaptive pacemakers. The usage of heart valves has expanded and the results have improved.

In general, if one looks at the history of MCSSs and plots survival times in animals and in patients versus time, one sees a very progressive increase in both animal and patient survival times.

Three to Five Years

In the next three to five years, short-term ventricular assist devices should see more widespread use. Sarns/3M Healthcare Group will be making the Pierce-Donachy pump available under an IDE within the next year, and it is reasonable to predict that other companies will attempt to expand their usage under IDEs. Thus, the use of these devices should continue to increase gradually. It is doubtful that the use of short-term total artificial heart devices will expand due to the success that is occurring with the current left heart assist devices. In the next three to five years, long-term ventricular assist devices will continue to be tested for preclinical and clinical application. Novacor should be able to complete in vivo studies on its system and begin initial clinical trials within the next two to three years. Thus, clinical application of the Novacor system could occur within the next five years. Other systems being developed for long-term application may undergo in vitro testing to qualify for in vivo testing prior to clinical application within the next five years. Permanent total artificial heart devices currently under development will begin initial in vivo experiments within the next three to five years, and some fairly extensive in vivo and in vitro studies should have been completed on all four of the systems being developed under government contact.

Five to Ten Years

It is reasonable to assume that there will be the same trend in usage of short-term left ventricular assist and total artificial heart devices within the next 5 to 10 years. Perhaps improvements in the short-term left heart assist devices will result in more usage for cardiogenic shock support. Within the next 5 to 10 years, the permanent left heart assist system of Novacor should be well into clinical trials. Other groups manufacturing devices, such as Nimbus, Penn State, ABIOMED, and Thermedics, should within the next 5 to 10 years complete their animal in vivo studies and begin human in vivo studies. Within the next 5 to 10 years, permanent total artificial heart devices should be well on the way to becoming finalized designs. The current contracts call for the beginning of preclinical testing within the next five years. This would mean that the groups should have completed all of their preliminary in vitro and in vivo testing and have begun extensive reliability testing and animal studies. By 10 years from now, the first of these devices should receive some clinical application. Thus, it would seem reasonable to predict that within the next 10 years a permanent total artificial heart will be implanted in a human. This device should have as a minimum an 80 to 90 percent reliability for two years.

Ten to Thirty Years

Predictions for the next 10 to 30 years become much more difficult. Within the next 10 to 30 years, new materials should become available that will reduce or eliminate the complications associated with MCSSs. Almost surely new magnetic materials, new electronic components, and better conductors all will enable these devices to be improved. New electrochemical energy sources should become available and should be able to be incorporated into existing designs. Within the next 30 years, these devices should be available for widespread use and provide a satisfactory lifestyle, with five-year survival rates in excess of 50 percent.

It is always worrisome to make predictions about the future and much more so when they are made in writing. With that in mind, this author has attempted to be as conservative as possible. Looking at the history of mechanical circulatory assist devices, looking at the status today, and looking at the progress that has been made, one should feel fairly comfortable with predicting their widespread usage in the future. This is not to predict that these devices will be without problems of bleeding, infection, and thromboembolic complications, but that such problems will be much reduced and the devices will provide a satisfactory lifestyle for patients in the future.

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D

Epidemiology of End-Stage Heart Disease

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AN EXAMINATION OF THE EPIDEMIOLOGY of end-stage heart disease is a necessary first step in determining the nature and magnitude of the target population for fully implantable long-term mechanical circulatory support systems (MCSSs). In attempting to estimate the target population for these devices, it is important to focus on heart failure initially, because the purpose of MCSSs is either to support the failing heart (ventricular assist devices) or to replace it (total artificial hearts). To determine the number of individuals with the most severe illness (primary group), mortality statistics will be examined. Further, the circumstances of death (not sudden) and the presence of comorbid conditions that would limit the utility of the devices will be considered. To estimate the number of individuals who are less disabled by their heart disease (secondary group), prevalence statistics will be evaluated.

PRIMARY GROUP: CURRENT STATUS

The National Center for Health Statistics (NCHS) reports that in 1988 there were 42,940 deaths in the United States for which congestive heart failure (CHF) was designated as the underlying cause of death (Thom, 1991). In the Framingham cohort, approximately 40 to 50 percent of CHF deaths

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were sudden, which was defined as death within one hour in patients who were clinically stable (Kannel et al., 1988). Francis (1986) reviewed the incidence of sudden death in patients with CHF in 12 published reports and found that 8 cited sudden death rates of between 43 and 63 percent. Of 642 men with moderate failure (New York Heart Association Classes II and III) in the Veterans Administration Cooperative Study on Vasodilator Therapy of Heart Failure, 45 percent died suddenly (Cohn et al., 1986). Application of these percentages to the 42,940 CHF deaths in 1988 reveals that between 15,888 (0.37 x 42,940) and 25,764 (0.60 x 42,940) people did not die suddenly. This group could have benefited from MCSS.

The presence of medical and psychosocial comorbidities would likely preclude MCSS use in some of these individuals. Data, however, are not available regarding the presence of comorbid illness in individuals with end-stage heart failure. A very approximate estimate of the prevalence of comorbid conditions can be derived from the population-based study conducted by Kottke and associates (1990). In their attempt to estimate the need for long-term MCSSs, they reviewed all deaths in a five-year period in Olmsted County, Minnesota, using restrictive criteria for comorbid conditions, as well as age and time elapsed between onset of symptoms and death. They found that of the 248 people age 15 to 69 years old who died of cardiac disease, 52 percent died so quickly that intervention with an MCSS was not possible, 14 percent had comorbid conditions that would prevent them from benefiting from a device, and 20 percent died suddenly and had comorbidity. This left 35 individuals (14 percent) who were considered to be candidates for cardiac replacement.

Kottke and colleagues projected that there would be 16,500 potential candidates for cardiac replacement nationally each year. This estimate was based on assumptions that the 95,000 residents of Olmsted County were representative of all Americans, and that the population of the United States was 225 million at the time of the study, calendar years 1979 through 1983. Extrapolating the estimate based on the 35 candidates over five years yields approximately 16,500 annually.

With caution, the figure of 14 percent can be applied to the 42,940 CHF deaths to estimate the number of potential candidates for MCSS. This calculation reveals that 6,012 individuals per year may have benefited from these devices. This, however, may be misleading because only 31 percent of the Olmsted County deaths were attributed to chronic heart failure, whereas 54 percent were related to acute myocardial infarction (MI). The authors are not explicit in defining the diagnostic criteria for these conditions. They do, however, state that all of the 35 people designated as potential candidates for cardiac replacement had "severe depression of left ventricular function." Acute MI, chronic heart failure, inability to wean from cardiopulmonary bypass, idiopathic cardiomyopathy, and cardiac tu

mor were the "sources" of heart disease. It is unclear whether the term "heart failure" is used in the same way as in the NCHS mortality statistics.

If it is assumed that the Olmsted County deaths were indeed due to a broader range of heart problems than merely heart failure, then the 14 percent figure could be applied to NCHS mortality statistics for coronary heart disease (CHD), cardiomyopathy, and heart failure-the most frequent sources of ventricular dysfunction. The National Heart, Lung, and Blood Institute (NHLBI) (1990) reports that for 1987 there were 512,138 deaths due to CHD, 18,660 deaths from cardiomyopathy, and 41,210 attributed to heart failure, for a total of 572,008 deaths. Fourteen percent of this is 80,081, which is—as expected—considerably higher than the 6,012 calculated from the 1988 CHF mortality figure.

Because they do not take age or comorbidity into account, the calculations presented thus far are higher than are appropriate for the purpose of estimating a target population for MCSSs. It has been determined that these devices would generally be contraindicated in children who were still growing (less than 15 years old), as well as in the elderly (85 years and older). The above calculations, however, include all age groups.

To determine the number of people between the ages of 15 and 85 who might benefit from an MCSS, the numbers of deaths due to CHF and CHD in this age range were calculated. The most recent age-specific death rates available (Thom, 1991) were applied to age-specific projections of the United States population for 1990 (Spencer, 1989). These calculations reveal 29,649 deaths from CHF in the 15- to 85-year-old group and 384,102 deaths from CHD in the 25- to 85-year-old group. (Death rates from CHD for those less than 25 years old are not available but are presumed to be very low.)

Next, the 14 percent figure was applied to reflect the number who did not die suddenly and who did not have comorbid conditions which would preclude device use. For CHF 4,151 (0.14 x 29,649) individuals between the ages of 15 and 85 and for CHD 53,774 (0.14 x 384,102) individuals between 25 and 85 may have benefited from MCSS.

