Informing Judgment:

Case Studies of Health Policy and Research in Six Countries

September 2001

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FOREWORD

The authors of the case studies in this report describe and assess collaborative efforts using evidence from research to guide policymaking for health care. Each case study is itself collaborative. Researchers and public-sector policymakers are co-authors of three cases (Australia, British Columbia, Norway); executives of pharmaceutical firms joined in writing two cases (South Africa, United Kingdom); one case is the work of a policymaker and researchers at a large nonprofit health care organization in the United States (Kaiser Permanente); and in one instance public officials helped to prepare the case but declined co-authorship (South Africa).

At an editorial meeting in October 2000 the authors agreed on one overriding generalization about collaboration to use research in policymaking: *The proper purpose of collaboration between researchers and policymakers is to use evidence from research to inform judgments for which policymakers are accountable.* The Introduction describes the implications of this generalization for researchers and policymakers, implications that are practical and often painful. For example, setbacks in implementing policies described in the case studies have occurred in four of the six countries since the authors met.

Andrew D. Oxman, then Chair of the Cochrane Collaboration Steering Group, and Daniel M. Fox, President of the Milbank Memorial Fund, organized the project that led to this report. The Cochrane Collaboration is a nonprofit international organization, founded in 1993, that aims to help people make well-informed decisions about health care by preparing, maintaining, and promoting the accessibility of systematic reviews of the effects of health care interventions. The Milbank Memorial Fund is an endowed foundation, founded in 1905, that works with decision makers and researchers on significant issues in health policy. The Fund participated in some of the activities that led to the creation of the Cochrane Collaboration and has helped to bring systematic reviews to the attention of the people responsible for health care policy, particularly in the United States.

We thank Andy Oxman and the authors for persisting in this project despite the distraction of their other obligations. We also thank two staff members of the Fund who have considerable experience in research and policymaking for reviewing the next-to-final drafts of the Introduction and the cases: Paul Cleary, Editorial Director and Professor of Health Care Policy at Harvard Medical School; and John Colmers, Program Officer and former Executive Director of the Maryland Health Care Commission.

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INTRODUCTION: LESSONS FROM SIX CASE STUDIES

Daniel M. Fox and Andrew D. Oxman

Three Types of Politics

Each of these cases is a story about three types of politics in a particular country. First, each case is about the politics of research; that is, the judgments of and relationships among the health care scientists who plan, conduct, assess, synthesize, and communicate findings based on evidence. Second, each is about the politics of health policy: who does what to, for, and with whom in particular jurisdictions in order to decide what clinical interventions will be considered appropriate and, hence, paid for. Finally, each is about the politics of collaboration between researchers and policymakers: how the evidence and findings produced by the former informs the judgments of the latter.

The context and content of each case is different. For example, some of them describe long-standing, relatively well-financed collaboration between researchers and policymakers. Other collaborations began more recently. Despite these and other differences, the authors of the case studies reported here found that there were many similarities in their experiences and much to learn from one another. At least for those involved in preparing these studies, the stories that were told resonated across widely divergent political environments.

The authors are also the actors in each case; researchers and policymakers describe and assess work they did together. Each author has strong feelings about what was proper and prudent in every incident described in a case. Moreover, the researchers and policymakers often have well-informed opinions about one another's work. Policymakers often know a great deal about the theory and methods of research disciplines. Similarly, researchers frequently have opinions about policies chosen and alternatives that were rejected.

Informing Judgment: The Overriding Lesson

The foreword to the report tells the story of the project that yielded these cases. The note on the authors identifies the authors. The authors of each case acknowledge persons who materially assisted them in their work, including several who, for good reasons, chose to remain anonymous. We report below the results of an intense meeting at which the authors criticized and clarified one another's work and tested generalizations that seemed applicable to all or at least most of the cases.

The discussion of the six cases led to an overriding generalization: *The proper purpose of collaboration between researchers and policymakers is to use evidence from research to inform judgments for which policymakers are accountable.*

This generalization has three implications for people in every country who do or aspire to do research that informs policy, to translate research so that it is most useful to policymakers, as well as to make policy that is grounded in the best available evidence.

The first implication is that policymakers alone are accountable for decisions about policy. The persons to whom they are accountable include more senior officials, voters, and the media. They are also accountable to their own sense of right and wrong. Policymakers, moreover, make judgments using a variety of information, of which scientific evidence is just one type. This other information includes evidence, for example, about financial feasibility and voters' preferences, as well as information about things such as political culture, interest groups, advocates and opinion makers, and the media. It is important that policymakers and researchers have a common appreciation of these different types of evidence and the role each plays in informing judgments about health policies.

The second implication is that researchers are accountable in different ways than policymakers. Researchers are accountable both to their scientific colleagues and to their policymaking collaborators. They are accountable for providing the best available evidence they derive from the theory and methods they use in their work.

Third, researchers can help inform the judgments of policymakers. Researchers and policymakers can sustain a mutually productive relationship if they are explicit about how each of them will carry out their distinct roles. Most important, it is useful to regulate the process by formal and informal contracts. These contracts should, for instance, describe mutually agreed-upon rules about such matters as confidentiality, communication, and the practice of collegiality. As one policymaker put it, "The clearer the rules the better." Decision-making processes should be transparent to others, as well as those involved in them. At the same time, the policymakers and researchers agreed that it is frequently important to have "windows of opportunity" during which they can reflect candidly without risking premature public disclosures.

Other Significant Lessons

The researchers and policymakers who wrote the cases agreed on other generalizations that elaborate on the overriding lesson that the purpose of their collaboration is to inform policymakers' judgment.

- Because both research and policymaking are complex activities and very different from each other, mutual understanding requires conscious effort. Thus, to inform policymaking more effectively, researchers need better systematic understanding of political culture. They need to know more, that is, about the range of interests, perceptions, and priorities to which policymakers respond. As one researcher said, "The route from research to policy is not linear." Another added, "There is no such thing as bias-free people." A policymaker declared that researchers should not complain about being involved in political controversies: "Political noise, especially from interest groups and advocates, is often what motivates policymakers to ask researchers to help them."
- Policymakers can help achieve mutual understanding by respecting researchers' knowledge, competence, and needs. As one policymaker said, "The process has to deliver for researchers, as well as policymakers, to maintain their commitment." Similarly, policymakers and researchers must learn to accommodate differences in the time frames within which they operate. A researcher noted that "in the process of working together to inform one policy decision, researchers may gain insight into other research that could be influential and learn how best to link research to policy."
- Collaboration builds on good experiences for both researchers and policymakers. To achieve good experiences, a policymaker said, the "rules of engagement must include appropriate expectations and appropriate definitions of success."
- Effective collaboration between researchers and policymakers is likely to be enhanced if both groups continue to work together after the policymaking process to evaluate the results of implementing the policy. Experience matters in policymaking. The experience of collaboration in developing policy is valuable in assessing and then improving it. The authors of the cases, for example, agreed that they had benefited from working together to evaluate and generalize about their work, even though the experience of any country or organization cannot be transferred without translation.
- Trust between individuals is built up over years. The process of making health policy should create and maintain opportunities for long-term collaboration between policymakers and researchers when this is possible.
- Beyond using research to inform decisions about implementation and appraise the effects of specific policies, there is a need for more rigorous evaluation of hypotheses about ways in which health policymaking processes might be improved.

Arraying the Cases: The Table of Contents

We arrayed the cases according to the length and strength of the collaborations they describe. The cases from Australia and British Columbia discuss longstanding relationships between researchers and policymakers. The United States case is about Kaiser Permanente, an integrated health system serving nine million people in which policy and research have been linked for many years by formal relationships and institutional culture. The cases from Norway and the United Kingdom describe relatively new relationships and institutional arrangements. The South African case documents the extraordinary difficulty of using research to inform policy in a poorer country.

What This Project Hopes to Achieve

All six cases are rich descriptions and analyses of the complexity of the ways research informs policy. All six demonstrate that collaboration between policymakers and researchers is about context—about history, culture, beliefs, and interests—as well as about interpreting and applying evidence. At the same time, because health policymakers confront similar decisions internationally—for example, about what health technologies to fund—a great deal can be gained by sharing reviews of evidence across contexts, while making judgments within specific contexts and taking into account other evidence that is context specific. The Cochrane Collaboration is an example of the potential for international collaboration of this kind.

As one of the authors said, "we should celebrate success and share good examples." Many more cases can be written and read with profit by researchers and policymakers. The Milbank Memorial Fund would be pleased to commission and publish additional cases about the collaboration of researchers and health policymakers and, when appropriate, to convene their authors across national boundaries. Interested persons may contact either of us for information about the criteria for commissioning cases and the process for reviewing and accepting them for publication. We would also be interested in building upon the experience reported here through developing and supporting an international network with the aim of promoting the exchange of information about ways success might be achieved, and mistakes avoided, in promoting the use of evidence from research to inform judgments for which policymakers are accountable.

Subsequent Events

Another reason for exchanging information is that the politics of policymaking are volatile. As the authors and editors prepared these cases for publication, significant events occurred in several countries. In Australia and the United Kingdom, there were indications that progress in the use of evidence to guide policy on prescription drugs had, for the moment, been reversed. In Canada and Norway, prospects for continuing some of the work reported in the case studies appeared to diminish. In contrast, changes in South African policy on treatment to reduce transmission of HIV from mothers to their babies suggested that research findings had been more influential than the authors had concluded in

their earlier drafts. The authors of several cases added information about these events. Events in Australia were so dramatic, however, that we commissioned a journalist to describe them. To emphasize that it does not necessarily represent the views of the authors of the case, this account is a separate chapter of the report.

Recent events and comments by some of the authors raise some questions about these cases and what we can learn from them. First, there was undoubtedly some degree of self-censorship in all of the case reports. This is not surprising given that the authors were deeply involved in each case. However, it may be that the case reports paint a picture that is overly optimistic.

Second, recent events in Australia and British Columbia suggest that even institutionalized decision-making processes that are established by legislation can be threatened, and potentially dismantled, by groups with vested interests or by changes in government. This can occur despite a great deal of public scrutiny, as may be happening in Australia, or quietly, as may be happening in British Columbia, where the Reference Drug Program's Expert Advisory Committee, which meets at the calling of the director of Pharmacare, has faded almost unnoticed into nonuse, at least for the time being.

Third, it is easier to say yes than no. This is illustrated by the decision of the National Institute for Clinical Excellence (NICE) in the UK to reverse its guidance regarding zanamivir for treating flu. Likewise, when NICE decided against beta interferon for multiple sclerosis, it quickly found itself facing hostile publicity and an appeal from patients' groups and specialists, as well as the manufacturers. Similar reactions occurred in Norway in response to advice not to include montelukast for asthma on the list of drugs covered by the National Insurance Administration. Pharmaceutical manufacturers have more resources than patients or physicians to promote their interests, but they are not the only group with a stake in drug policies. Moreover, the pharmaceutical industry will often ally itself with physician and patient organizations to further its interests, as has occurred in most of the cases reported here. When these interests are consistent with the public's, this is not a problem. However, there is often a conflict between the commercial interests of the pharmaceutical industry and the interests of those who fund and benefit from health services.

Fourth, senior policymakers are rarely in place for prolonged periods of time. As a corollary to the Peter Principle (that in a hierarchically structured administration, people tend to be promoted up to their "level of incompetence"), policymakers who are good and strive actively to promote better decision making, including better use of research evidence, are more likely to move on sooner rather than later. "Policymakers" in this context includes both senior civil servants and elected officials. In addition, elections, the propensity to frequently reorganize government, and the natural tendency of public officials to protect their turf all add to the challenge of establishing and maintaining long-term collaboration between policymakers and researchers. Researchers, of course, also frequently move on.

Despite these constraints and setbacks in four of the six cases, we choose to remain optimistic. The path toward improving the use of research evidence to inform policymakers' judgments is not straightforward and the lessons learned from these six cases do not offer any simple solutions. They are, nonetheless, valuable lessons, and the six cases offer insights, inspiration, and an opportunity to "celebrate success," even if those successes do not last forever. The final lesson that can be drawn from these cases and more recent events is that both policymakers and researchers must continue struggling to help ensure that judgments about health policies are well informed by research evidence. The alternative is to acquiesce to poorly informed health policies.

The Use of Evidence in Drug Selection: The Australian Pharmaceutical Benefits Scheme

Suzanne Hill, David Henry, and Alan Stevens

EXECUTIVE SUMMARY

The Pharmaceutical Benefits Scheme is the national drug subsidization/reimbursement plan in Australia. It ensures that the population has access to important products in the community and is the system by which prices of prescription products are set. Effectively, if a licensed prescription drug is not in the plan, it will have a very small market in Australia.