Application of the 14 percent figure from the study by Kottke and associates presupposes that the rates of sudden death and comorbid conditions for those between 70 and 85 years old are similar to rates for those between 15 and 69 (the age range in the work of Kottke et al.). No research could be found indicating that the percentage of deaths that are sudden is significantly different for the elderly. If anything, the rate of sudden death—defined as death within one hour in patients who were clinically stable—may be slightly lower in older people, because they are less likely to be clinically stable. One might also assume that older people have more comorbid conditions. Additionally, the phenomenon of "selective survivors" may be operating: people who live a long time do so because they

are healthy. The 14 percent figure, therefore, is probably appropriate for the entire age group considered (15 to 85). The potentially lower sudden death rate and higher comorbidity rate-if present-may negate each other.

It is tempting to examine statistics on cardiomyopathy, since currently it is the most common indication for heart transplantation (Kriett and Kaye, 1990). In the study by Kottke and associates, however, only 1 of the 35 potential candidates (3 percent) for cardiac replacement had cardiomyopathy. NHLBI (1990) reported 18,660 deaths from cardiomyopathy in 1987. This represented only 2.4 percent of all deaths from heart disease that year.

In summary, the best estimates for the current target population for MCSS are 4,151 for CHF and 53,774 for CHD, for a total of 57,925. Whereas these are the most precise figures obtainable, they must be viewed with much caution since they were calculated using percentages of sudden death and comorbidity derived from Olmsted County data. It is known that Olmsted County residents have better access to medical care, are more predominantly white (99 percent), and are of higher socioeconomic status than the U.S. population as a whole. The estimates for the target population for the primary group, thus, may be low.

The total of 57,925 is considerably higher than the estimates presented by the two most recent attempts at defining a target population for MCSSs. Lubeck and Bunker (1982) estimated that there would be 33,600 artificial heart candidates under the age of 65. They assumed, however, that there would be no implants in patients who were "stable" under medical management, regardless of the severity of their disease; it would almost always be an emergency procedure. They acknowledged that, should the artificial heart prove to be highly successful, this estimate could double to approximately 66,000. Conversely, if insurmountable problems are encountered, the number of candidates would be substantially lower, or approximately 16,000. As noted above, Kottke et al. (1990) estimated a target population of similar magnitude (16,500). The higher upper age limit (85 versus 65 and 69 in the other two analyses) likely accounts for the larger estimate in the present projection. If the upper age limit were reduced to 75 rather than 85, then the same calculations would produce a target population of 1,769 for CHF and 29,598 for CHD, for a total of 31,367.

PRIMARY GROUP: FUTURE PROJECTIONS

Since long-term, fully implantable circulatory support devices are not yet in use clinically, it is essential to attempt to estimate the number of people who might benefit from these devices in the next 30 years. Weinstein and associates (1987) developed a computer simulation model which forecasts future mortality from CHD in the U.S. population. This model projected an

annual increase in mortality for each five-year interval from 1990 to 2010. Using the current CHD target population figure of 53,774 calculated above and applying the percentage increase in mortality for each five-year period as projected in the computer model results in the figures for CHD presented in Table D.1.

Because Weinstein and associates did not project CHF mortality, an alternative method for determining future trends in CHF mortality was developed. Assuming that trends in CHF mortality will continue into the immediate future, a simple linear regression using year and number of deaths was performed. The number of deaths per year was available as far back as 1950. It is apparent that the number of deaths attributable to CHF increased each year. After it was determined that a linear relationship existed, the parameter estimates were used to determine the number of deaths for future years.

To project the number of deaths in the relevant age group, the percentage of all current CHF deaths that occurred in the 15- to 85-year-old age group was calculated: 29,650/46,421 = 0.6387. Assuming that this percentage will be relatively constant, for each future year this figure was applied to the number of deaths derived from the linear regression equations. Then, to account for the effect of sudden death and comorbidities, 14 percent of the resulting numbers were computed and are displayed in Table D.1.

The total number of potential users of circulatory support devices is projected to increase over the next 30 years: from approximately 60,300 in 1995 to 72,869 in 2020. If the upper age limit were reduced to 75 instead of 85, then (as shown in Table D.2) there would be approximately 32,718 potential users in 1995. This figure would increase to about 39,334 by 2020. All of these projections assume that recent trends in cardiac risk factor levels and the development of new technologies and treatments for

TABLE D.1 Projected Number of Individuals <85 Years Old Who Might Benefit from Circulatory Support Devices: 1995 to 2020

Year	CHD	CHF	Total
1995	56,484	3,816	60,300
2000	59,367	4,297	63,664
2005	60,527	4,779	65,306
2010	62,902	5,260	68,162
2015	64,130	5,741	69,871
2020	66,647	6,222	72,869

CHD, coronary heart disease; CHF, congestive heart failure.

heart disease will persist. The impact of primary prevention and medical care on mortality trends, however, is extremely difficult to determine. The increase in the target population for long-term MCSS reflects the anticipated growth of the general population during the next 30 years, and in particular the movement of the "baby boom" generation born in the 1940s and 1950s into the age range of increased risk of heart disease.

TABLE D.2 Projected Number of Individuals <75 Years Old Who Might Benefit from Circulatory Support Devices: 1995 to 2020

Year	CHD	CHF	Total
1995	31,090	1,628	32,718
2000	32,677	1,831	34,508
2005	33,315	2,036	35,351
2010	34,622	2,241	36,863
2015	35,298	2,446	37,744
2020	36,683	2,651	39,334

CHD, coronary heart disease; CHF, congestive heart failure.

SECONDARY GROUP

The primary problem with using mortality data to estimate the target population for long-term implantable circulatory support devices is that some people with end-stage heart disease, but who are not yet dying, might also benefit from these devices. By definition, individuals in the secondary group are less disabled by their disease than the moribund patients who comprise the primary group. To determine the number of individuals in the secondary group, prevalence statistics will be examined.

Prevalence estimates can vary considerably depending on the source of the data. For example, data obtained by interview (e.g., the National Health Interview Survey) are apt to be very different from hospital discharge data (e.g., the National Hospital Discharge Survey). Whereas the former depend on the awareness and willingness of the respondent to report the condition, the latter are limited by the inclusion of only those whose condition is severe enough to require hospitalization. Because individuals with end-stage heart disease who would be candidates for these devices are likely to be hospitalized, using hospital discharge data seems appropriate. It is important to note, however, that this source of data is limited by the fact that it is hospital discharges rather than individuals that are enumerated. Thus, one individual who is hospitalized on three occasions would be

counted three times, resulting in an overestimate of the need for these devices. Additionally, since most prevalence data do not discriminate according to the severity of illness, it is likely that a substantial proportion of those included would not be sick enough to require circulatory support devices.

Congestive Heart Failure

The best available estimate of the prevalence of CHF in the United States is 3,037,665 (Thom, 1991). This figure was obtained by applying the rates observed in two community studies conducted in 1962 by Gibson and colleagues (1966) to 1988 census figures. Whereas age-specific data are not available, it is known that more than half (1,654,700) are 75 years old and over. Additionally, most of these individuals with CHF are not sufficiently disabled to benefit from device therapy.

Estimating prevalence from hospital discharge statistics yields a more severely ill group. National Hospital Discharge Survey data reveal that in 1988 there were 663,000 hospital discharges with CHF as the primary diagnosis, and 1,858,000 as one of all-listed diagnoses. Whereas the number in the relevant age group (15 to 84 years old) is not known, approximately 80 percent of both groups are discharges of individuals over 64 years old. Although this population is sick enough to require hospitalization, it is unclear how many are sick enough to warrant a circulatory support device. Additionally, information is lacking on the presence of comorbid conditions which would preclude benefit from device therapy. Lastly, as stated above, these numbers represent discharges rather than individual patients and thus constitute an inflated estimate of the need for these devices.

To obtain a more realistic estimate, age-specific data on the number of hospitalizations, excluding deliveries, for individuals interviewed in the National Health Interview Survey were analyzed to determine the proportion of discharges that represent individual patients. Percentages ranged from 69 percent for those over 74 years to 81 percent for those between 25 and 44 years old; older people are hospitalized multiple times more frequently than younger individuals. Application of a 70 percent figure to the 663,000 hospital discharges reveals that approximately 464,100 individuals were hospitalized with CHF in 1988. From this figure, the number who died of CHF (4,151) must be deducted, resulting in a prevalence of 459,949. Because people with CHF are hospitalized more frequently than the general population, the prevalence is probably closer to 400,000. This figure, however, does not take into account age, severity of illness, or comorbidity.

As with mortality, there has been an annual increase in the prevalence of CHF in the United States since 1971. Rates of hospitalization for CHF more than tripled from 1971 to 1988: from 8.2 to 27.2 per 10,000 popula

tion (Thom, 1991). Since 1980, rates increased more sharply for the 45- to 64-year-old group (70 percent) than for the 65-and-over group (33 percent). Because a majority of devices would probably go to those under 65, this trend is important to consider if the quality of prevalence data ever improves sufficiently to be used as the basis for future projections.