Since 1992, the selection of drugs for inclusion on the PBS has been based on the use of comparative cost-effectiveness analyses. This approach has required the explicit use of clinical and economic evidence in decision making about drug subsidization and has also required ongoing collaboration between academics and policymakers. Over the past eight years, the policy has been extensively reviewed, challenged, and kept under scrutiny, but despite these factors it has remained in operation. The system is now seen as a model for other countries seeking to develop mechanisms for making rational choices about drug subsidization. The focus of this case study is the selection process. The study summarizes the history of the program and some of the reviews that have taken place, and explores some of

the reasons for the strength of the system and the utility of the approach.

Barriers

Collaboration

- Limited technical capacity in health economics in both government staff and academia at the start of the evolution of the process in 1991; not necessarily a barrier, but delayed development of the process
- The need to identify groups in academia that did not have conflicts of interest in relation to pharmaceutical/drug companies, and who were therefore able to carry out the technical work need to ensure the system was effective
- The need to provide sufficient financial incentives to enable academic groups to work with government rather than with industry

Use of Research Evidence in Policymaking

- Especially at the beginning of the system's implementation, the lack of appropriate evidence (particularly in terms of costs) to support cost-effectiveness analyses of new pharmaceuticals
- Initially, lack of expertise in assessing evidence, and uncertainty about methods for applying it to relevant populations
- The insistence on confidentiality of evidence

Facilitators

- A legislative framework that provided the basis for the committee to make its recommendations to the minister for health and was explicit regarding the criteria to be used to make the decisions
- Development and dissemination of guidelines for the submission of applications, based on evidence
- In the early stages (1991–1995), cooperation between stakeholders (government and industry) in guideline development
- Commitment to developing technical capacity in academia and government to support the decision-making process
- Explicit and consistent processes for decision making
- Efficient administrative structure to support processes required for implementing policy
- Inclusion of experts (i.e., clinicians and academics) on the expert advisory committee and appropriate technical committees
- Personal relationships between policymakers and academics

Lessons Learned

- Bipartisan political commitment is essential, manifested by strong legislation.
- A robust and defensible process is also essential.
- There is inevitably a degree of adversity in relation to economic (buying/selling) decisions; any system should be able to withstand this and use it to its advantage.
- Freedom from conflicts of interest by those involved in the decision-making process must be real and perceived to be so.

INTRODUCTION

Australia is a developed country with a population of approximately 19 million people. As a market for pharmaceuticals, the Australian population represents approximately 1 percent of the total world market, although strategically many multinational pharmaceutical manufacturers see it as a gateway to the Southeast Asian market because it has a competent drug regulatory authority.

Politically, Australia is a federation of eight states and territories. The government is a parliamentary multiparty democracy, based on the Westminster model. Each of the states has a state or territorial government. In broad terms, the federal government is responsible for community services, whereas state governments are generally responsible for state issues including infrastructures such as public hospitals, roads, and primary and secondary education. The political environment is basically extremely stable. The main political parties are the conservatives (Liberal/National) currently in government and the socialists (Labor).

The Health Care System

Australia has a comprehensive social security system, including universal health insurance. The provision of health care is a joint state/federal responsibility. In general terms, the Commonwealth is responsible for health care services provided in the community, and states are responsible for services provided by hospitals; increasingly, these boundaries are becoming blurred. The states are provided with block grants for health by the Commonwealth and then have discretion to spend these according to individual state needs and policies. Australia has a comprehensive public health insurance system and a high standard of public health care. The public sector provides care for most of the population, with 30–45 percent of the population electing to purchase private health insurance in addition to the public insurance.

The private hospital sector tends to provide mostly elective surgery, but other services covered by the private insurance industry include allied health care services and, increasingly, alternative and complementary health care services such as naturopathy.

The National Health Act (1953) provides part of the legislative framework for the national health insurance program, which was introduced in 1983. The program is known as Medicare and provides for reimbursement to the patient for health care professional fees, investigations, and procedures (e.g., surgical operations) that are listed on the Medicare Benefits Schedule (MBS). Items are included on the MBS following approval by the Commonwealth minister for health, after review of applications and expert advice from an independent advisory committee and consultation with the profession.

The state and Commonwealth governments develop an annual agreement about what will be covered by Medicare (and therefore paid for by the Commonwealth), and what will be covered by the states under their block grants. Needless to say, in the current environment of resource constraints and economic rationalism, the annual agreement can be very difficult to negotiate. However, there is generally a trend toward supplying services in the community rather than in hospitals or health care institutions.

Community access to pharmaceuticals (because of subsidization/reimbursement) is ensured by the Pharmaceutical Benefits Scheme (PBS), which also operates under the National Health Act. This program provides access to drugs in the community as well as access to some drugs provided by hospitals. This will be described in more detail below.

The Pharmaceutical Sector

The pharmaceutical industry in Australia consists of subsidiaries of multinational companies, generic manufacturers, and recently, a very small number of local companies that are developing new chemical entities. There is an increasing export industry in pharmaceuticals, primarily to the expanding Southeast Asian market. The pharmaceutical sector and associated professionals are extensively regulated in Australia, primarily as a result of the universal health insurance and pharmaceutical benefits programs.

Wholesale and retail supply of medicinal products is overseen by a national drug regulatory authority, the Therapeutic Goods Administration (TGA), under the powers of the Therapeutic Goods Act.

The state and territory governments are responsible for the professional and commercial practice of pharmacy, while the Commonwealth government has a regulatory interest through the National Health Act in the administration of the PBS. The number and location of pharmacies that may supply pharmaceutical benefits in Australia are controlled by the Commonwealth by an independent statutory authority, the Australian Community Pharmacy Authority. This was established under section 99J of the National Health Act in 1995. The remuneration paid to pharmacists for dispensing pharmaceutical benefits is also controlled by the Pharmaceutical Benefits Remuneration Tribunal, established in 1981 under section 98A of the National Health Act.

There is tight regulation of who can sell which types of pharmaceuticals. All chemical products are classified according to a Drugs and Poisons Schedule, and sale is restricted according to the classification. The classification of new chemical entities occurs at the time of registration/licensing. In general, prescription drugs are classified as Schedule 4 or Schedule 8 (drugs of potential dependence), and over-the-counter products are unscheduled or classified as Schedule 2 or 3. Schedule 3 products may be sold only at pharmacies, and it is required that a pharmacist supply them. Schedule 2 products may be sold only at pharmacies, but no pharmacist supply is required. Unscheduled products may be sold by supermarkets and require no professional input into their sale.[1]

The schedule status of a substance also determines how it can be advertised: Schedule 4 products may not be advertised directly to the public, although consideration is being given to industry requests to change this and allow direct-to-consumer advertising. There have been recent changes to the Therapeutic Goods Act and regulations that permit limited advertising of Schedule 2 and 3 products directly to the public.

The Pharmaceutical Benefits Scheme is the national drug subsidization/reimbursement plan. It is the system by which prices of prescription products are set, and it provides access to pharmaceuticals for the Australian public in the community. Effectively, if a licensed prescription drug is not on the plan, it will, in the great majority of cases, have a relatively small market. The private market for prescription drugs is estimated to be approximately 6 percent of the total market in Australia (Drug Utilization Subcommittee 1998). However, recent changes have seen a number of pharmacists enter into agreements with specific companies to dispense certain items at lower markups, and this is resulting in a growth in the private prescription market.

The PBS: General Description

Currently (as of February 2001), the PBS covers approximately 650 drugs, available in approximately 1,500 forms and strengths (items) and marketed as approximately 2,000 different drug products (brands). Different levels of usage restriction apply to these products. The list of benefits is comprehensive and covers drugs that are (1) prescribed by a registered medical practitioner or, for some drugs, by a registered dental practitioner, and (2) dispensed by an approved pharmacist. Drugs that are included in the plan are listed in the Schedule of Pharmaceutical Benefits, published

quarterly.

The Government reduces the cost of pharmaceutical benefits to patients by

1. Negotiating an agreed wholesale price with the supplier of a product;
2. Remunerating dispensers an amount determined by the independent Pharmaceutical Benefits Remuneration Tribunal (much lower than private dispensing rates);
3. Subsidizing the cost of the product to patients above a specified prescription charge or co-payment.

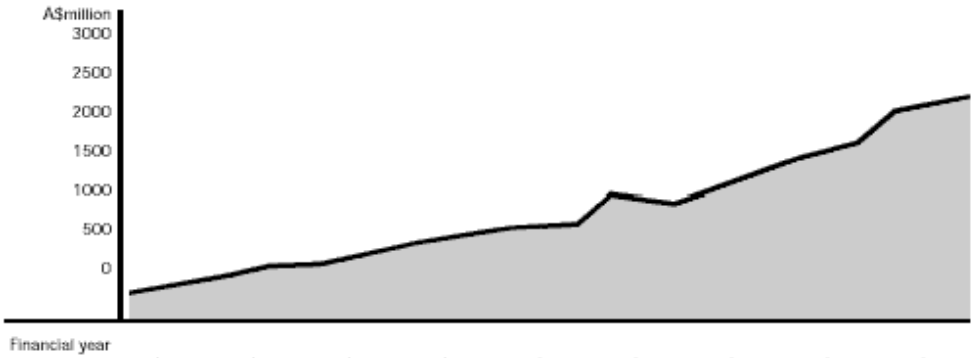
The key features of the plan are these:

- Most necessary pharmaceutical needs are subsidized by government.
- It is a universal plan covering Australian residents in the community.
- It gives priority to the treatment of medical conditions that are not amenable to self-diagnosis and self-treatment.
- Patients may select any general practitioner and have PBS prescriptions dispensed by the pharmacist of their choice.
- Patients make co-payments as a prescription charge per PBS item based on the patient's welfare situation, not the therapeutic importance of the medicine.
- There are two levels of co-payment, one for general patients (currently A$20.60) and a lower one for "concessional" patients—that is, those with social security cards (currently A$3.30). There is also a "safety net" to limit the patient's annual expenditure on prescriptions. Once this is reached, further prescriptions are supplied at reduced charges (free for concessional patients and at concessional rates for general patients).

New products cannot be added to the Schedule of Benefits made available under the PBS unless there is satisfactory evidence of comparative clinical effectiveness, safety, and cost-effectiveness. Once this is established, use may be restricted to certain therapeutic areas. The restriction on use is determined via a centralized, pre-use authorization process for some products (those requiring "Authority Approval") or by specification of indications and patient populations ("Restricted Benefit"). Products that are not restricted are available as "general benefits"—that is, for any indication.

Price controls are also applied. These are based on benchmark pricing within pharmacological groups, certain therapeutic groups, or on economic analyses evaluated by the Pharmaceutical Benefits Advisory Committee (PBAC). There is control over retail markups and dispensing fees for pharmaceutical benefits. Nonbenefit products do not have controls imposed on prices. Special arrangements apply to the supply of certain highly specialized and other drugs available for patient treatment groups with special needs or for people in isolated areas. The costs of the PBS over the last 20 years are shown in Figure 1.

FIGURE 1. COSTS OF THE PBS, 1979–1998



History of the Development of the PBS

In line with the international move toward nationalized health systems in the period following World War II, the Australian government in place at the time introduced a system to ensure the population's access to essential pharmaceuticals. The program was controversial from the beginning. The first act passed to establish the scheme (1944) was successfully challenged in the High Court as not in accord with the Australian Constitution. The main opponent was the medical profession.

After changes to the Constitution, a second act was passed (the Pharmaceutical Benefits Act, 1947). The

Pharmaceutical Benefits Advisory Committee (PBAC) was established to oversee development of the list of drugs to be supplied as benefits. The committee of six consisted of members of the pharmacists' professional association and the medical professional association. This committee provided expert advice to the minister for health about which drugs should be included on the schedule. The minister would then make the final decision. 2

The first benefits were made available in 1948. The grounds for inclusion of a drug on the schedule were that "it should contribute to the medical efficiency of the formulary."

Over the next 20 years, the composition of the PBAC was modified slightly by the addition of two additional members who were nominees of the Australian Medical Association. The membership was kept secret until 1970, and reasons for its recommendations about items added or not added to the schedule were not publicized. In 1973 the PBAC started to provide information to doctors and pharmacists about its activities, but did not provide formal reasons for recommendations.

Although the PBAC made recommendations to the minister about drugs to include in the schedule, it did not consider costs. Prices for pharmaceuticals provided on the PBS were initially negotiated between the manufacturer and the Department of Health. Because at the time most pharmaceuticals were supplied by UK manufacturers, the prices were initially based on UK prices.