Coronary Heart Disease

National Hospital Discharge Survey data indicate that there were over 2 million discharges for CHD in 1988. Of these, 716,000 were for acute MI, 411,000 were for atherosclerotic heart disease, and 921,000 were for other ischemic heart diseases. Seventy percent of the total of 2,048,000 minus the 53,774 who died of CHD results in a prevalence of 1,379,826. Again, because individuals with CHD are hospitalized more frequently than the general population, the prevalence is likely to be nearer to 1,000,000. Lack of information regarding age, severity of illness, and comorbidity, as outlined above for the CHF estimates, limits the usefulness of these data also.

In their review of trends in CHD, Higgins and Thom (1989) report that hospital discharges for CHD increased from 1970 to 1978, and then appeared to decline and rise again to a stable level. They point out that rates are influenced by admission policies, medical practice, and diagnosis-related groups. Hospital stays are shorter now, and more procedures are done on an outpatient basis. Despite this, the prevalence of CHD may be rising. As the population increases disproportionately at older ages and survival following acute MI improves, it is likely that there will be increasing numbers of elderly individuals with CHD. Some of these people may be young enough to benefit from a circulatory assist device.

Prevalence trends were also examined in the population-based Minnesota Heart Survey (Burke et al., 1989). In individuals age 30 to 74, the rate of discharge diagnoses for acute CHD decreased from 1970 to 1980, and then increased significantly from 1980 to 1985. There was no change in MI rates from 1970 to 1985.

In summary, the best available prevalence estimates are 400,000 for CHF and 1,000,000 for CHD. Since these numbers have not been adjusted for age, severity of illness, or comorbidity, they significantly overestimate the number of individuals in the secondary group. Although precise current numbers or future projections cannot be derived for this group, data indicate that the prevalences of both CHF and CHD are increasing.

INTERNATIONAL DATA

The focus of this paper has been an epidemiologic analysis of heart disease in the United States. Although little is known about the incidence

and prevalence of heart disease internationally, mortality data are available and trends have been determined for a number of countries. It is known that countries such as Australia, Belgium, Canada, Finland, Israel, Japan, and New Zealand have experienced declining CHD mortality similar to the trend noted in the United States (Thom, 1989; Beaglehole, 1990). With considerable caution, the same calculations performed on U.S. mortality data to determine a target population for MCSS use might be undertaken for these countries. Potential differences in diagnostic customs and classification procedures, however, make international comparisons, and thus the validity of such calculations, highly speculative. Additionally, calculations using percentages of sudden death and comorbidity derived from Olmsted County—where socioeconomic status is higher and access to medical care is better—would result in spuriously low international estimates.

TABLE D.3 Age-Adjusted Coronary Heart Disease Mortality Rates in Selected Industrialized Countries for Ages 35 to 74 in 1987

	1989	Rate/100,000	
Country	Population	Men	Women
Australia	16,090,000	333.1	126.2
Belgium	9,897,000	221.1	71.9
Canada	25,334,000	309.2	104.3
England/Wales	56,648,000	439.9	154.8
Finland	4,990,000	506.6	153.0
France	55,813,000	127.1	34.0
West Germany	60,162,000	289.5	90.3
Israel	4,477,000	305.2	140.5
Japan	123,231,000	52.2	21.4
Netherlands	14,689,000	284.2	85.0
New Zealand	3,397,000	446.7	165.2
United States	247,498,000	306.6	122.1

Mortality rates for CHD in selected industrialized countries are displayed in Table D.3. Countries such as Canada, England and Wales, and Germany have high enough mortality rates, as well as large enough populations, to produce a group of potential MCSS users of sufficient magnitude to warrant consideration when one is estimating the need for these devices.

CONCLUSIONS

Calculations based on mortality data (primary group) reveal that currently about 58,000 individuals might benefit from circulatory support sys

tems. The target population is projected to increase over the next 30 years: to approximately 64,000 in 2000, 68,000 in 2010, and 73,000 in 2020. These estimates are considerably lower if the upper age limit is reduced from 85 to 75 years (31,000 currently, 35,000 in 2000, 37,000 in 2010, and 39,000 in 2020).

The inferior quality and lack of specificity that characterize prevalence data preclude their utility in estimating the potential application of longterm MCSSs. Although it is intuitively sensible to consider the number of individuals with end-stage heart disease who are currently alive, this information simply is not available. Population-based data concerning the natural history of heart disease in general, and heart failure in particular, could not be located.

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E

Assessing the Cost-Effectiveness of Development and Use of the Total Artificial Heart

This appendix was prepared by Louis P. Garrison, Jr., of the Project HOPE Center for Health Affairs. He worked closely as a consultant with committee members and project staff to develop both the model and the estimates. The Markov model estimates were prepared using a software package called Decision Maker (Version 6.2). A copy of the computer model can be obtained from the National Technical Information Service (NTIS), U.S. Department of Commerce, Springfield, Virginia 22161.

Given (1) our lack of clinical experience with the TAH and (2) the obvious uncertainties associated with research and development activities, it should be apparent that this kind of exercise cannot provide definitive conclusions or precise estimates. Rather, the intent was to explore some of the likely outcomes and trade-offs under alternative sets of plausible as

THIS APPENDIX DESCRIBES the framework and results of an analysis of the cost-effectiveness of the eventual development and use of the total artificial heart (TAH). The analysis was conducted in support of and collaboration with the Institute of Medicine (IOM) Committee to Evaluate the Artificial Heart Program of the National Heart, Lung, and Blood Institute (NHLBI). The overall aim of the analysis was to provide information to support the committee's consideration of two questions. First, how well is the TAH likely to perform when it is in routine use, approximately in the year 2010? Second, what are the possible outcomes, in terms of device availability and cost, of higher levels of NHLBI support for TAH research and development? Both of these questions were addressed using a cost-effectiveness framework.

sumptions and scenarios that were developed through discussions with the committee and other experts.

BACKGROUND

Aside from medical therapies, heart transplantation is currently the only clinical option for patients suffering from end-stage heart failure. As discussed in Chapter 4, the number of potential heart transplant recipients greatly exceeds the available supply of donor hearts. Several types of longterm mechanical circulatory support devices are being developed in order to treat these heart failure patients. Currently, the ventricular assist device has the best prospect of being available in the near future. Although this device will potentially be able to serve a large number of heart failure patients, it is unlikely to work satisfactorily for the subset of patients with both right and left heart failure. Hence, several groups in the United States, four of which have NHLBI support, are continuing their efforts to develop a total heart replacement device.

In order to address the issue of the level of resources that society should devote to research and development of the TAH, it is important to develop an understanding of the likely costs and outcomes of such investments. Given the uncertainties of such a question, however, it is not obvious that a quantitative, as opposed to qualitative, approach is either necessary or preferred. Nonetheless, the committee chose to have data gathered and compiled to illustrate some of the quantitative dimensions of the issue.

The information was compiled in a cost-effectiveness analysis (CEA) framework for two separate but related issues:

1. The future cost-effectiveness of the artificial heart in use, compared to alternative surgical and medical therapies.
2. The cost-effectiveness of alternative research and development strategies for developing TAHs.

The framework and estimates associated with each of these issues are presented in the following sections. Although the R&D investment must come before the TAH is available for use, it is useful to consider first the cost-effectiveness in use since the diffusion of the device becomes the benefit of the investment.

ESTIMATING THE COST-EFFECTIVENESS OF THE ARTIFICIAL HEART IN ROUTINE USE

Approach

To estimate the cost-effectiveness of the artificial heart in routine use, a Markov simulation model was used, permitting variations in assumptions

about cost, clinical, and outcome variables. Both the structure of the model and the parameter estimates were developed in collaboration with the committee and its expert consultants. In forecasting the parameter estimates, it is necessary to have a frame of reference in terms of both time and the case mix of patients. The committee saw the period beginning in 2010 as the earliest when a TAH might be in routine use.

The typical patient is seen as a moribund 50 year old (New York Heart Association Class IV) with life expectancy measured in days or weeks. It is assumed that 75 percent of the patients would be male and 25 percent female. In the model, this directly affects the average mortality from all other causes.

Structure of the Model

The clinical process of receiving a TAH was conceived of as a Markov process in which the typical patient moves through a sequence of potential "states" on a monthly, probabilistic basis. The cost effectiveness of TAH implantation was considered relative to two alternative therapies-conventional medical treatment and heart transplantation. The 10 possible states under TAH implantation are shown in Table E.1. For example, a patient who receives a TAH in the first month and is discharged alive could, in the second month, fall into one of nine different states, including having the device fail, having a well-functioning device, and being hospitalized for complications.