In 1963, after concern was expressed about the increasing prices in Australia relative to those in the United Kingdom, a separate body, the Pharmaceutical Benefits Pricing Bureau (PBPB), was established. This bureau initially was made up of departmental officers who started to collect information systematically about pharmaceutical prices that could be used in price negotiation. Over the next 20 years, a system was established that led to Australia's having some of the lowest prices for drugs in the developed world (Industry Commission 1996).

At the same time, other changes were taking place in the pharmaceutical sector. By the mid-1980s a number of multinational pharmaceutical companies had established bases in Australia, and the local manufacturing industry was developing. Another key development was the rise in the consumer activist movement, associated particularly with the identification and outbreak of HIV. Attention became focused on the drug regulatory authority, as it was seen to be limiting access to potentially life-saving new drugs because of its slow registration/licensing processes. A need to introduce new Commonwealth legislation to take better control of the regulation of therapeutic goods became apparent.

The industry was expressing concerns about prices and the effect of the various pricing policies on the industry's viability. There was also a concern about the overall rising costs of the PBS. As a result, between 1987 and 1992, a number of key changes were made to the pharmaceutical sector:

- An amendment to the National Health Act to require the PBAC to consider costs and effectiveness in its recommendations to the minister about the addition of new drugs to the schedule
- With regard to PBAC membership, additional ministerial appointees who did not come from the representative bodies, and the appointment of a number of key academics interested in the use of cost-effectiveness analysis (terms of membership for the PBAC were not specified at that time)
- Provision for the PBAC to appoint technical subcommittees to assist it in its deliberations
- Establishment of the Pharmaceutical Benefits Pricing Authority, replacing the PBPB, to take into consideration a pharmaceutical company's contribution to the Australian economy when negotiating prices of pharmaceuticals
- New legislation covering all products rather than only imported ones with respect to the regulation of pharmaceuticals; consolidation of drug regulatory activities into one division of the Commonwealth Department of Health; and establishment of a national register of therapeutic goods

RATIONALE FOR THE POLICY

The rationale for introducing assessment of drug costs and effectiveness as part of the PBAC's deliberations has been outlined above. There was a basic tension between the community's health services needs and the needs of the economy in terms of industrial development. This tension still exists today. PBAC costs were rising, there was an increasing number of new and expensive products being developed, and the government of the day was also trying to implement a national medicinal drugs policy that required a viable pharmaceutical industry. There was a perceived need for a rational and defensible decision-making process that could provide a way of managing the addition of new drugs to the schedule.

The key stakeholders were the pharmaceutical industry, the government, consumer groups, pharmacists, and the medical profession. At the time legislation for cost-effectiveness analyses was introduced, the government saw it as a means to reduce escalating PBS costs. There was opposition from the industry to such legislation, which was seen as a way of lowering prices of products further and containing overall costs.

At that time health care consumers were not involved in the decision-making processes. The main consumer concerns apparently were to ensure continuing access to new medicines, but this view does not appear to have been expressed in any major public arena.

Academic groups were extensively involved in developing guidelines for implementing the policy. There is no record of

either the medical profession's or the pharmacy profession's views.

The main justification for the policy was the rising cost of drugs on the PBS. In the process of developing guidelines, comprehensive reviews of current economic methodology and theory were carried out (Evans, Freund, Dittus, et al. 1990) and presented as reports to the Department of Health. These reports also considered the role of economic analyses in decision making, and drew extensively from the experience of health technology assessment.

History of Implementing the Policy: Problems and Resistance

The Initial Phase: 1989–1994

The first step in implementing the policy was the legislative amendment passed in 1987. The second step was the development of a set of technical guidelines that could provide a framework for the methods used in assessing cost-effectiveness. The guidelines were drafted by external consultants, with some input from the pharmaceutical industry. The draft was issued in 1991, and over the next 12 months, the industry started to lodge submissions for inclusion of new drugs on the PBS according to the guidelines.

In 1993 the PBAC appointed its second technical subcommittee to assist in reviewing and assessing the cost-effectiveness data. The Economics Subcommittee (ESC) members were (are) clinicians, epidemiologists, and health economists. The pharmaceutical industry also had (has) a representative on the committee. At the same time, the process of PBAC application assessment began to undergo revision to accommodate the more technical evaluation that was now needed.

The guidelines were formalized in 1992, and beginning in January 1993 the pharmaceutical industry was required to submit applications for drugs to be listed on the PBS according to these guidelines. This precipitated a number of problems and started a degree of confrontation that persists.

The first problem was the industry's limited technical capacity to produce applications that contained the necessary information. The guidelines specified a combination of clinical and epidemiological data based on requirements of drug regulatory authorities, but extended them to include data on comparative effectiveness of the new product with the currently available therapy. Assembling and interpreting the clinical data required epidemiological expertise as well as access to relevant trials—neither of which were common. The epidemiological basis of the guidelines did not accord with industry expectations of cost-effectiveness analysis; pharmaceutical companies were anticipating an approach that emphasized the use of outcome data and economic modeling. The philosophy adopted by the ESC and the PBAC reinforced the emphasis on clinical assessment as the first step in evaluating a cost-effectiveness analysis.

The second problem was lack of cost information relevant to the Australian setting that could be used to construct an economic argument for listing a new drug. This was resolved by the development of a local Manual of Costs as part of the guidelines.

The third problem was lack of expertise in health economics within the pharmaceutical companies. Clearly, as this expertise had not been a regulatory or marketing requirement previously, there was a lag while the technical capacity was developed. The Department of Health at this stage was also in the process of developing expertise in the same area.

Consolidation and New Guidelines: 1995

Between 1992 and 1995, both the Department of Health and the pharmaceutical industry became more experienced in constructing and assessing economic evaluations. The relationship between the two groups at this time was more antagonistic, but there was no systematic attempt to undermine the process that was being established. The guidelines were reviewed as experience highlighting their deficiencies was accumulated, and a second edition was published in 1995. However, although developed in consultation with the industry, this edition of the guidelines was seen as much more proscriptive and rigorous than the first.

The change was based very much on the experience of the PBAC, ESC, and departmental staff, particularly in regard to the use of clinical evidence. The second edition of the Australian guidelines effectively requires a company to undertake a systematic review of the relevant biomedical literature, identify the best randomized controlled trials, formally assess the quality of the trials, and, where appropriate, pool the data. At the time (1994), the Cochrane Collaboration, an international nonprofit data-analysis collaborative, and others were only beginning to establish standardized methods for collating and assessing clinical evidence, so the guidelines were in advance of what are now reasonably well accepted approaches in this area.

The methods for economic evaluation were less clearly prescribed in the 1995 guidelines. This resulted from the decision-making group's experience, which strongly suggested that clinical assessment was the key aspect of many decisions. This emphasis was in contrast to that presented in other pharmacoeconomic guidelines at the time, in particular the revised Canadian guidelines, and it prompted a volley of criticism from the industry. In some ways, the criticism can be seen as a philosophical debate about whether the guidelines emphasized economic evaluation techniques, such as cost-utility analysis, or reflected the experience and preference of the committee for making its

decisions on trial-based economic evaluations.

A trial-based economic evaluation is one in which the outcomes used are those measured in comparative clinical trials, such as changes in blood pressure or in a symptom score, or, when measured directly, survival. The key advantage of such an approach is that it reduces uncertainty about the estimate of benefit, and thus uncertainty about the estimated incremental cost-effectiveness ratios. The disadvantage of this approach is that it is limited to the outcomes measured in the clinical trials and the duration of those trials. This means that, for example, a trial-based economic evaluation of a new antihypertensive drug might provide information only about the "incremental cost per millimeter mercury change in blood pressure over 12 weeks," if that was the key result measured in the trial. The question is then how best to extrapolate the results of clinical trials to develop economic evaluations that are cost-utility evaluations—cost per life year gained or per quality-adjusted life year (QALY) or per disability-adjusted life year (DALY), metrics more familiar to health economists for decision-making purposes. The problems with pharmacoeconomic analyses using these outcomes (or trial-based outcomes) have been discussed in detail by Hill, Mitchell, and Henry (2000).

In 1995 a further difficulty arose. The assessment of the economic evaluations submitted by industry was at that time being handled by a small group of staff (four) within the Department of Health. The workload at each meeting was increasing, as was the complexity of the applications. In the middle of that year the situation became critical when, at one meeting, it was made apparent that the committee had not been able to appraise all of the applications submitted by the industry because there were too few evaluators in the department to handle the volume of work. This problem prompted the establishment of the first external evaluation group, the Newcastle Evaluation Group (NEG), based at an academic institution. Although most of the NEG members were university staff, the external evaluation contract was the first formal link between the Department of Health and an academic center and, in some ways, represented the beginning of an academic discipline of pharmacoeconomics in Australia. The unit was gradually established at the University of Newcastle, initially consisting of a multidisciplinary team with expertise in clinical pharmacology, pharmacy, epidemiology, and biostatistics.

Challenge and Review: 1996–Present

The publication and implementation of the 1995 guidelines in many ways marked the beginning of a period of evaluation and review of the system that had been established so far, as well as the beginning of legal challenges to the system by the pharmaceutical industry. The first environmental shift was a change in government in 1996, from the Labor party, which had been in power for 13 years, to the more conservative Liberal/National party. The main change was in the government's attitude toward industry; the Liberal/National party has always been much more supportive of private industry than the Labor party.

From 1996 to the present, there have been a number of reviews and evaluations of the PBS listing process. These are discussed in detail below.

Other changes over this period include the consolidation of links with the academic center, resulting in academic review and evaluation of various aspects of the system, including technical and process issues. As part of this, the guidelines (1995 edition) have undergone review, particularly with regard to the methods to be used for economic modeling. A revision of the guidelines has commenced, with minor changes conveyed to the industry on an ongoing basis. Some major issues are yet to be addressed.

Evaluating the Policy as Implemented

The policy of using economic evaluation as a key component of decision making about pharmaceuticals in Australia has not been evaluated in the academic sense, although this type of evaluation has been considered from time to time. Instead, the program and policy have been the subject of numerous reviews and evaluations by internal groups within the Department of Health (such as the department's internal auditors), external groups, such as the Australian Industry Assistance Commission, and also legal challenge. The key reviews are considered below.

Industry Commission Report, 1996

This review was commissioned in 1995 by the Australian Industry Assistance Commission, with terms of reference that included the aim of improving the pharmaceutical industry's economic performance. The commission was required to consider how the PBS affected the economic viability and prospects of the Australian industry, and also the effects of the pharmaceutical industry assistance plan. Although at the outset this review was not a detailed evaluation of the PBS, consideration of the listing process became an important part of the commission's review of the pharmaceutical industry.

The report from the review was published in May 1996. It was very critical of the PBS's assessment and selection process and recommended major changes to it. The findings were that

- the PBS was the most important impediment to industry growth in Australia;
- the PBS produced low prices, volume constraints, and listing delays and thus was a significant factor in influencing company investment decisions in Australia;
- the listing process should be reformed as a matter of urgency;

- the welfare of the community was enhanced by the plan but that the PBS was threatened by growing pressure on it;
- there was a risk that the community's future access to some drugs might be adversely affected;
- it was therefore necessary to review the social and economic policy underpinnings of the PBS.

The key recommendations of the review in relation to the PBS were that

- companies should have the opportunity of delaying cost-effectiveness analysis for two years (after the drug is listed) to allow for the collection of costing data based on actual use;
- the PBS listing processes be subject to a review.

Other recommendations in the review concerned the regulatory authority, the industry assistance program, and the classification or scheduling of pharmaceuticals.

The government did not accept the commission's recommendations regarding the PBS. In part this may have been due to the change of government that had occurred between the commissioning of the review in 1995 and the publication of the report in 1996. However, the new government was (and is) generally more sympathetic toward the industry view, which was undoubtedly the major emphasis in the report.

It is interesting to speculate about the reasons for the rejection. The main problem identified was the practicality of allowing a drug to be listed without qualification for two years, prior to undertaking any economic evaluation. The implementation of this approach would have required a major shift in policy, from the "holding the gate shut" approach that had been in place to the development of a "negative list" along the lines of the UK's National Health Service. Withdrawing a drug from practice because of economic arguments would be extremely difficult, if not impossible; it had been tried by the PBAC on previous occasions and invariably provoked a negative public response, as well as in some cases, genuine hardship for patients.

Australian National Audit Office Review, 1997

The Australian National Audit Office (ANAO) began a two-part review of the Department of Health's programs for marketing approval and listing of pharmaceuticals in 1995. Following the release of the Industry Commission report in 1996, the ANAO was asked to incorporate a review of the listing process in its planned audit. The review was carried out over 1996–1997 and published in November 1997.

The objective of the PBS audit was to evaluate the Department of Health's performance in pursuit of selected PBS program objectives and outcomes. This included investigation and evaluation of the efficiency, administrative effectiveness, and accountability of the management of the listing process.

The review was extensive and included the establishment of a database of major applications for PBS listing, a technical consultancy to assess the guidelines and the use of economic analysis, and an analysis of the selection process for pharmaceuticals, including the operation of the PBAC and its subcommittees. The main findings of the review were presented in terms of the system's efficiency, administrative effectiveness, and accountability. These are summarized below.

Efficiency

- The running costs for administration of the PBS in 1996–1997 were A$10.1 million to support management of the expenditure of A$2.5 billion on pharmaceuticals.
- The time taken to list products was a major indicator of efficiency; the time had fallen since 1991, despite a significant increase in the number of applications being considered and a decrease in the number of staff.
- The proportion of major applications that were approved for listing declined after the requirements for economic analysis were introduced.

Administrative Effectiveness

- The progressive introduction of the evidence-based approach to assessing applications, requiring companies to submit data from clinical trials and an economic analysis, has been a major contributor to the administrative effectiveness of the listing process.
- The guidelines for the industry were soundly based, providing a suitable foundation for provision by the industry of sufficient evidence to facilitate solid decision making.
- Departmental processes, including the advisory committees' processes, worked effectively.
- The selection processes were rigorous and allowed high levels of clinical experience and judgment to be applied to the selection of drugs.

Accountability

The Department of Health was found to have followed the government guidelines for reporting to Parliament on its performance, but the ANAO believed that the reporting process could be improved to facilitate understanding of the

reasons for selection of drugs, thus enabling the development of more reasonable expectations of the PBS listing and selection process among the various stakeholders.

The report also noted that the quality of information varied considerably among applications and suggested that there was room for improvement in the industry's compliance with the guidelines. The majority of industry representatives interviewed during the audit accepted the evidence?based approach and the use of economic analysis, although many of them had reservations about the listing process, including the complexity of the guidelines and the overall transparency of the process, as all decisions and data were considered to be "commercial in confidence" information.

The ANAO report made 15 recommendations aimed at improving the listing process. These included emendations to the technical approach used in the guidelines and measures to improve the transparency. Some of the recommendations required an increase in the resources available for the evaluation process undertaken by the Department of Health, including the establishment of links with other academic centers. The recommendations have been gradually implemented by the department over the past three years.

Tambling Review, 1999–2000

The Tambling Review was undertaken in late 1999 partially in response to continuing concerns expressed by the industry regarding the PBS processes, and was chaired by Senator Grant Tambling, the parliamentary secretary responsible for the PBS under the minister for health. The review group comprised members of the pharmaceutical industry, a consumer, a general practitioner, a pharmacist, the chair of PBAC, and government representatives. The review was much less extensive than either of those by the Industry Commission or the ANAO, and was conducted much more informally. Most of the recommendations were either an extension of those from the ANAO report or aimed at improving the transparency of the process. There was some initial concern that this review would result in hostile recommendations, but such was not the case. Importantly, however, recommendations about changing the constitution of the committee were implemented 18 months after the review's completion. (See Epilogue.)

Communication and Funding of the Evaluations

Because all of the evaluations to date have been undertaken by either governmental or quasi-governmental groups, all have been communicated to the public and the industry via Parliament and the media. It is debatable how much information these evaluations have provided to the general public, as many of them are highly technical in nature. The industry, on the other hand, has scrutinized the reviews and reports closely, and they have been widely reported in the overseas industry information sources.

Evaluations of the PBS selection process carried out to date have been funded by various parts of the Department of Health or by other government organizations. More recently, the pharmaceutical industry and the Pharmacy Guild have funded a review by an independent consulting group, M-TAG Pty Ltd.

Plans for Ongoing Evaluation

The current government has made it clear that there will be continued scrutiny of the PBS and its functioning. There are two reasons for this: one is the increasing cost of the program, and the other is continuing pressure from the pharmaceutical industry. The latter is reflected in the current legal challenges to the system (see below).

Academic evaluation of the PBS is also increasing. The evaluation contract with the academic center includes a requirement for analysis of the listing process and its possible impact on the public and the industry. To date, the analysis has been based on retrospective review of the applications database, and has focused on the technical aspects of the applications rather than the impact of the PBS on health outcomes. There has also been departmental funding for other projects, including work on consumers' perceptions of PBS spending, and on the impact changing co-payment structures have had on access to medicines for socioeconomically disadvantaged groups within the community. There are no detailed plans for future academic evaluation of the program, as it is likely to be developed by consultation between the department and individual academic groups as questions arise. This approach may not be ideal, but it is a pragmatic option that is feasible at present.

Industry-related organizations, particularly those that provide economic consultancy services to the industry, are also starting to evaluate the program from an academic standpoint. This development may be in response to the increasing interest in the program internationally, and recent developments in other countries to implement similar decision-making systems.

Facilitators and Barriers to the Use of Evidence

The use of evidence in this process has been facilitated by a number of factors. First, the fact that there had been regulatory requirements for clinical trials of pharmaceuticals for many years prior to the introduction of the evidence-based selection process meant that good-quality evidence was available. It may not always have addressed exactly the question being considered by the PBAC, but at least there was a "culture of clinical trials" around the whole area of pharmaceutical development. This is in contrast with other forms of health technology, such as surgical interventions, where it is only recently that randomized clinical trials have begun to be standard. A ministerial advisory committee, the

Medicare Services Advisory Committee (MSAC), was established in Australia in 1998 to provide similar advice about health technologies generally as that provided by the PBAC about pharmaceuticals. The MSAC has had much greater difficulty in basing its decisions on clinical evidence because of the relative paucity of relevant clinical trials.

The second key factor in facilitating the use of evidence in drug selection has been the existence of robust legislation underpinning the process. This legislation was recently subjected to legal challenge in federal court, although the ruling has been appealed. The substance of the challenge was to dispute the right of the PBAC to consider total costs of drugs in making its recommendations to the minister, as well as considering "leakage" of a drug's use outside the defined population. In the judgment, Justice Mathews reviewed the development of the legislation and its introduction into Parliament. She expressed the view that the legislation was designed to allow the PBAC to consider "overall effectiveness of a drug (including leakage), together with its overall cost." The judgment is currently being appealed before the full bench of the federal court.

The third factor was the development of technical capacity *within*, as well as external to, the Department of Health. In the original report on the use of economic analysis for the selection of drugs for the PBS, Evans and colleagues (1990) noted the lack of expertise in health economics in Australia. Three options were suggested for developing the selection process with regard to such technical expertise: that the entire process be handled within the department by staff with the appropriate skills appointed to the task; that it be done by an external group as well as by department staff; or that it be done entirely externally. The report recommended the third option. However, it is the other two methods that have been used; initially all the technical work was done in-house, but since 1995, about 60 percent of it has been done by a group based in an academic institution. In-house expertise has been retained; the staff of the Pharmaceutical Evaluation Section (PES) who carry out the evaluations and oversee those undertaken by the academic group includes a health economist plus three pharmacists who have additional qualifications and training in health economics, biostatistics, and epidemiology.

The importance of having technical expertise within the Department of Health cannot be overemphasized. The department, after all, has to implement and refine the decisions, and this cannot happen unless staff members understand fully the technical reasoning behind them. Moreover, the department has to advise industry on how to develop applications, and this obviously requires technical capacity. Other areas of decision making that require specific technical skill but lack personnel who possess it have been less effective.

The fourth factor contributing to the policy's success has been the administrative processes developed to allow the explicit use of evidence in making recommendations. Recent changes to the system allowing publication of some of the recommendations has enhanced this aspect of the process by making clear the clinical evidence that is used as the basis of the decision.

The key barriers so far have been:

- the relative lack of health economics expertise in Australia in both the pharmaceutical industry and the government (although this situation is now improving);
- the industry's opposition to the policy. It needs to be said, however, that the industry is not unanimous in its views, as was made clear in the ANAO report. Some companies see the Australian selection system as an opportunity to obtain higher prices for useful products that represent value for money. The ANAO report noted that industry views were closely related to the level of success that a given company had in its applications resulting in PBS listings;
- lack of wide public understanding of the drug selection process, which has been exacerbated by the industry's insistence that its data remain confidential, and the secrecy provisions of the National Health Act that have applied in the past to decision making and that only now are beginning to undergo review. In particular, the secrecy surrounding such decisions has resulted in a very limited understanding by the medical profession as a whole of the way the system works, and at times has led to the medical profession's lobbying on behalf of the pharmaceutical industry to have cost-ineffective drugs listed in the PBS.

Current Status

The PBS selection process continues to be used in Australia and is being considered as a model by a number of other countries. There is still a tension between the government and Department of Health's role as purchaser and decision maker with regard to drug selection for listing and the industry's role as seller; this is to be expected and is probably healthy. Technical aspects of the process are being reviewed on a continuing basis; it is likely that a revised edition of the guidelines will be published in the next 12 months. The evaluation capacity is being expanded; the 1999-2000 federal health budget contained provision for the funding of potentially two more external evaluation groups in academic centers. The details of committee membership are also being refined; for example, it has been recommended that a health economist be appointed to the PBAC, rather than having an economist only on the ESC.

It is likely that the industry's challenges to the system will continue in some form or another, as many companies see the system as a threat. In particular, current interest in methods of paying for pharmaceuticals in the United States has prompted concern among some companies about the prospects of America's health care system adopting Australia's drug selection process.

Reflection and Generalization

In many ways the evidence-based selection process for pharmaceuticals has developed very much as it was outlined in the Evans report (Evans et al. 1990). This is due in part to the continuing involvement in the process of some of the people involved in the original report and guideline development. The process has been modeled on drug regulatory systems to a certain extent, which has probably contributed to its survival and development. Perhaps the only departure from the original plan is the degree to which comparative clinical effectiveness, rather than more economic considerations, seems to influence decisions, although increasingly economic models are informing the decision making. The PBAC has also begun to define other factors that influence its decisions, such as clinical need and the "rule of rescue."

In addition to the reasons discussed above, the development of appropriate methodology for assessing clinical and economic evidence should be considered as a factor contributing to the success, as well as continuing political support, of the drug selection process.

Epilogue

In December 2000 the government decided to implement the recommendations of the Tambling Review regarding changes to the membership of the PBAC: "nominations . . . should be sought from a broader scope of organisations than currently and . . . the National Health Act should be amended accordingly." The necessary legislative amendments were introduced on Parliament's last sitting day for the year and were passed, following amendments by the opposition parties. The main change was to ensure that at least eight of the twelve PBAC members were to be selected from nominations made from representative organizations.

The effect of these amendments was that the PBAC and its subcommittees as they existed in December 2000 ceased to do so at the end of that month. This change was to allow a new committee to be appointed, in line with the new legislation. Considerable controversy arose during the appointments process. Some of the previous committee members were eligible for renomination to the new committee; at the time this study was written, the new PBAC had just been appointed, including only two of the twelve members who had previously served.

Applications for listing on the PBS were due to be assessed by the committee in March 2001. It is likely that the PBAC and its decisions will be closely scrutinized over the coming months.

GLOSSARY

ANAO
Australian National Audit Office

ESC
Economics Sub-Committee: Subcommittee of the PBAC, comprising health economists and clinical epidemiologists, who provide expert technical advice on economic evaluations to the PBAC.

HIV
Human immunodeficiency virus

MBS
Medicare Benefits Schedule: List of medical services covered by Medicare program.

Medicare
National health insurance program

MSAC
Medicare Services Advisory Committee: Committee of external clinical experts who provide advice to the minister of health regarding the addition of new medical services to the MBS.

NEG
Newcastle Evaluation Group

NHS
National Health Service (UK)

PBAC
Pharmaceutical Benefits Advisory Committee: Committee of external clinical experts who provided advice to the minister of health regarding the approval of drugs for inclusion on the PBS.

PBB
Pharmaceutical Benefits Branch: Division of the Department of Health responsible for the administration of services that relate to the supply of pharmaceuticals, including the PBS, pharmacy registration, and the PBPA.

PBPA
Pharmaceutical Benefits Pricing Authority: Board or committee appointed by the minister for health responsible for negotiating the final price of a pharmaceutical that is to be included in the Schedule of Pharmaceutical Benefits.

PBPB
Pharmaceutical Benefits Pricing Bureau: First authority established to negotiate prices of pharmaceuticals in Australia.

PBS
Pharmaceutical Benefits Scheme

Pharmaceutical Evaluation Section
Staff within the PBB who are responsible for the technical evaluation of applications for listing of drugs on the PBS.

TGA
Therapeutic Goods Administration: Australian national drug regulatory authority.