In the model, the patient is followed through this process over a 20-year period (240 monthly cycles in the model). Each month the TAH recipient is

TABLE E.1 States in a Markov Model of Artificial Heart Implantation

TAH Recipient States	Heart Transplant Recipient States
Implantation	Transplantation
Well-functioning implant	Well-functioning organ
Complications-Infection	Complications
Complications—Thromboembolism	Rejection[a]
Complications—Bleeding	Death
Complications—Psychological	
Complications—Other	
Soft device failure	
Hard device failure	
Death	

[a] Includes both early (acute) rejection and late (chronic) rejection. TAH, total artificial heart.

in one of the 10 states. The "outcomes" associated with each monthly cycle can be classified into the two broad categories of costs and benefits, although there are several possible ways to define these. As indicated in Table E.2, this analysis considers costs narrowly: only medical costs are analyzed. Benefits are measured quantitatively in terms of average expected life years gained and of quality-adjusted life years (QALYs) gained. The quality adjustments are made through utility ratings of each state.

TABLE E.2 Assumptions for Cost-Effectiveness Analysis of Total Artificial Hearts in Routine Use

1.	The analysis takes a societal perspective.
2.	The cost-effectiveness analysis considers only medical costs and health effects, and will not incorporate indirect benefits, such as productivity increases.
3.	Costs are measured in constant 1991 dollars.
4.	Both costs and survival are discounted using several alternative rates. No adjustment is made for risk aversion.
5.	The risk of death from other causes increases with age according to standard mortality tables.
6.	Survival is adjusted for quality-of-life differences among states.

Several of these assumptions are summarized in Table E.2. Note also that the analysis takes a societal perspective and makes estimates in real dollars (i.e., constant 1991 dollars).

Parameter Estimates

The clinical and cost parameters of the model were estimated by an expert panel of cardiologists, surgeons, and engineers. The panel members were asked to predict the probabilities and outcomes of the events associated with the 10 states in the Markov model. For each state, they estimated the annual probability that a TAH recipient would experience the state, the probability that death would result, the number of days spent in the hospital in both routine and intensive care, and the associated physician fees (see supplementary Tables E.14 and E.15 at the end of the appendix). In addition, for some states, such as device failures, the probabilities of related events such as replacement and repair were estimated.

The base case probabilities are shown in Table E.3. It is estimated that 10 percent of those who receive the TAH implant will die during that initial stay. Annually, for the first seven years, an average of 5 percent are expected to experience a major or "hard" device failure, with 85 percent of them dying. This failure rate increases in subsequent years to over 50 percent after year 10. Also, for the first three years, 5 percent are expected to have a less serious "soft" device failure, requiring either a repair or replacement. This rate also increases in subsequent years.

TABLE E.3 Estimates of Clinical Parameters

State/Parameter	Base Case	State/Parameter	Base Case
TAH recipient			
Implantation % who die	0.10	Psychological % who experience	0.02
		Of those, % who die	0.00
Hard device failure			
% who experience[a]	0.05		
Of those	0.85	Other complications	0.20
% who die		% who experience	
% with replacement	0.10	Of those, % who die	0.20
% with repair	0.05		
		Well	
Soft device failure		% who experience	[b]
% who experience[a]	0.05	Of those, % who die (average)	0.014
Of those			
% who die	0.10	**Conventional medical therapy**	
% with replacement	0.50	Survival (months)	6
% with repair	0.40		
		Transplantation	
Infection		Transplant	
% who experience	0.05	% who die	0.05
Of those, % who die	0.15	% with major complications	0.25
Thromboembolism		Rejection	
% who experience	0.10	% who experience[a]	0.05
Of those, % who die	0.15	Of those, % who die	0.02
Bleeding		Other complications	
% who experience	0.10	% who experience[a]	0.30
Of those, % who die	0.015	Of those, % who die	0.03

NOTES: All parameters are expressed as a probability on annual basis unless otherwise noted. "% who experience" is expressed as annual rate; other probabilities are expressed as a percentage of those experiencing the state.

[a] Rates vary in following years.

[b] Determined as residual.

TAH, total artificial heart.

TAH recipients are also subject to complications including infection, thromboembolism, bleeding, and psychological problems. The probability of dying as a result of each of these complications was also estimated. For example, annually an average of 5 percent of recipients are expected to have an infection requiring hospitalization. Fifteen percent of those hospitalized are expected to die. Age-specific general population mortality rates (for a recipient who ages from 50 to 70) were used to model deaths from other causes.

The probability of a month with a "well-functioning device" is estimated as a residual, i.e., what happens if none of these adverse events occurs. Since the estimates are based on expert judgments and not actual clinical experience with the TAH, developing the model from these micro-level parameter estimates does not necessarily generate plausible aggregate survival probabilities. As a consistency check, the experts were also asked to estimate the annual year-to-year overall survival probabilities as well. Their overall estimates imply a five-year survival rate of 60 percent for TAH recipients.

Relevant estimates were also made for the alternative therapies of conventional medical therapy and heart transplantation. For the former, an average survival of six months was projected. For the latter, as shown in Table E.3, the expert panel projected organ rejection probabilities and other complications in the aggregate. Thus, the model used for heart transplantation was much simpler, hence sacrificing some clinical detail.

Cost parameter estimates are shown in Table E.4. These were developed

TABLE E.4 Cost Parameter Estimates (expected cost during month in state)

State	Base Case Cost per Month	State	Base Case Cost per Month
TAH recipients		Conventional medical therapy	
Evaluation (4 patients)[a]	$ 45,600	All forms of care	$4.800
Initial implantation[b] (incl. device cost and hospitalization)	$157,000		
Hard device failure[b]	$19,500	**Heart transplantation**	
Soft device failure[b]	$74,800	Evaluation (5 patients)[a]	$19,600
Infection	$20,400	Initial transplant stay (incl. organ procurement and hospitalization costs)	$58,100
Thromboembolism	$17,000		
Bleeding	$30,900		
Psychological complication	$20,700	Rejection stay	$12,600
Other complications	$26,700	Complication stay	$11,000
Well-functioning device	$800	Well-functioning transplant	$ 1,500

NOTE: Cost estimates are based on expert panel estimates (see Tables E.14 and E.15) of hospital length of stay percent of days in ICU and physician fees; hospital costs assume a cost per day of $1 000 (regular room) and $2 000 (ICU).

[a] For TAH evaluation expert panel estimates assumed hospitalization in all cases in contrast to evaluation of potential transplant recipients some of whom require less extensive hospitalization.

[b] For TAH recipients the state of initial implantation includes device priced at $100 000. However for hard and soft failures only a fraction of patients receive another device (i.e. some die or have device repair). TAH total artificial heart; ICU intensive care unit.

based on utilization estimates made by the expert panel. The utilization estimates are shown in supplementary Tables E.14 and E.15, at the end of the appendix. The TAH device, in the base case, is expected to cost $100,000. The initial hospitalization associated with implanting the device is projected to cost $57,000. In addition, evaluation costs for four patients per eventual recipient are estimated at $45,600. Thus, the initial costs total more than $200,000 per recipient. This can be compared to $77,700 for the initial heart transplantation hospitalization, including the costs of evaluations of four other candidates who did not receive a transplant and procurement of the donor organ.

Complications and device failures can also lead to costly hospitalizations, ranging from $19,500 per hard device failure to over $30,000 for bleeding or other complications. The estimate for each state is the mean (weighted) cost based on the several events that can happen to a person in that state, such as death or complications, which may vary in their resource use.

The entire committee participated in rating the utilities associated with each of the states, depending upon whether the patient had a well-functioning TAH or was hospitalized. Using the time trade-off method, a utility was rated for each state on a scale in which 1.0 was well, 0 was death, and states worse than death were valued between 0 and -1.0. Their mean utility estimates are shown in Table E.5A. The estimation process and results are described in detail in Patrick and Erickson (forthcoming); the relevant states are described in the appendix to Chapter 6. It is noteworthy that those on conventional medical therapy were rated as having very poor or negative utilities. Table E.5B shows the mean utility for each state in the model for TAH and heart transplant recipients. The values are weighted averages of the values in the top panel, depending on the expected number of days per month spent in the hospital (and in the intensive care unit or not). These mean values were used to adjust life

TABLE E.5A Utility Values for End-Stage Heart Disease States by Time Trade-off Method

	Mean Utility		
Patient Group/ Health State	Long-Term Health State	In Regular Hospital Bed	In ICU/CCU
Medical treatment only (moribund)	0.08	0.01	-0.11
TAH recipient	0.66	0.52	0.40
Heart transplant	0.75	0.55	0.42

ICU/CCU, intensive care unit/coronary care unit; TAH, total artificial heart.

years gained for differences in quality of life. The mean value for a month on conventional therapy was estimated at 0.07.

TABLE E.5B Implied Utility Values for End-Stage Heart Disease States in Model

	TAH Recipient	Heart Transplant Recipient	Medical Treatment Only
Well-functioning/ average state	0.66	0.75	0.07
Implant/transplant Complications	0.50	0.59	NA
Infection	0.57	NA	NA
Thromboembolism	0.58	NA	NA
Bleeding	0.52	NA	NA
Psychological	0.56	NA	NA
Other/all	0.54	0.68	NA
Hard failure/rejection	0.43	0.67	NA
Soft failure	0.56	NA	NA
Death	0	0	0

NOTES:
(1) Values are derived as weighted averages of numbers in Table E.5A based on average hospital stays (see Tables E.14 and E. 15).
(2) For heart transplantation recipients, all complications were modeled together.
(3) For conventional therapy, only one average state was modeled; the estimate of 0.07 reflects 20 days of hospitalization (or approximately 11 percent of the 6 months of life expectancy).
TAH, total artificial heart; NA, not applicable.