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Update to the Australian Case Study

Ray Moynihan

Summary

As this report goes to press, Australia's Pharmaceutical Benefits Advisory Committee (PBAC) has been almost totally reconstituted, with only two of the previous 12 members present on the new committee, and the unprecedented inclusion of a drug industry figure as a full voting member. In a lengthy public debate in the media and Parliament, a range of informed observers and the federal opposition have accused the Australian government of bowing to a pharmaceutical industry campaign to undermine the independence and rigor of the nation's pioneering method of cost-

effectiveness assessment. Strongly rejecting those accusations, the federal government has justified its shake-up by arguing that the old PBAC was too antagonistic to industry, and that the new committee will continue the important cost-effectiveness analysis central to the efficient functioning of the Pharmaceutical Benefits Scheme.

Phamaceutical Board Shake-Up

During the last weeks of the final session of the Australian Parliament in December 2000, the government announced its intention to rush through new laws to change the membership rules of the PBAC. According to government spokespeople, the new rules were designed to broaden the range of groups nominating members to the PBAC, and to introduce time limits on membership ensuring turnover of talent and opportunities for fresh blood. While those changes were uncontentious, and had been suggested previously by a government review, the rushed nature of their implementation provoked widespread community suspicion.

Most importantly, the proposed new laws had no provision for a "transitional period" from the old committee to the new one, and it included strict time limits on membership, which were to be applied retroactively. This would have resulted in the immediate loss of key members, their expertise, and corporate memory. A range of groups expressed concern that the rushed implementation of the changes could produce a weakened committee.

The Australian Medical Association warned that "the pharmaceutical companies may want to increase their influence on this committee" (Moynihan 2000). The former secretary of the Health Department suggested that if the committee was undermined, the future of the Pharmaceutical Benefits Scheme would itself be in doubt. "If drugs go on the list which don't give value for money, costs will further increase, which means Treasury will try and abolish the Scheme" he said (Moynihan 2000).

The Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) sent an urgent message to the health minister saying its members viewed "with grave concern the current threat to the independent functioning of PBAC . . . which has the potential to compromise seriously the integrity of the drug regulatory processes to the detriment of the Australian people. . . . Unmodified, the current proposals will result in a loss of trust in well-established regulatory processes that have served the Australian people well and are widely recognised as international benchmarks" (ASCEPT 2000).

For its part the pharmaceutical industry appeared to welcome the government's proposed changes to the PBAC, with one company spokesperson saying the proposed reforms would "improve access and availability of new medicines" (Moynihan 2000).

Following public debate of these issues in the media, the federal opposition parties negotiated a compromise with the government, enabling amended legislation to be passed before the close of Parliament in 2000. The strictly retroactive nature of the time limits on membership was changed, and it was expected by the opposition parties that a substantial number of the old committee members would continue on the new PBAC, guaranteeing a smooth transition in this complex area of technical decision making.

Following the passing of the amended legislation in December 2000, the old PBAC was effectively dissolved and construction of the new PBAC began immediately. Under the new rules an expanded list of medical, economic, and consumer groups nominated potential appointees, and the health minister began inviting people to join the 12-person committee from among that list. The minister was also able to appoint a small number of experts from outside the nominated pool, whom he deemed would bring the necessary skills and expertise to the committee's deliberations.

Early in 2001, before the new PBAC was announced, information emerged publicly that the government had decided to appoint an industry figure as a full voting member of the PBAC, the panel empowered with assessing the value of new medicines and making recommendations that have a direct impact on almost A$4 billion of annual taxpayer subsidy of company sales. The new appointee was a former long-time drug company executive and until 2000 had been chief executive of the industry's primary lobby, the Australian Pharmaceutical Manufacturer's Association, for almost five years.

That revelation led no less than five proposed new appointees to decline invitations from the government to join the reconstituted committee. It also generated public outcry from professional and consumer groups, health experts, scientific opinion leaders in Australia and internationally, medical journal editors, newspaper editorialists, and the federal opposition. Some pharmacy groups, pharmaceutical company spokespeople, the federal government, and newly appointed PBAC members defended the appointment of the industry figure.

Defenders of the appointment argued that the industry figure brought important knowledge, that he no longer had any connections to any pharmaceutical companies, and that one person could not exert undue influence among a board of 12. Critics argued that by definition an industry seat was inappropriate, that it might inhibit frank discussion among members, and that PBAC votes were often close enough for one vote to matter.

The idea of an industry seat at the PBAC table had been explicitly sought by companies previously, and specifically rejected by the government's own Tambling Review in 2000, which did not recommend it because it "could result in an untenable conflict of interest with industry involved in decisions in which individual companies have a strong financial

interest" (Senator Tambling Review Group 2000).

By the second week of February 2001, the government publicized details of the new board's membership, including the former industry lobbyist and, due to the refusal of several experts to rejoin, only two members of the old PBAC. Through February, the changes to the PBAC were vigorously debated in both houses of the Australian Parliament. The opposition alleged that the government was doing the bidding of the pharmaceutical industry. During one debate the federal opposition leader cited a critique of the changes from the deputy editor of the *Journal of the American Medical Association*, who said, "This is a victory for a super-rich industry that will become even richer at public expense. It is shameful that the politicians have allowed this to happen" (Commonwealth of Australia 2001).

Strongly defending its changes as being in the best interests of the Phamaceutical Benefits Scheme, the government repeatedly blamed disgruntled former members of the old PBAC for creating damaging public controversy. Singling out certain individuals, the health minister accused them of having "spat the dummy" (Commonwealth of Australia 2001).

As part of the parliamentary debate, the opposition then revealed that the new industry appointee to the PBAC remained a current director of a small, research-based biopharmaceutical company, despite public assurances from the health minister that the former lobbyist was "no longer involved with industry" (Commonwealth of Australia 2001). Rejecting the criticisms of a potential conflict of interest, the government continued to stand by the appointment.

The Pharmaceutical Industry's Campaign

The government's latest actions have taken place within the context of a pharmaceutical industry campaign in Australia over recent years targeting the operations of the PBAC. While the full details of the campaign strategy have not yet been made public, informed observers, including a senior industry figure, suggest there have been at least two main aims: to win industry representation on government committees like the PBAC, and to have drugs listed more easily in the national Pharmaceutical Benefits Scheme.

The long-time managing director of Roche in Australia told a number of national media outlets of the existence of what he called an industry campaign. In December 2000 he said, "There is an industry campaign and it's led by Pfizer. It is a campaign to try and force government to list drugs more easily" (Moynihan 2000). In February he was quoted as saying that Roche had been approached to join a campaign to have industry representatives appointed to government boards, but had declined to join (Ferguson 2001). This informal campaign has operated in addition to the more formal cooperation among the pharmaceutical industry, the PBAC, and the federal Health Department that has occurred over many years through annual meetings and various joint committee structures.

Most visible within the industry has been the U.S.-based corporation Pfizer, which took legal action against individual PBAC members in 1999 over their previous rejection of public subsidy for Viagra. Pfizer executives were particularly concerned that the PBAC had overstepped its powers in rejecting Viagra by considering the total budgetary impact of a successful listing on the national pharmaceutical scheme.

In a judgment handed down in 2000 a federal court judge resoundingly rejected Pfizer's case on all grounds (*Pfizer v. Birkett* 2000), though a decision on a subsequent appeal is pending. Documents revealed during the court case indicate that if Viagra had been listed on the Pharmaceutical Benefits Scheme, it could have cost the Australian taxpayer more than A$50 million a year (*Pfizer v. Birkett* 2000).

Over the past two years Pfizer has also engaged the services, either directly or indirectly, of at least three former senior staff from the Office of the Minister for Health and Aged Care. Those staff include a long-time media adviser to the minister, and a chief of staff who provided consultancy services to Pfizer soon after leaving the minister's office in mid-2000. While their activities are not known, Pfizer has publicly confirmed that all three former government staffers were engaged at some point in the company's work for reform of PBAC processes.

Concurrent with Pfizer's political and legal activities has been the work of the Australian Pharmaceutical Manufacturer's Association (APMA). That organization's new chief executive, who came to the association from the federal Department of Industry, declared in February 2000 that reform of drug subsidy listing processes was one of his key tasks for the forthcoming year. A confidential internal APMA document from October 2000, later published in the national media, revealed that the industry was "greatly concerned" about what was described as a hostile attitude among members and staff of the old PBAC (Australian Broadcasting Corp. 2001b).

Another important forum has been the Pharmaceutical Industry Working Group, a powerful panel comprising key government ministers of both the health and industry portfolios and a number of drug company executives, including a senior Pfizer executive. The PBAC has had no representation at that panel's meeting and its deliberations were conducted in secret (though some minutes were later released after Freedom of Information actions).

Responding to opposition questions in Parliament, the government also confirmed the existence of an informal group known as the "Bennelong Group," a gathering of drug company executives with plants based in the prime minister's Sydney electorate. The most recent meeting between the drug executive group and the prime minister was in November 2000, though all parties state that innovation and investment, rather than the PBAC, were discussed at that meeting.

Conclusion

Throughout the period of turmoil, the Australian government has consistently rejected claims that it has bowed to industry pressure to bring changes to PBAC processes and membership. The health minister has argued that the newly reconstituted committee has the expertise to efficiently manage drug subsidization assessment, and is even better than the old committee. "We still have exactly the same system for listing drugs. We still have the PBAC with its clinical effectiveness and cost-effectiveness" (Commonwealth of Australia 2001).

During a special "Matter of Public Importance" debate in Parliament, the minister justified the shake-up by saying he could no longer rely on advice from the old committee and that there was "an increasingly fractured relationship between the committee and industry" (Commonwealth of Australia 2001). He also cited drug company legal action against the committee as another reason, and argued that he wanted to see PBAC processes become more "collaborative."

For some observers, the integrity and independence of the Australian process of drug subsidization have been threatened by the changes to the PBAC, leaving a cloud over the future of the Pharmaceutical Benefits Scheme and affordable medicines for all. For others, the inclusion of a former industry representative demonstrates a "partnership" approach that may enhance, rather than compromise the process.

Industry's view of the new committee is clearly represented by the current chief executive of the Australian Pharmaceutical Manufacturer's Association, who concluded an interview on national radio in this way: "I'm totally impressed with the new committee. I mean I think the minister has put together a committee which is beyond anyone's comprehension of what would be the top committee" (Australian Broadcasting Corp. 2001a).

Whatever the long-term implications for Australia's system of drug subsidization, the recent changes will likely bring increased and sustained public scrutiny, both domestically and internationally.

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Applying Research to the Policy Cycle: Implementing and Evaluating Evidence-Based Drug Policies in British Columbia

Malcolm Maclure, Robert S. Nakagawa, and Bruce C. Carleton

EXECUTIVE SUMMARY

Since 1995, the province of British Columbia (BC) in Canada has had a Reference Drug Program (RDP) and several related policies that have attracted both praise and criticism as a strategy for cost containment (Woollard 1996; McLaughlin 1997; Brunt, Chappell, Maclure, et al. 1998; Bourgault, Elstein, Le Lorier, et al. 1999; Narine, Senathirajah, and Smith 1999). The policies were introduced by Pharmacare, the publicly funded drug insurance program operated by

the provincial Ministry of Health, which covers all its citizens to varying degrees depending on their age, health, and economic status. Pharmacare had been struggling for years with double-digit growth in annual drug costs. The aim of RDP was to provide similar insurance coverage for similar drugs without increasing other health service costs or incurring adverse health events. RDP was challenged by the pharmaceutical industry as being hazardous to patients but was defended by the Ministry of Health as being evidence based. The degree to which RDP achieved its goals is being evaluated by independent researchers at Harvard (Schneeweiss, Sourmerai, Glynn, et al. 2000), McMaster University (Grootendorst, Dolovich, Holbrook, et al. 1999), the University of Washington (Hazlet and Blough 2000), and by one of us (B.C.C.) at the University of British Columbia (Carleton, Maclure, Dormuth, et al. 1999).

This paper summarizes the social and political context of RDP, its rationale and implementation, and lessons we learned about how researchers and decision makers can collaborate during drug policy design, implementation, and evaluation. Collaboration was marked by researchers participating in policy implementation committees and subsequently initiating policy evaluations. Policymakers responded by encouraging evaluations and monitoring their progress. As a result, policy was more firmly grounded in scientific evidence.

Researchers needed to adapt to the policymakers' context, which includes competing definitions of medical necessity and a policy cycle that accelerates and decelerates like a roller coaster. The type of evidence and manner of its input into policy decisions varied from slow, thorough analyses of drug cost growth and alternative policy interventions, to short briefings on policy choices and timely sound bites on urgent details of implementation. External funding of researchers and ongoing forums for expert participation in assembling the evidence base were key to bridging the gap between the different cultures of researchers and policymakers. Sustained involvement of researchers in an advisory committee on policy implementation built mutual respect and understanding between researchers and decision makers, leading to the smooth implementation of a randomized controlled policy trial. However, the personal collaborative relationships established between the policymakers and researchers were not easily transferable to new staff who did not share the history.

INTRODUCTION

The Health Care System

British Columbia is the third-largest province (population: 4,023,100) (BC Stats 2000) among ten provinces and three territories in Canada (population: 30,491,300) (Statistics Canada 2000). The federal government built the foundation of the Canadian health care system by providing indirect funding via a large transfer of moneys to provincial governments for health insurance, on the condition that the provincial insurance plans comply with the Medical Care Act of 1966 and its successor, the Canada Health Act. The Act requires

1. *Public administration*. The health care insurance plan must be administered and operated on a nonprofit basis by a public authority, responsible to the provincial government.
2. *Comprehensiveness*. The plan must insure all health services that were formerly privately insured provided by hospitals, medical practitioners, or dentists, and, where permitted, services rendered by other health care practitioners.
3. *Universality*. One hundred percent of the insured persons of a province must be entitled to the insured health services provided for by the plan on uniform terms and conditions.
4. *Portability*. Residents moving to another province must continue to be covered for insured health services by the home province.
5. *Accessibility*. The health care insurance plan of a province must provide for:
   a. insured health services and reasonable access to insured health services;
   b. reasonable compensation to physicians and dentists for all insured health services rendered;
   c. payments to hospitals with respect to the cost of insured health services.

The federal government retains the ability to withhold some or all of the transferred amount if the provinces do not comply with the Act. However, the federal government's influence declined in the mid-1990s when, coping with the large national debt, it began drastically reducing its transfer payments to the provinces.

Variation among Provincial Drug Plans

As the Canada Health Act does not encompass drug therapy outside hospitals, each province has developed its own plan for prescription drug insurance. The result is wide variation in the administrative structures, parameters of coverage, and drug formularies of the provincial plans. Some provinces have established their own legislation that guarantees them the lowest drug prices offered anywhere in Canada.

The BC Ministry of Health provides its citizens with seven drug plans available through Pharmacare. These plans provide coverage to specific groups of individuals based on demographics, location, or financial means. Within each of the plans there are varying co-payments and deductibles. For those who do not qualify for one of the six specialized plans, there is a universal plan. The plans are

Plan A: for seniors age 65 or greater

Plan B: for residents of long-term care facilities
Plan C: for Social Services clients
Plan D: for cystic fibrosis patients
Plan E: universal coverage
Plan F: children-at-home program
Plan G: for mental health center clients

Insurance coverage for prescription drugs is also provided by private sources. Approximately 55 percent of prescription drugs in Canada are funded by private insurers, compared with 45 percent funded by provincial and federal governments (Lewis, Blundell, Cashin, et al. 1997). Private insurers often emulate the provincial drug plans' formularies and drug programs for their beneficiaries. Private insurance coverage for pharmaceuticals in BC may include those individuals who have not yet reached their deductibles in the universal plan. Most of these plans are employer sponsored.

During the 1990s, all drug programs in Canada were struggling in different ways with major cost escalation. Economists at the University of British Columbia (UBC) (Morgan 2001) have recently confirmed what has been long suspected: the largest cause of cost growth has been increased prices of new drugs that replace older, less costly drugs. The common belief that rising drug prices are not the major cost drivers is based on an unrealistic interpretation of the standard method of calculating inflation: the change in price of goods and services that were available last year. By considering a new drug as a totally new product unavailable last year, such a calculation can be performed so that it always omits expensive new drugs. The UBC economists performed the calculation with a more realistic assumption; for example, a new drug for hypertension is a form of blood pressure treatment, and blood pressure treatment was available last year. Given that price growth is the major cost driver, reference pricing—similar insurance coverage for similar treatments—is a logical policy to consider.

National Drug Licensing and Price Control

The authority to sell a drug in Canada is regulated by the federal government. The Therapeutic Products Programme of Health Canada reviews the manufacturer's submissions to determine whether a drug is safe and effective for use in Canada. The information reviewed is provided by the manufacturer, who also identifies the desired indication for the drug. The review gives no consideration to the price of the drug, or to its relative place among existing drug therapies.

Until 1987, drug prices in Canada were determined entirely by the drug manufacturers. The Patent Medicines Prices Review Board (PMPRB) was established in 1987 under the Patent Act to protect consumer interests while increasing the years of patent protection for pharmaceuticals (Patent Act 1987). The PMPRB is an independent, quasi-judicial body created to monitor both introductory drug prices and any price increases during the period of patent protection. Its mandate is threefold:

- to ensure that the prices charged by manufacturers of patented medicines in Canada are not excessive;
- to report annually to Parliament on the price trends of all medicines in Canada;
- to report annually to Parliament on the ratio of research and development expenditures to sales by patentees.

Although the PMPRB is funded by the federal government, it is an independent organization reporting directly to Parliament. In performing its function, the PMPRB establishes maximal, nonexcessive prices for all new chemical entities. The PMPRB has a limited jurisdiction and does not have the mandate to control or influence drug prices for any unpatented drugs. Although there may be some relationship between price and the cost of research, development, and production of drugs, the primary determinant of price in Canada is still what the international market will bear (Angell 2000).

Policy Overview

BC Pharmacare introduced a Reference Drug Program (RDP) in October 1995. RDP established a means of drug insurance coverage based on the principle that society should pay for an evidence-based standard of drug therapy. If there is no evidence that a higher price buys better effectiveness or fewer toxicities, then the extra cost should not be covered in a publicly funded insurance program.

RDP was modeled on the reference pricing systems implemented in New Zealand and in Germany and other European countries in the 1980s and early 1990s (Lopez-Casasnovas and Puig-Junoy 2000; PHARMAC 1999; Selke 1994; Schneeweiss, Schoffski, and Selke 1998). Under RDP, one or more drugs of proven clinical effectiveness with better prices than their competitors in the same class are identified as the "reference drug(s)," and their price is fully covered.

A key feature of RDP in British Columbia is its flexibility to allow full funding of non-reference drugs if a physician reports that the patient has a specific clinical need or if the central computer of the provincial pharmacy prescription network (PharmaNet) has flagged the patient as an exception by virtue of his or her use of certain other drugs. If a physician reports by fax or telephone that a patient is unable to tolerate the reference drug or does not show a therapeutic benefit, then Pharmacare grants a "Special Authority," usually within 48 hours, for another drug in the class to be fully funded. When a physician prescribes a non-reference drug without a Special Authority, the PharmaNet computer alerts the dispensing pharmacist, who informs the patient and/or physician of the policy and suggests the following options: (1) if

there is a patient-specific reason for the use of a non-reference drug, the physician requests and is granted a Special Authority by Pharmacare; (2) if there is no patient-specific reason for the use of a non-reference drug, the physician changes the prescription to a reference drug; or (3) the patient pays the difference in price between the prescribed drug and the reference drug.

Thus, RDP can be viewed as a funding mechanism that incorporates varying levels of evidence from clinical advisers, researchers, physicians, and pharmacists in determining which medicines it is medically necessary to cover.

Medical Necessity

The term "medical necessity" is frequently used to justify health care funding. Much of the debate about drug policy can be traced to disagreements about the interpretation of this term. A Canadian study (Charles, Lomas, and Giacomini 1997) of the meanings of medical necessity identified four definitions, described below, that have been applied at different times in order to achieve different policy objectives.

1. What Physicians and Hospitals Do

This first definition prevailed in the 1960s and 1970s, when public funding of health insurance was expanding. In the area of drug therapy, there were few prescription drugs available, in comparison with the large therapeutic armamentarium of today. In addition, there was little therapeutic duplication of drugs available. For these reasons, virtually all prescription drugs were paid for under the Pharmacare program. Pharmacare had no formal review process for drugs, unlike hospitals, which had established Pharmacy and Therapeutics committees that developed and administered their formularies on behalf of medical staff. The idea behind this first definition is favored by proponents of unrestricted formularies. It is the belief that an individual physician's clinical experience and judgment cannot be improved upon by an expert committee because a patient's individual circumstances are crucial to the selection of an appropriate drug. This view assumes that physicians prescribe drugs appropriately in most instances, an assumption that conflicts with numerous studies (Lexchin 1998; Straand and Rokstad 1999; Anderson, Beers, and Kerluke 1997; Buetow, Sibbald, Cantrill, et al. 1996; Chin, Wang, Jin et al. 1999). This view is also naive with respect to the realities of modern medical practice, in which physicians preferentially cite commercial rather than scientific sources of drug information when making prescribing decisions (Avorn 1982; Lexchin 1993). It also ignores the ongoing use of hospital formulary committees in the institutional setting.

2. The Maximum We Can Afford

The second definition became popular in the mid-1980s as conservative fiscal policies took hold. By 1977 Pharmacare had expanded coverage to include the entire population of 2.6 million British Columbians (BC Stats, 2000); when a family's annual prescription drug costs exceeded Can$100, Pharmacare covered 80 percent of drug costs over that amount. But it was financially imprudent to extend coverage to all prescription drugs for all people. In other words, most prescriptions to the majority of the population—the relatively young and healthy—were not considered by the government to be medically necessary for Pharmacare to cover (definition 2) because these patients already paid for the drugs. If Pharmacare were to have covered those drugs, drug use would change little and no improvement of health was expected. This is a financial definition, and would likely be favored by ministries of finance.

3. What Is Publicly Funded across All Provinces

The third definition emerged as inequalities of coverage among provinces became apparent. Definition 3 is circular as a result of the 1984 Canada Health Act (see under "The Health Care System," above). The Act states that "the health care insurance plan of a province must insure all insured health services . . ." (Canada Health Act 1984), which it defines as services that are medically necessary, without defining what *medically necessary* means. The drug industry and patient advocacy groups use definition 3 when they tell BC Pharmacare, "You should cover drug X because another provincial drug plan covers it." Sometimes they imply that the other provincial program found the drug scientifically justifiable (definition 4, below). Often, however, they argue that, although there is not yet direct evidence of the superiority of drug X, its mechanism means it is theoretically likely to be demonstrated as superior in trials that are underway, and other provinces (definition 3) have decided that patients should be given that hope. Since the Canada Health Act does not apply to drugs prescribed outside hospitals, there is no parity among provincial drug plans. Furthermore, each province has its own independent review and approval process for insurance coverage of new drugs.

4. What Is Scientifically Justified

The fourth definition was embraced by policymakers in the 1990s as the concept of evidence-based medicine spread. It is attractive to drug benefits programs worldwide because growing numbers of expensive new drugs have no demonstrated superiority over existing drugs. By the same token, medications with the most evidence of effectiveness and safety are often the least expensive because their patent protection ceased many years ago. For example, evidence shows that high blood pressure is usually treated best with either a low-dose thiazide diuretic or a beta blocker, at minimal cost (National Institutes of Health et al. 1997). Although this was well established in 1995, about 20 percent of seniors initiated on a blood pressure-lowering drug in British Columbia were prescribed, contrary to guidelines, calcium channel blockers costing more than Can$1.00 per day (Maclure, Dormuth, Naumann, et al. 1998).

From 1994, Pharmacare gradually began to apply this definition to requests for new drugs to be added to the formulary. The result was RDP and several related policies.

The Policy Cycle

To understand how research evidence and definition 4 influenced the making of Pharmacare policy, we first present a brief synopsis of the "policy cycle" (Spasoff 1999, p. 16) and the political context in British Columbia. Spasoff used the concept of a policy cycle to explain how different types of research evidence are needed at different points in the policymaking process (Figure 1). We find the model fits with our experience of the planning, implementation, and evaluation of RDP, and use it as our outline for the remainder of this paper.

FIGURE 1. HOW DIFFERENT TYPES OF EVIDENCE INFORM DIFFERENT STAGES OF THE POLICY CYCLE (BASED ON SPASOFF 1999), AS ILLUSTRATED BY THE IMPLEMENTATION OF THE REFERENCE DRUG PROGRAM (RDP) IN BRITISH COLUMBIA, 1995–1999

An important fact that Spasoff does not emphasize is the dynamics of the cycle. In our experience, a major influence on how researchers collaborated with policymakers was the stop-and-go motion of the process. RDP required approval at

various levels of government as well as support from the communications branch of the Ministry of Health. This often entailed delaying the next stage of RDP in a queue of other policy priorities. Once the drug class for the next stage was chosen and the implementation approved, the pace of activity was frenetic for Pharmacare's small staff. A recovery period followed, during which less hurried evaluation and assessment of other interventions took place.