Both costs and benefits were discounted using several alternative discount rates—0, 3, 6, and 10 percent. For TAH recipients, over 50 percent of the costs are typically borne initially, associated with the implantation of the device. Yet, most of the benefits—in terms of quality-adjusted life years—come later. Hence, discounting costs and benefits will tend to reduce cost-effectiveness, that is, increase the C/E ratio. The 3 percent discount rate is used for all base case simulations.

Base Case

It is instructive first to compare TAH survival results using the event simulation with the experts' overall TAH estimates, and with their estimates for heart transplantation. These were as follows:

Year	TAH Event Simulation	TAH Overall Estimate	Heart Transplant Event Simulation	Heart Transplant Overall Estimate
1	0.79	0.80	0.92	0.95
2	0.69	0.75	0.88	0.93
3	0.61	0.70	0.87	0.91
4	0.53	0.65	0.85	0.90
5	0.46	0.60	0.83	0.89
10	0.11	0.26	0.72	0.75

The TAH results from the event simulation are worse in terms of survival, but not outside a reasonable confidence interval around the overall estimates. The much lower survival probability shown in the tenth year for the TAH event simulation is due largely to a built-in acceleration in the model in the rate of hard and soft device failures. Survival probabilities for TAH recipients are significantly poorer than the survival experience expected in the future for heart transplant recipients, based on either event simulation or overall estimates.

Tables E.6A and E.6B summarize costs, survival, and cost-effectiveness results for the base case for the three alternative therapies. Expected costs over the 20-year horizon are estimated to average $327,600 for each TAH patient. Average costs for conventional therapy are projected at $28,500, and the model for heart transplant patients yields average total costs of $298,200.

The average survival for TAH recipients is 53 months (4.42 years); for conventional medical therapy, 6 months; and for transplant patients, 135 months (11.3) years. Clearly, heart transplantation would be the modality of choice if a suitable donor heart can be found. It should be noted that expected average survival of 11.3 years (based on event simulation) would be a substantial improvement over current levels, based on the experts' assumption of clinical progress in transplantation between 1991 and 2010. The TAH is expected to both cost more and yield poorer survival than heart transplantation.

Cost-effectiveness for the artificial heart and transplantation, relative to conventional therapy, depends importantly on the quality adjustment. The quality adjustment has two offsetting impacts on life years. Because states associated with the TAH yield a utility of 0.66 at best (0.75 for heart transplant), quality-adjusted survival is at least one-third shorter. On the other hand, since conventional therapy produces very low positive utilities, the adjustment essentially makes the TAH and heart transplantation slightly more favorable in terms of quality-adjusted life expectancy.

Adjusting for quality of life effectively reduces TAH survival to 34.6 months (2.88 years). Compared with conventional therapy, the cost

effectiveness of the artificial heart is estimated at $76,000 per life year gained before the quality adjustment and $105,000 per QALY after the adjustment has been made.

TABLE E.6A Cost-Effectiveness Results for Base Case: Cost and Outcomes by Therapy

Therapy	Aggregate Cost (K$)	LY (yr)	QALY (yr)
1. Artificial heart	$327.6	4.42	2.88
2. Transplantation	$298.2	11.30	8.45
3. Conventional medical treatment	$ 28.5	0.50	0.03

NOTE: Cost and outcomes discounted at 3 percent per annum; 20-year horizon.
K$, $1,000; LY, life years gained; QALY, quality-adjusted life years

TABLE E.6B Cost-Effectiveness Ratios for Base Case

Comparison [a]	Incremental Cost (K$)	Change in LY	Marginal Cost/LY (K$/yr)	Change in QALY	Marginal Cost/ QAYL (K$/yr)
Artificial heart vs. conventional medical (line 1- line 3)	$299.1	3.92	$76	2.85	$105
Transplantation vs. conventional medical (line 2 – line3)	$269.7	10.80	$25	8.42	$32
Transplantation vs. artificial heart (line 2 - line 1)	$-29.4	-6.88	D	-5.57	D

NOTE: Cost and outcomes discounted at 3 percent per annum; 20-year horizon.
[a] Comparing the indicated lines of Table E.6A.
K$, $1,000; LY, life years gained; QALY, quality-adjusted life years; D, dominated (clearly advantageous in both costs and benefits; therefore preferred).

Sensitivity Analyses

Table E.7 summarizes the results of sensitivity analyses of both clinical and cost parameters. The upper portion of the table shows changes that would reduce the cost-effectiveness of the TAH. The alternative estimate

TABLE E.7 Sensitivity Analyses: Artificial Heart Model

Parameter	Base Case	Alternate Estimate	Net Cost (K$)	Net LY (yr)	Net QALY (yr)	Marginal Cost/LY (K$/yr)	Marginal Cost/QALY (K$/yr)
Base case	—	—	$299	3.9	2.8	$ 76	$105
Worsening Cost-Effectiveness (changes that increase the C/E ratio)							
Operative mortality	0.10	0.15	$291	3.6	2.7	$ 80	$109
Hard failure mortality	0.85	0.50	$327	4.3	3.1	$ 76	$106
Hard failure rates			$282	3.3	2.4	$ 86	$117
Years 1-7	0.05	0.10					
Years 8 and 9	0.15	0.15					
Year 10 and later	0.50	0.50					
Soft failure rates			$303	3.8	2.8	$ 80	$110
Years 1-3	0.05	0.10					
Years 4-7	0.10	0.10					
Years 8 and 9	0.15	0.15					
Year 10 and later	0.30	0.30					
Infection/year	0.05	0.15	$299	3.8	2.8	$ 79	$108
Emboli/year	0.10	0.15	$299	3.8	2.8	$ 79	$108
Bleeding/year	0.10	0.15	$306	3.9	2.8	$ 78	$108
Other complications	0.20	0.25	$300	3.7	2.7	$ 80	$110
All of above	—	—	$313	2.6	2.0	$108	$142
All of above and costs 25% higher	—	—	$366	2.6	2.0	$126	$165
Improving Cost-Effectiveness (changes that lower the C/E ratio)							
Operative mortality	0.10	0.05	$307	4.2	3.0	$73	$102
Hard failure rates			$312	4.2	3.1	$73	$102
Years 1-7	0.05	0.05					
Years 8 and 9	0.15	0.05					
Year 10 and later	0.50	0.50					
Soft failure rates			$293	4.0	2.9	$73	$101
Years 1-3	0.05	0.05					
Years 4-7	0.10	0.05					
Years 8 and 9	0.15	0.05					
Year 10 and later	0.30	0.30					
Infection/year	0.05	0.02	$299	4.0	2.9	$75	$103
Emboli/year	0.10	0.08	$299	4.0	2.9	$75	$104
Bleeding/year	0.10	0.05	$293	3.9	2.8	$75	$103
Other complications	0.20	0.15	$298	4.1	3.0	$73	$101
All four lower complications and lower hard failure mortality	—	—	$337	5.0	3.6	$67	$ 95

for each parameter was chosen from the upper end of the range of the experts' estimates. The marginal cost-effectiveness values (Cost/LY and Cost/QALY) are expressed relative to conventional medical therapy, and all benefits and costs are discounted at 3 percent.

Parameter	Base Case	Alternate estimate	Net Cost (K$)	Net LY (yr)	Net QAYL (yr)	Marginal Cost/LY (K$/yr)	Marginal Cost/QAYL (K$/yr)
All of above	—	—	$335	6.1	4.3	$55	$ 78
All of above and costs 10% lower	—	—	$311	6.1	4.3	$51	$ 73

NOTE: Alternative cost estimates reflect change to hospital and physician costs; device cost is unchanged.
K$, $1,000; LY, life years gained; QALY, quality-adjusted life years; C/E, cost-effectiveness.

Taken singly, changes in any one of the complication rates or in operative mortality have a relatively small impact on cost-effectiveness-—generally less than 10 percent. The sensitivity of the results to changes in the cost parameters is shown using an overall adjustment of 25 percent, which just increases the cost per life year by that percentage. Taken together, all of these changes would shorten life expectancy considerably and increase cost per life year substantially. Relative to conventional medical therapy, this would imply a cost per QALY of $165,000.

Possible parameter values that would improve cost-effectiveness are shown in the lower portion of Table E.7 and are based on the lower end of the ranges exhibited in the responses of the experts. As in the above panel, each of these variations has a relatively small impact on costeffectiveness if taken alone. Together, however, if these parameters held, cost-effectiveness relative to conventional therapy would improve from $105,000 per QALY to $73,000 per QALY. Of course, the latter estimate would hold only if costs are 10 percent lower and if all of these clinical parameters were at their lower bound, which is very unlikely.