The stop-and-go motion was also influenced by political opposition and election timing. The brand-name Pharmaceutical Manufacturers Association of Canada (PMAC) advertised against RDP before the details of the policy were announced, and later challenged Pharmacare in the courts for allegedly overstepping its authority. The suit was rejected by the Supreme Court of British Columbia. PMAC appealed to the Supreme Court of Canada, which refused to hear it.

RDP was introduced by a social democratic party, the New Democratic Party, within one year before an election. The minister of health described RDP as "praised across the country and internationally. The only adverse impact is on the profit margins of the brand-name drug industry" (Government of British Columbia News Release 1998). The introduction of RDP in British Columbia was politically possible because pharmaceutical manufacturing is located primarily in the two largest provinces, Ontario and Quebec. The lack of significant drug manufacturing in British Columbia gives Pharmacare greater autonomy to introduce evidence-based policy. Still, threats from the drug industry concerning research funds spent in the province occasionally succeeded in slowing RDP implementation.

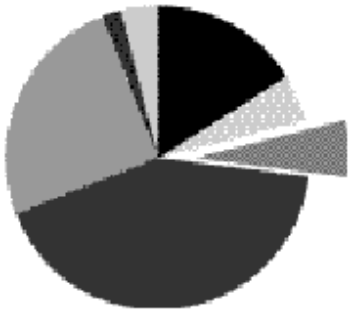
Complicating the politics of RDP is the perception by many individual physicians that RDP challenges their prescribing autonomy. Focus groups with physicians showed that many of them viewed RDP as further proof that the ministry was concerned more about costs than quality of care.

THE RATIONALE FOR RDP

Assessment of Drug Utilization and Costs

The number of new drugs introduced each year to diagnose, treat, and prevent disease and discomfort has been steadily growing, and their introductory prices have risen dramatically. In 1986–1987, the Pharmacare budget was only Can$165 million. By 1995–1996, it was Can$406.6 million, amounting to 6 percent of the Can$6.6 billion budget for the Ministry of Health (Figure 2). Thus, in the space of nine years there was an increase of almost 250 percent. This does not include the expense of hospital drugs or those paid for directly by consumers.

FIGURE 2. PHARMACARE EXPENSES



Community Services	16%
Other	5%
Pharmacare	6%
Hospitals	42%
Medical Services Plan	25%
Emergency	2%
Prevention & Promotion	4%

In the period 1990–1994, immediately prior to the establishment of RDP, Pharmacare's drug costs were growing at an unsustainable rate of about 15 percent per year. This growth rate was significantly greater than other indicators (Figure 3). In addition, there was a looming threat of reduced transfer payments from the federal government. Innovative

approaches were needed to balance the budget.

Pharmacare aimed to prioritize its expenditures so as to continue providing comprehensive drug coverage. Until 1994, Pharmacare's drug benefit list included most drugs licensed for sale in Canada. A more rigorous process of drug review was initiated in that year. The goal of this review process was to determine whether a drug should be included for coverage by the Pharmacare program for eligible beneficiaries.

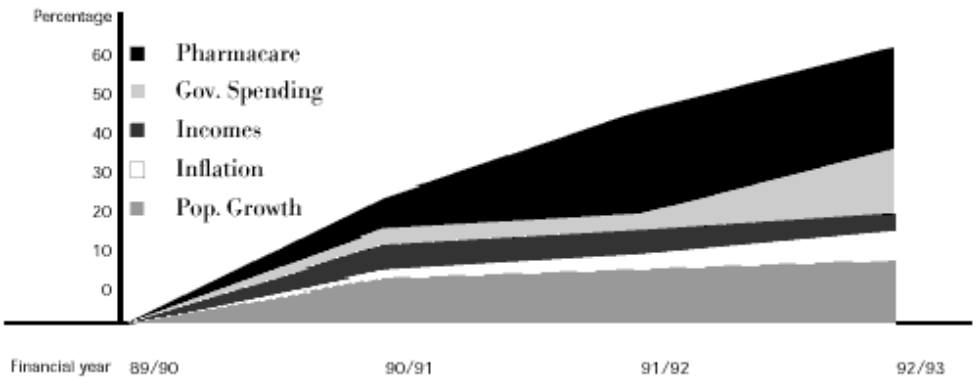
During this period an independent research paper on the determinants of growth in the Pharmacare budget (Anderson, Kerluke, Pulcins, et al. 1993) was very influential because it addressed Pharmacare's main problem rigorously and favored Pharmacare's perspective. It concluded that 34 percent of the cost increase was due to new drugs or increased prices of old drugs, and that population aging had almost nothing to do with increased drug use. This pointed to a general strategy of avoiding the extra prices of new formulations and drugs that were therapeutic duplicates of existing drugs, which was contrary to the interests of the pharmaceutical manufacturers.

The main lesson of this assessment is that studies of the causes of drug cost increases that go beyond descriptive statistics on drug utilization and cost trends and that allow for informed predictions are valuable for policy strategy.

Assessment of Potential Interventions

A review of the Pharmacare benefit program was conducted in 1993, involving provincewide public consultations by an independent panel. The panel concluded that patients with the financial means should contribute to their drug costs, regardless of their age. It recommended replacing the separate plans for seniors, long-term care patients, people receiving social assistance, and families with excessive drug costs with a single universal drug benefit plan, based on ability to pay. Political hesitation to implement this was later reinforced when a visiting scholar, Stephen Soumerai, was invited in 1994 to present to Pharmacare his research on impacts of drug cost control programs (Soumerai, Ross-Degnan, Fortress, et al. 1993). He emphasized that very small co-payments can cause some patients to stop taking essential medications (Soumerai, McLauglin, Ross-Degnan, et al. 1994).

FIGURE 3. PHARMACARE EXPENSES COMPARED TO OTHER INDICATORS



Rather than across-the-board co-payments, Pharmacare took the approach that it would fully cover at least one drug in each class of essential drugs, but the nonessential component of drug costs—the extra cost of higher priced drugs in a class of therapeutically equivalent drugs—would require co-payments. The first initiative in this direction was called the Low Cost Alternative Program (LCA), analogous to "generic substitution" (known in Germany as Stage I of Reference Pricing; see Selke 1994). Under LCA, when chemically identical drugs are supplied by different companies, Pharmacare pays only the price of the least expensive alternative. Prior to the implementation of this payment policy, community pharmacists routinely dispensed generic drugs to those patients who paid their drug expenses directly. Provincial legislation permits generic substitution of chemically identical drug products. The LCA program extended this practice to those patients whose drug costs were paid for by Pharmacare. Patients have the option of paying the extra price for other alternatives. LCA saved about Can$20 million during the first year, an annual rate of saving that has probably continued or grown as additional drugs reached the end of patent protection. No review of literature was required to support LCA because it was standard practice in both community and hospital pharmacies. Likewise, no health outcome evaluations of the policy were deemed necessary.

The second initiative was to create the Therapeutics Initiative (TI) to review published evidence of comparative clinical effectiveness of new drugs (Therapeutics Initiative 2000). The TI provides its evaluation of the therapeutic effectiveness

of new agents to Pharmacare's Drug Benefit Committee for consideration in making recommendations for drug listings. The TI was also funded by Pharmacare to educate physicians in more evidence-based prescribing, although an evaluation showed that its impact was insufficient to be a major cost-saving strategy (Maclure et al. 1998). The TI disseminated to all BC physicians reviews of the comparative effectiveness of existing drugs.

In 1995 Pharmacare began applying the logic of LCA to chemically distinct entities within single drug classes (e.g., histamine-2 receptor antagonists) that, according to published evidence, are therapeutically equivalent (known in Germany as Stage II of Reference Pricing; see Selke 1994). By 1995 this type of reference pricing had been used in the Netherlands, Denmark, and New Zealand, and Italy had announced plans to adopt it. Each country used a different approach, but reportedly succeeded in producing price reductions (PHARMAC 1999; Selke 1994; Jacobzone 2000). The pharmaceutical industry countered that the policy had not worked in Europe, because overall drug costs continued to grow. However, there was not enough published evidence to support industry's claim. Personal connections provided access to supportive unpublished evidence. The deputy minister of health in New Zealand in the mid-1990s had been a senior official in the BC Ministry of Health earlier in the decade, and made occasional return visits to British Columbia. Thus, Pharmacare learned how New Zealand had saved Can$30 million in its first year of reference pricing (PHARMAC 1995).

Although the direct evidence supporting RDP was largely unpublished, there was abundant, evidence by analogy with formulary management as practiced in hospitals for decades. A hospital formulary is a list of drugs deemed by the hospital's medical staff, through its Pharmacy and Therapeutics Committee, to be sufficient to provide a contemporary standard of drug therapy for inpatients. Often, drugs commonly used in the community are not included in a hospital's formulary. When an individual patient cannot tolerate any of the formulary drugs, or does not obtain the desired therapeutic effect, a non-formulary agent may be prescribed. This is exactly analogous to RDP in British Columbia, with its Special Authority. Formularies are considered to be a standard of practice in hospitals to ensure rational, cost-effective drug therapy. Likewise, RDP has the potential to be a standard of practice for drug plans.

The lessons learned from this assessment of potential interventions is that although studies of drug efficacy and effectiveness are voluminous, studies of the impacts of drug policies are few. More are needed if policymaking is to become more evidence-based.

Policy Choices

Having decided on RDP as a strategy, major tactical decisions had to be made. Which classes of drugs should be tackled first? And what was the likely choice of reference drug within each class?

The criteria for the selection of RDP therapeutic areas were that they must

1. Have a positive or neutral therapeutic effect on patient care
2. Be easy for the Pharmacare staff to make operational efficiently
3. Have a well-defined and feasible Special Authority process
4. Have the potiential to significantly reduce drug expenses for the province
5. Be based on sound scientific evidence

In addition to meeting the criteria, the first three drug classes under consideration were seen as relatively straightforward and easy to implement: gastric acid suppression drugs (H2RAs), nitrates for heart pain, and the nonsteroidal anti-inflammatory drugs (NSAIDs) used mainly for arthritis. There was much published evidence comparing the clinical effectiveness of H2RAs and NSAIDs. Although there were no published comparative trials of different forms of nitrates, it was presumed that this was because clinicians and pharmaceutical companies believed there was little or no difference among them in efficacy. Estimates of potential savings of Can$30 million in the first year also influenced these choices.

Another tactical decision, based on clinical experience of hospital formularies, was to permit rapid individual exemptions (via Special Authority) based on a patient's nonresponse or adverse reactions. This would make RDP more flexible than reference pricing in other countries. Long before RDP was contemplated, Pharmacare had sponsored the building of PharmaNet, a computer system linking all pharmacies in British Columbia to a central computer with an online record of each patient's prescription drugs. By law, all prescriptions filled by community pharmacies in the province must be entered into PharmaNet. The first wave of RDP took effect on October 1, 1995, two weeks after PharmaNet was fully functional in all pharmacies. The PharmaNet system helped RDP implementation by enabling instantaneous adjudication of patients' benefit status and calculation of their co-payment and current deductible accumulation. It permitted use of a variety of exemptions and more complicated rules that would have been too confusing for clinicians or patients to remember. For example, PharmaNet was used to generate automatic exemptions for patients already taking medications that had known interactions with reference drugs, or were markers of illnesses that qualified the patients for exemptions.

The lessons learned from these decisions were that although published research helped policymakers choose which drug classes to start with, research was not relevant to many questions about tactics and timing of policy choices and how PharmaNet could be used in policy implementation. To some extent, this lack of relevance inhibited collaboration with researchers, who felt that their expertise was not needed for such administrative decisions.

IMPLEMENTATION

After the broad policy choices had been approved by the minister of health and the cabinet, the rush to implement the details began. An expert committee was brought together to advise the executive director of Pharmacare on implementation. The RDP Expert Advisory Committee (RDPEAC) consisted of physicians, pharmacists, economists, and pharmacologists and was chaired by one of us (R.S.N.), a hospital pharmacist with expertise in the implementation of therapeutic cost-containment programs in the institutional setting. The RDPEAC was asked to provide expert advice on how best to implement RDP for the identified classes of drugs. The committee's first recommendation was that RDP be implemented in stages. Thus, RDP was applied to the first three categories of drugs over a period of months rather than simultaneously. The latter approach would have been too difficult for the committee and for Pharmacare because many smaller policy choices remained in each drug category: Which should be the final choice of reference drug? Should any drugs be excluded from partial payment because of toxicity or ineffectiveness? What criteria should be stated for individual patient exemptions? Which medical specialties, if any, would be exempt? What ancillary policies would be needed to ensure RDP's success?