Using the usual range of discount factors, cost per QALY for the TAH, in comparison with conventional therapy, would vary as follows:

Discount Rate	Cost per QALY
0%	$ 98,000
3%	$105,000
6%	$109,000
10%	$117,000

The impact of discounting at 10 percent is to increase the C/E ratio by 11 percent above the base case. Hence, the relative cost-effectiveness of TAH implantation is not greatly affected by choice of discount rates.

Table E.8 compares the cost-effectiveness estimates generated here with those found for other heart disease treatments from previous studies. It is clear that the value of $105,000 per QALY for the TAH is considerably beyond the upper bound of what many would consider as generally acceptable for medical treatments and procedures. Heart transplantation projected at $32,000 per QALY in the future, however, would compare quite favorably with several of these other treatments.

COST-EFFECTIVENESS OF TAH RESEARCH AND DEVELOPMENT

Description of Scenarios

In addressing its mandate, the committee considered alternative NHLBI investment strategies and how they would affect the development of the device. These strategies are assumed to affect TAH development in terms of (1) the timing of the initial availability of a Food and Drug Administration-approved device and (2) the cost of the device to hospitals.

This poses the following trade-off. More front-end investment dollars (i.e., NHLBI project dollars) for R&D may make the device available sooner, but by definition at a higher development cost. More lives, and thus life years, would be saved as a result. Also, if more R&D dollars improve manufacturability, then the cost of the device when in routine use could be reduced for all patients.

In consultation with experts available to the committee, three alternative scenarios of this R&D investment decision were developed and are summarized in Table E.9. First, the base case (Scenario 1) assumes that *two* groups will receive *$2 million* of annual support throughout the preclinical testing period, and that *one* of the groups will produce a device approved to begin clinical trials by 1998. During the clinical trial period, from 1999 to 2003, one device will be under trial, and that research group will continue to receive $2 million in annual support. The ultimate cost of the device to hospitals is projected to be $100,000 (in 1991 dollars) for the first 6 years, dropping then to a cost of $78,500 for the next six years, and eventually to $70,000.

It is important to emphasize that this base case is assumed to be the "default" strategy. In other words, it is assumed that this is the minimum amount that NHLBI will invest in the TAH over this period. Thus, the two alternative scenarios represent increases in investment dollars above this minimum. These scenarios were developed based on IOM staff discussions with members of the TAH research teams involved in the development of these types of devices.

TABLE E.8 Summary of Cost-Effectiveness Ratios of Selected Heart Disease Treatments

Treatment	Cost per Life Year or Quality Adjusted Life Year Gained (in 1991 dollars)
Coronary Artery Bypass Graft Surgery	
Left main coronary artery disease	$6,900
3-vessel coronary artery disease	
Severe angina	14,400
Very mild angina, poor LV function	9,500
Very mild angina, good LV function	143,800
2-vessel coronary artery disease	
Severe angina	33,500
Very mild angina	89,900
I-vessel coronary artery disease	
Severe angina	57,400
Very mild angina	899,300
Beta-Blockade Post-Infarction	
High risk	4,400
Medium risk	7,200
Low risk	28,800
Intracoronary Streptokinase	
Inferior infarction	7,500
Anterior infarction	2,900
Coronary Care Units (vs. intermediate care)	
High risk	69,900
Low risk	294,400
Mobile Coronary Care Units	53,900
Percutaneous Transluminal Coronary Angioplasty	
Severe angina	6,900-12,700
Mild angina	47,200-102,400
Automatic Implantable Cardioverter Defibrillator (AICD)[a]	22,900
Electrophysiologic Testing[b]	32,400
Heart Transplantation[c]	32,000
Implantation of Total Artificial Heart[c]	105,000

[a] For treatment of recurrent life-threatening ventricular arrhythmia, relative to drug treatment.
[b] For treatment of symptomatic bifascicular block, relative to observation; cost updated from 1985.
[c] Relative to conventional medical therapy.
LV, Left ventricular.
SOURCES: For last two entries, this appendix; for percutaneous transluminal coronary angioplasty, Wong et al. (1990); for AICD, S. G. Pauker, personal communication, 1991; for electrophysiologic testing, Beck et al. (1987); for balance, M. C. Weinstein, personal communication, 1991 (all but last two updated from 1988 for inflation by a factor of 1.15).

TABLE E.9 Scenario Assumptions for Cost-Effectiveness Analysis of Impact of Increased Funding of TAH Development

	Scenario 1	Increased Funding	
	(base case)	Scenario 2	Scenario 3
Preclinical Testing			
Number of R&D groups	2	3	4
Amount per year per group	$2 million	$3 million	$4 million
Duration of testing (years)	5	4	3.75
Dates of testing	1/1/94-12/31/98	1/1/94-12/31/97	1/1/94-9/30/97
Clinical Trials			
Number of R&D groups	1	2	3
Amount per year per group	$2 million	$2 million	$2 million
Duration of trials (years)	5	5	5
Dates of trial (s)	1/1/99-12/31/03	1/1/98-12/31/02	10/1/97-9/30/02
Approved Device			
Earliest approval date	1/1/05	1/1/04	9/30/03
Device selling price	$100,000, first 6 yrs.; $78,500, second 6 yrs.; $70,000 thereafter	$78,500, first 6 yrs.; $70,000 thereafter	$70,000

NOTE: All amounts are in 1991 dollars.
TAH, total artificial heart; R&D, research and development.

Scenario 2 differs in that *three* groups receive *$3 million* each in annual funding during 1993-1997, with the result that the device will become available *12 months sooner* and at a *lower cost* to hospitals of $78,500 (dropping to $70,000 after six years). Also, *two* groups will have devices under clinical trials, and each group will receive $2 million in annual support from 1998 to 2002. Under Scenario 3, *four* groups each receives *$4 million* annually over this initial period, with the device becoming available *15 months* earlier than under Scenario 1. Also, *three* groups will have devices in clinical trials from late 1997 to late 2002. Each of these groups will receive $2 million in annual support. The device will cost hospitals $70,000.

Pursuing either alternative Scenario 2 or 3 has three major impacts with regard to costs and benefits. First, the cumulative R&D investment dollars under these two scenarios are greater. But this expenditure produces two benefits. The earlier availability of the device means that an additional 12 (or 15) months of TAH implantation will be carried out. This, in essence, produces a cohort of individuals (in approximately the year 2010) who would not have received the device otherwise. The second benefit, the reduction in device cost, will affect not only this 12-15 month cohort, but

also all patients who receive the device for the ensuing 12 years. The cost savings from this will more than offset the increased front-end R&D expenditures.

Based on the epidemiological analysis discussed in Chapter 4, the following analysis works with three alternative aggregate annual volume assumptions: 2,000; 10,000; and 20,000. For moribund patients, the lowest assumption is the most plausible, and it is considered to be the most likely at this time.

Results

Table E.10 shows the R&D costs under three alternative investment scenarios. Scenario 2 costs twice as much as Scenario 1, and Scenario 3 costs three times as much as Scenario 1. This more or less holds regardless of the discount rate. At a 3 percent discount rate, the additional cost of Scenario 2 is $22 million, and that of Scenario 3 is $50 million. As explained above, two different, essentially unrelated benefits may result-earlier availability and lower device cost.

TABLE E.10 Investment in Artificial Heart R&D: Cost Streams for Three Scenarios

	Scenario ($ millions)				Scenario ($ millions)		
Year	1	2	3		1	2	3
A. Stream of annual cost				**B. Net present value of total costs**			
1991	0	0	0	Discount rate			
1992	0	0	0	0%	30	56	90
1993	4.0	9.0	16.0	3%	24	26	74
1994	4.0	9.0	16.0	6%	21	40	65
1995	4.0	9.0	16.0	10%	20	39	63
1996	4.0	9.0	16.0	**C. Additional costs compared with Scenario 1**			
1997	4.0	9.0	13.5	Discount Rate			
1998	4.0	4.0	6.0	0%	—	26	60
1999	2.0	4.0	6.0	3%	—	22	50
2000	2.0	4.0	6.0	6%	—	19	44
2001	2.0	4.0	6.0	10%	—	19	43
2002	2.0	4.0	4.5				
2003	2.0	0	0				
2005 through 2010	0	0	0				
Total	$30	$56	$90				

R&D, research and development

Table E. 11 shows the additional life years saved under Scenarios 2 and 3. Again, this is due solely to the additional patients kept alive by the earlier availability of the device (1 year under Scenario 2 and 15 months under Scenario 3). Depending on the volume of patients and the discount rate, thousands of life years could be saved, even at the lowest volume. For example, at a 3 percent discount rate and 2,000 patients per year, 5,051 (Scenario 2) and 5,993 (Scenario 3) life years could be saved. Adjusting for quality of life, this corresponds to 3,250 QALYs under Scenario 2 and 4,087 QALYs under Scenario 3.

Table E. 12 shows the incremental cost-effectiveness of the additional R&D investment under Scenarios 2 and 3. In the base case, considering the R&D investment stream and the future reductions in device cost, the marginal cost per QALY is approximately $97,000, lower than the $105,000 under the treatment CEA because the TAH price does not remain a constant $100,000. The two alternative scenarios, although involving higher R&D costs, result in lower device costs for a time and in the device becoming available sooner.

TABLE E.11 Quality-Adjusted Life Years Saved Under Three Alternative Investment Scenarios

Year	Life Years Saved Under Scenario 1	2	3
A. Total quality-adjusted life years saved (Volume = 2,000; Discount Rate = 0%)			
2007	0	0	0
2008	0	0	1,425
2009	0	5,700	5,700
2010	5,700	5,700	5,700
2011 through 2038 (ea.yr.)	5,700	5,700	5,700
2039	5,700	5,700	5,700
Total	171,000	176,700	178,125

	Life Years Saved Under Scenario 1	2	3
B. Present value of quality-adjusted life years saved (Volume = 2,000)			
At discount rate			
0%	171,000	176,700	178,125
3%	63,714	66,964	67,801
6%	25,932	27,816	28,315
10%	8,786	9,778	9,974
C. Present value of additional quality-adjusted life years relative to Scenario 1 (Discount rate = 3%)			
At annual volume			
2,000	—	3,250	4,087
10,000	—	16,250	20,435
20,000	—	32,500	40,870

TABLE E.12 Cost-Effectiveness of Alternative R&D Scenarios

	Scenario 1	Increased Funding	
	(base case)	Scenario 2	Scenario 3
Assumptions			
Date of first implant	1/1/10	1/1/09	10/1/08
Device selling price			
First 6 years	$100,000	$ 78,500	$ 70,000
Second 6 years	$ 78,500	$ 70,000	$ 70,000
Thereafter	$ 70,000	$ 70,000	$ 70,000
Net treatment cost per patient (discounted as of date of first implant)	$299,100[a]	$273,400[b]	$263,200
Results			
Total costs (millions)	$6,155	$6,287	6,335
Total QALYs gained	63,714	66,964	67,801
Marginal cost per QALY of TAH in clinical use (all annual cohorts) [c]	$97,000	$94,000	$93,000
Incremental R&D cost-effectiveness, compared with Scenario I (per QALY)	NA	$41,000	$44,000

NOTES: Assumptions applicable to all scenarios: 2,000 patients per year; R&D investment during 1994-2003; 3 percent discount rate; 2.85 net QALYs gained per TAH recipient; total costs and total QALYs are discounted to 1991; horizon is 2039 for all three scenarios.

[a] Will decrease in 2015 and again in 2021 with reductions in device cost to $78,500 and $70,000.

[b] Will decrease in 2015 with reduction in device cost to $70,000.

[c] Cost per QALY of TAH use compared with medical treatment only. R&D, research and development; QALY, quality-adjusted life year; TAH, total artificial heart; NA, not applicable.

For example, under Scenario 3, the additional discounted R&D costs are $50 million (Table E.10, section C). Putting aside the earlier availability of the device, the cost savings from the price reduction alone are about $230 million. Thus, on those grounds alone, this marginal investment would be desirable *if* the result were certain (which it is not) and *if* the cost per QALY for the TAH in clinical practice, compared with medical treatment, were acceptable (which it may not be).

Having the device available sooner increases the total costs (due to the treatment costs per patient) as well as total discounted life years saved, compared to Scenario 1. In considering the marginal impact under Scenario 3, for example, the net cost savings of approximately $180 million ($230 million - $50 million) effectively offset a portion of the additional dis

counted treatment costs for the 2,500 recipients (in the 15 months). Thus, the incremental cost of obtaining the additional 4,087 QALYs is about $44,000, far below the cost per QALY of TAHs implanted in 2010 and thereafter. Similarly, under Scenario 2, the incremental cost per QALY is approximately $41,000.

TABLE E.13 Sensitivity Analyses: Cost-Effectiveness of Alternative R&D Outcomes

Device Parameters		Cost-Effectiveness Implications			
Cost ($000s)	Year Available	Total Costs ($ millions)	Total QALYs	Marginal Cost per QALY for All Annual Cohorts[a] ($000s)	Incremental R&D Cost-Effectiveness[b] ($000s per QALY)
Base case					
$100[c]	2010	$6,155	63,714	$97	NA
Alternative outcomes[d]					
$78.5	2009	$6,287	66,964	$94	$41
$78.5	2008	$6,597	70,312	$94	$67
$78.5	2007	$6,917	73,761	$94	$76
$70	2009	$6,258	66,964	$93	$32
$70	2008	$6,567	60,312	$93	$62
$70	2007	$6,886	73,761	$93	$73
$50[e]	2009	$5,694	66,964	$85	*f*
$50	2008	$5,975	70,312	$85	$13
$50	2007	$6,264	73,761	$85	$37

NOTE: Same assumptions as for Table E.12: 2,000 cases per year; base case time frame, 2010-2039; all costs and QALYs discounted at 3 percent; horizon 2039 for all three scenarios.

[a]Cost per QALY of TAH use compared with medical treatment only.

[b]Compared with Scenario 1 (base case).

[c]As in Table E.12, cost declines to $78,500 in 2016 and $70,000 in 2022 (total cost differs from the original base case, in which the $100,000 device cost did not decline).

[d]Alternative outcomes with device cost at $78,500 assume investment Scenario 2; those with device cost at $70,000 or $50,000 assume investment Scenario 3.

[e]Alternative outcomes with $50,000 device cost are compared with base case with device cost of $50,000; total cost is $5.780 billion.

[f]Cost reducing in toto.

R&D, research and development; QALY, quality-adjusted life year; NA, not applicable.

Sensitivity Analyses

Clearly, if the cost savings from Scenarios 2 and 3 were certain to be realized and if the TAH were, in 2010 and beyond, to be an acceptable use of resources, then either of those two scenarios would be preferred to Scenario 1 (which of course is not to say that any of the three should be undertaken). The additional savings in terms of life years would further strengthen the case. However, the committee understandably expressed considerable uncertainty about the likelihood of these scenarios. Hence, sensitivity analysis was undertaken to judge the potential impact of this uncertainty.

Table E.13 summarizes the sensitivity of the incremental C/E results to changes in assumptions about device cost savings and availability. One result is noteworthy: earlier availability alone tends to increase marginal cost per QALY as the aggregate (more or less constant) cost savings are subtracted from a larger sum of incremental operating costs.

Given the uncertainties involved, it is entirely possible that one could pursue investment Scenario 2 or 3 but obtain the result of Scenario 1 (i.e., device cost of $100,000 and availability in 2010). Nonetheless, spreading the additional R&D costs (of Scenario 2 or 3) over a discounted base of 62,375 QALYs (under Scenario 1) would have a small impact (an increase of less than $1,000) on the base case cost per QALY of $97,000. Of course, this assumes that Scenario 1 is the worst case outcome, which it may not be. It is certainly possible that the device could cost more, have worse outcomes, or not be available by 2010.

CONCLUSION: MAJOR FINDINGS AND LIMITATIONS

The approach taken here is unusual in several respects. First, costeffectiveness analyses typically rely to a much greater extent on the existing clinical literature. Of course, this could not be done since the TAH is a technology under consideration for the future and does yet exist. Second, cost-effectiveness analysis has rarely been used to frame long-run public R&D investment decisions in the health sector. At the very least, this attempt illustrates some of the difficulties and long-run trade-offs that are involved in such questions.

The key finding was that, as experts currently conceive of the technology, the total artificial heart is likely to be more expensive than technologies currently in use. At approximately $100,000 per QALY gained, its C/E ratio is substantially less favorable than the C/E ratios for heart transplantation and renal dialysis and, therefore, many would currently regard it as questionable or borderline on a cost-effectiveness basis. The experts' vision of the TAH describes a technology that could in the future provide

clinical benefits that many patients would like to have available. However, the experts forecast outcomes much less favorable than what they see as the future of heart transplantation.

TABLE E.14 Utilization and Cost Estimates for Developing Costs for Each State

Cost Category	ALOS (days)	In ICU
TAH recipients		
Evaluation (4 candidates per recipient)	4	90%
Initial implantation		
Preoperative stay	2	80%
Those who die or have complication	35	50%
Discharged with no complications	22	40%
Hard device failure		
Those dying in hospital	6	100%
Successful replacement	25	50%
Successful repair	21	50%
Soft device failure		
Those dying in hospital	10	100%
Successful replacement	20	30%
Successful repair	15	30%
Complications		
Infection	18	10%
Thromboembolism	15	10%
Bleeding	25	20%
Psychological	20	0%
Other noncardiac	20	30%
Transplant recipients		
Evaluation (5 candidates per recipient)	3	30%
Initial transplant		
Preoperative stay	3	30%
Those who die or have complication	40	25%
Discharged with no complications	17	20%
Rejection	12	5%
Conventional medical therapy		
Establish drug regimen	20	30%

ALOS, average length of stay; ICU, intensive care unit or coronary care unit; TAH, total artificial heart.

The long-run R&D investment decision is also difficult given the uncertainties associated with the outcomes. On the one hand, for only an additional $20 to $50 million over the next 15 years, we might be able to save hundreds of millions of dollars in device costs and thousands of life years. On the other hand, even with these gains, the TAH's cost per quality-adjusted life year gained is still likely to be on the order of between $80,000 and $100,000. Despite considerable uncertainties, as a marginal decision, the two alternative R&D scenarios do not appear to be particularly risky or costly. However, since they also have only a minimal impact on the over-all cost per QALY, they do not make the overall decision concerning the desir

ability of investing in TAH development any easier. As suggested above, it is entirely possible that the device could cost more, have worse outcomes, or become available later than is assumed under the base case scenario.

TABLE E.15 Fee and Follow-up Cost Estimates for Developing Costs for Each State

Cost Category	Fee	Cost Category	Fee
TAH recipients		Transplant recipients	
Physician fees		Physician fees	
Initial implantation	$15,000	Initial transplant	$15,000
Hard device failure	$3,000	Complication	$35 per day
Soft device failure	$2,000	Routine follow-up (total)	$3,000
Complication	$35 per day		
Routine follow-up (total)	$2,000		
		Annual routine follow-up costs	
Annual routine follow-up costs		All hospital care	$8,000
All hospital care	$3,000	Drugs	$7,000
Drugs	$1,000		
Device-related (e.g., batteries)	$4,000	**Conventional medical therapy**	
		Total physician fees	$2,000
		Out-of-hospital emergency and physician care (for 50% of patients)	$1,000

TAH, total artificial heart.

Several limitations of this analysis should be reemphasized. Neither the clinical or cost parameters were developed from meta-analysis or other syntheses of the literature. Only a small number of exceptionally knowledgeable experts were consulted, and there was a substantial spread in many of their estimates. Also, although computationally complex, the models, especially for heart transplantation and conventional therapy, are crude approximations of what *could* be developed from current literature, given more resources and time. The cost parameters attempted to measure economic costs to society, but given the lack of accurate information on something as basic as the cost of a day in an intensive care unit, the cost estimates should also be considered approximations.

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Glossary

Allograft	Transplantation of an organ between members of the same species. Also called homograft.
Appropriateness of care	An aspect of quality care that emphasizes "using what works."
Artificial heart	A generic term referring to a device (or equipment, or system of these) designed to support or replace the pumping function of the heart or one of its ventricles. Depending on the context of the usage, the term can include one or more of these: total artificial heart, left ventricular assist device, and right ventricular assist device. The terms "artificial heart" and "mechanical circulatory support system" have frequently been used interchangeably in the literature but not in this report. This report uses the term "artificial heart" either as a generic, descriptive modifier, namely the NHLBI artificial heart program, or as a specific device, namely the total artificial heart.
Base case	In a cost-effectiveness analysis, the assumptions that represent the best estimates of all probabilities and costs.
Bench testing	Testing of a device against specifications in a simulated environment that does not include the living body of a human or animal. Also known as in vitro device readiness testing.
Bioengineering research	The application of engineering knowledge and concepts to the understanding of the human body and its interactions with machines, and to the development of new and improved medical devices.

Biventricular support	The use of either a total artificial heart or two ventricular assist devices to support or replace the function of both the right and the left ventricles.
Clinical practice guidelines	Systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.
Congestive heart failure (CHF)	Heart failure in which the heart is unable to maintain adequate circulation of blood in the tissues of the body or to pump out the venous blood returned to it by the venous circulation.
Coronary heart disease (CHD)	A condition that reduces the blood flow through the coronary arteries to the heart muscle. Also called coronary artery disease or coronary disease.
Cost-benefit analysis (CBA)	An analytical technique that compares the costs of a project or technological application to the resultant benefits, with both costs and benefits expressed by the same measure. This measure is nearly always monetary.
Cost-effectiveness analysis (CEA)	An analytical technique that compares the costs of alternative projects to the resultant benefits, with costs and benefits or effectiveness expressed by different measures. Costs are usually expressed in dollars, but benefits or effectiveness are ordinarily expressed in terms such as "lives saved," "disability avoided," "quality-adjusted life years gained," or any other relevant objectives.
Diffusion	The spread of a technological innovation over time.
Fully implanted mechanical circulatory support device	A mechanical circulatory support system in which all components are implanted so the patient can be free of all external apparatus and can continue normal activities for at least short periods of time. In some systems, the patient would wear a battery pack; others are powered by an implanted energy source that is charged periodically, e.g., several times a day.
Hard device failure	A term used to describe an occurrence or health state created from a mechanical failure of a circulatory support device that results in high risk of immediate death.
Health-related quality of life	The value assigned to duration of life as modified by the key facets of life such as impairments, functional states, and social opportunities that are influenced by health factors such as disease, injury, treatment, or health policy.
Health state utility	An index indicating the value attributed to a specific health state. The value reflects the overall "quality" of life associated with a health state from the perspective of the individual assigning preferences. Health state utilities are commonly used in cost-effectiveness analysis.

Heart failure	A condition in which the heart is unable to pump blood at an adequate rate or in adequate volume.
Heterotopic graft	Transplantation of a donor organ without removing the patient's organ. Also called piggybacked transplant.
Incidence	The rate of occurrence of new cases of a particular disease in a population.
In vitro bench testing	See Bench testing.
In vivo testing	Testing in the living body of a plant or animal.
Left ventricular assist device (LVAD)	A device that supports or replaces the function of the left ventricle by pumping blood from the left heart to the aorta. The patient's heart remains in place when this device or system is used.
Long-term device	A mechanical circulatory support system that is employed with the anticipation that it will function for years.
Manufacturability	A technology design, characteristic, or process that allows fabrication in quantity, achieving a balance between low cost and high quality for the purpose of maximizing production efficiency. Also called value engineering.
Mechanical circulatory support system (MCSS)	A generic term referring to a device used to supplement or take over the pumping function of the heart or one of its ventricles. The terms "artificial heart" and "mechanical circulatory support system" are frequently used interchangeably in the literature but not in this report. This term includes total artificial hearts and both types of ventricular assist devices.
Opportunity cost	The cost included in the CBA or CEA of an expenditure (such as the research and development cost of the artificial heart program) because resources directed to the expenditure are no longer available ("a lost opportunity") for alternate uses.
Orthotopic graft	Transplantation with the donor organ placed at the site of the organ that was removed.
Practice guidelines	See Clinical practice guidelines.
Prevalence	The number of persons in a population that are affected with a particular disease at a given time.
Quality-adjusted life years (QALYs)	A concept that provides a single combined measure of gains in both the quantity and quality of life. QALYs are used with cost-effectiveness analyses of health technologies, frequently derive their weights from utilities assessment, and are expressed as a ratio in terms of cost per QALY gained.
Quality of care	The degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge.

Right ventricular assist device (RVAD)	A device that supports or replaces the function of the right ventricle by pumping blood from the right heart to the pulmonary artery. The patient's heart remains in place when this device or system is used.
Short-term or temporary device	A mechanical circulatory support system that is employed for a relatively short period of time in anticipation of either recovery of function by the patient's natural heart or a second intervention such as cardiac transplantation that would permit removal of the device. An often-used definition is an implantation intended to be less than 180 days. A short-term device used in connection with transplantation may be referred to as a "bridge" to the subsequent procedure.
Soft device failure	A term used to describe an occurrence or health state created from a mechanical failure of a circulatory support device that results in a non-life-threatening condition.
Spin-off technologies	The development or application of technologies (or subcomponents) for a use other than the initially intended use. Also called spillover or fallout technologies.
Technological diffusion	The process by which the use of a technological innovation in a given social system spreads over a period of time.
Technological innovation	The process of creating or inventing any technology which is new for a given sector of society, organization, or user.
Tethered device	A mechanical circulatory support system that is constantly connected to external control or energizing systems by wires or tubes leading from the implanted device through the skin to the external component. By requiring continuous connection, all such devices tether the patient to the external component.
Thromboembolism	The blocking of a blood vessel by a particle that has broken away from a blood clot at its site of formation.
Total artificial heart (TAH)	A device that replaces the heart and its function. The patient's heart is removed when such a device is used.
Ventricular assist device (VAD)	A device that supports or replaces the function of a ventricle. LVAD and RVAD indicate which ventricle is supported or replaced.
Xenograft	Transplantation of an organ between members of different species (i.e., animal to human). Also called heterograft.

Index