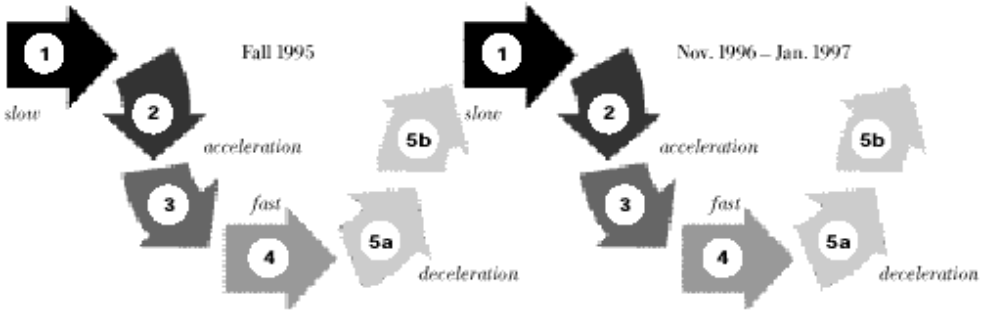
As each new drug class was identified and researched, the RDPEAC assembled the evidence base for inclusion in RDP. Each subsequent implementation phase built on the previous one, such that barriers encountered or successful strategies were incorporated.

The First Plunge

The RDPEAC joined the policy cycle at its fastest stage. Figure 4 illustrates the roller-coaster dynamics of the policy cycle—slow in steps 1 and 2, accelerating in step 3, hurried in step 4, decelerating in step 5. This dynamic was acutely evident every time a new class of drugs was considered for inclusion in RDP.

FIGURE 4. THE DYNAMICS OF THE POLICY CYCLE (BASED ON SPASOFF 1999).

The implementation of the Reference Drug Program in British Columbia, 1995–1999, felt like a roller coaster to both policymakers and researchers (numbers correspond to the stages of the policy cycle illustrated in Figure 1).



Evidence

RDP began with the histamine-2 receptor antagonists (H2RA). These drugs are used in the management of a variety of gastrointestinal conditions, including peptic ulcer disease and gastroesophageal reflux. In British Columbia at the time, there were four H2RAs available, with markedly different prices: cimetidine (Can$4.20 for a monthly maintenance dose), ranitidine (Can$13.20/month), famotidine (Can$22.50/month), and nizatidine (Can$28.20/month) (Therapeutics Initiative 1995). The RDPEAC judged all four to be equivalent in effectiveness and safety, based on critical reviews of the current medical and pharmacological literature (Feldman and Burton 1990; Cantu and Korek 1994; Rodriguez and Jick 1994; Carmichael and Zell 1987). This evidence was cited in Pharmacare's letter to clinicians announcing the policy. Cimetidine, having the lowest price, became the reference drug. Omeprazole (Can$69/month) is in a different class—proton-pump inhibitors—which are known to be more effective suppressors of gastric acid but, at the time, were thought to have unproven long-term safety. Omeprazole was therefore not subject to referencing with the H2RAs, but became part of the policy package.

What Was the Policy?

The policy specified that "all new and repeat prescriptions for an H2RA were to be funded at the level of cimetidine." An

additional clause to the policy was introduced after concern arose that the restriction of H2RAs might cause some physicians to use omeprazole instead. All new prescriptions for omeprazole would require either a prescription from a gastroenterologist or evidence of therapy failure after a six- to eight-week trial on an H2RA. Specifically, prescriptions written by gastroenterologists were fully reimbursed for omeprazole, but were not exempt from the H2RA restrictions, as relatively few clinical circumstances could justify the use of one H2RA over another. There was no exemption for those patients already taking omeprazole or H2RAs, but they were given an eight-week grace period to continue unrestricted use of these medications before the policy took effect.

This delay for current users was a direct result of researchers' being involved in the advisory committee. One of us (M.M.) ascertained that there were about 10,000 current users of omeprazole and about 10,000 new users per year. This suggested that a sudden surge of up to 50 or 100 Special Authority requests per day might occur, which Pharmacare was not yet prepared to handle. The Special Authority process allowed general practitioners to request that a non-reference drug for a patient be fully covered by Pharmacare due to special circumstances. Patients were granted an exemption if they were receiving drugs known to interact to a clinically significant degree with cimetidine: warfarin, phenytoin, theophylline, and cyclosporine. Patients were also given the choice of paying the difference between the alternative drug and the cost of cimetidine. The Special Authority process opened an opportunity for a researcher to collaborate with policymakers to analyze the initial patterns of requests.

Barriers

The policy triggered a wave of negative advertising from the pharmaceutical industry (Brunt et al. 1998). Pharmacists objected to the added burden of explaining RDP to both patients and physicians, while simultaneously dealing with the initial frustrations of using the PharmaNet system. Physicians felt that their prescribing autonomy was being threatened (Mullett and Coughlan 1998). Initially, many clinicians believed that the "cheapest agent," cimetidine, caused more adverse effects than the other non-reference drugs, despite evidence to the contrary. Critics claimed that the policy would negatively affect patients' health and cause cost shifting. No evidence to support these claims was provided, but the critics believed the burden of proof belonged to the policymakers to demonstrate that the policy would have no unintended effects. This was an unreasonable assertion, given that many medical, surgical, and drug therapy decisions in practice have not been proven to have no unintended consequences.

Lessons Learned

It was immediately clear that a key to success in the face of major criticism would be the staged implementation of RDP, drug class by drug class. This would allow time for separate consultations with different groups of specialists, adequate preparation of evidence-based communications and responses to critics, and better procedural troubleshooting by Pharmacare staff. It would also allow accumulation of experience and evaluations of immediate impacts that could be applied to future phases of RDP.

The second lesson was that the policy shifted 174,000 prescriptions to cimetidine from ranitidine, other H2RAs, and omeprazole, with no reports of adverse effects. The savings were projected to be about Can$12 million annually, from Pharmacare's annual budget of Can$400 million in 1996–1997.

A third lesson was that the evidence base for the policy would be used not just before the policy launch but also long after in responding to criticism from pharmaceutical manufacturers, physicians, and the public. In response to concerns that the policy was being developed without evidence of its impact on patients, an evaluation subcommittee, which one of us (B.C.C.) chaired, was formed, comprising outside researchers and a leading physician critic of the policy. The committee's purpose was to oversee evaluations of RDP impacts and provide assurance that the quality and effectiveness of the RDP policy were being monitored.

Fourth, researchers (Chappell, Maclure, Brunt, et al. 1997) studying the policymaking process were surprised by the many minor problems that could not have been anticipated in implementing RDP for H2RAs until the final weeks before the launch. These procedural obstacles crowded the agenda, allowing little time for reflection on evidence, other than what committee members could recall. Various decisions about implementation had to be based on quick consultations with experts.

It also became evident that responding to criticism from the public, physicians, and pharmaceutical manufacturers would be time consuming. This was a "learn as we go" approach whereby a lack of evidence for pragmatic issues did not prevent the policy from developing. Our decision, then, was to implement policy, assess its impact in order to better develop subsequent phases, and establish policy evaluation criteria such that formal evaluation could be done.

Questions That Remained

This initial phase of RDP implementation left Pharmacare confronting the most significant obstacle at that time: how could we more effectively communicate the evidence base of our policy to the stakeholder groups to ensure more efficient implementation? Surely, if the reasons were made clear, it would lessen resistance and increase support and development of the strategy. Getting BC physicians to absorb evidence-based messages was a difficult problem, however, as our research would soon confirm (Maclure et al. 1998).

The Pace Quickens on the Straightaway

The next two implementation phases of RDP occurred within the same month, affecting nitrates used for heart disease and the NSAIDs used mainly for arthritis. Nitrates were available in three different delivery forms: oral, topical paste, and transdermal systems. Isosorbide dinitrate (ISDN), administed orally, was the least expensive method of delivery (Can$4.62/month). Nitroglycerin paste, although perceived as inconvenient compared to nitroglycerin transdermal patches, was less expensive (Can$19.04/month for the paste compared to Can$60.04/month for the transdermal patch).

Evidence

At the time, there were no randomized controlled trials directly comparing the efficacy of alternative forms of nitrates. Placebo-controlled trials had been reviewed by local experts (North Shore Community Drug Utilization Program 1994; BCOHTA 1994). Based on these reviews the RDPEAC concluded that there was insufficient evidence that any one nitrate had a therapeutic advantage over another. Given the substantial financial benefit to a manufacturer to demonstrate therapeutic advantage, it was reasonable to consider all forms of nitrates to be equivalent in therapeutic effectiveness until proven otherwise. The committee recommended that patients receiving oral nitrates be switched to ISDN, and patients receiving transdermal nitroglycerin be switched to nitroglycerin paste.

More than 20 NSAIDs were available in Canada at the time of this policy implementation phase. Based on current medical and pharmaceutical literature (Rochon 1994; Bradley 1991; March 1994; Fries 1993; Langman 1994), all NSAIDs were judged equivalent in therapeutic effect, differing mainly in their adverse effect profiles. The difference in monthly therapy costs for these drugs ranged from Can$2.10 for low-dose aspirin to more than Can$80 for the newer NSAIDs. As was the case with the nitrates, few clinical trials were published comparing the effectiveness of the different NSAIDs. Among those trials, none demonstrated any consistent superiority of one NSAID over another. This evidence concerning nitrates and NSAIDs had been reviewed and disseminated to all actively prescribing physicians by the Therapeutics Initiative during the preceding 12 months.

What Were These Two Policies?

The nitrates policy was introduced on November 1, 1995. It stated that all new and repeat prescriptions for oral nitrates were to be funded up to the level of generic ISDN (Can$4.62/month), and for topical nitrates, up to the level of nitroglycerin paste (Can$19.04/month). Special Authority was granted to poorly controlled patients, those who showed intolerance to the reference drugs, and those with cognitive difficulties or manual dexterity problems. Cardiologists were not granted exemptions.

The policy regarding NSAIDs, effective November 27, 1995, stated that all new and repeat prescriptions for NSAIDs would be funded to the level of generic naproxen (Can$13.45/month). A physician's opinion that a patient needed a more expensive NSAID was not sufficient for issuing Special Authority. The policy stipulated that Special Authority would be issued only after the patient had tried a referenced NSAID (or acetaminophen) and found it ineffective. However, patients with rheumatoid arthritis, ankylosing spondylitis, collagen vascular disease, and gout were automatically given Special Authority on request by their physicians. Rheumatologists and dentists were also exempt.

Barriers

Less than a month after the two November policies were instated, the resistance began to pack a larger "punch." On December 18, 1995, the Pharmaceutical Manufacturers Association of Canada (PMAC) and seven of its member companies filed suit in the Supreme Court of British Columbia against the attorney general to stop the minister of health and Pharmacare from implementing all reference drug policies. (After ruling in the government's favor at the provincial supreme court and court of appeals, the case was finally refused hearing by the Supreme Court of Canada in February 1998.)

Accompanying this challenge was the continuing sharp criticism from various stakeholders. Some health professionals charged that the policy harmed the quality of patient care, led to increased illness, and resulted in an increase in the overall cost of patient care. Drug manufacturers felt the policy discriminated against those companies that invested in research and development, and continued to allege that proposed savings were not feasible, as there would be an increase in the use of medical services and a greater number of hospitalizations. Others felt that the policy was leading Canada into a two-tier system of health care.

However, there was support for the policy from the senior citizens in the province, who perceived the government as controlling costs responsibly without compromising the quality of care. These data were gathered by telephone interviews and focus groups conducted by the Seniors Drug Focus Project (see under "Evaluation," below). Preliminary impact assessments by ministry analysts at this time also showed no increase in the use of other health services as a result of RDP policy.

Lessons Learned

The savings Pharmacare experienced as a result of applying RDP to the first three of its drug categories (H2RAs,

nitrates, and NSAIDs) were estimated at Can$25 million annually (Office of the Auditor General of British Columbia 1999). Another significant outcome was the countermove made by one pharmaceutical company that launched its transdermal nitroglycerin product at a cost of 32 percent of competitors' products, matching the reference drug price exactly. While it was claimed that this price was determined independently of the RDP program, the timing and exact matching of the price made this seem unlikely. Consultation with cardiologists and general practitioners in the development of the nitrate policy was deemed unnecessary because there was no clinical basis by which a specialist or general practitioner would be able to identify a patient requiring one nitrate over another. The lack of sufficient advance notice (17 days) given to physicians and pharmacists before the NSAIDs policy was implemented upset some people. This resulted in pharmacies having excessive stock levels of the non-reference drugs, and physicians, pharmacists, and patients having to deal suddenly with a significant change in policy. Following this, we ensured a more substantial advance notice for all subsequent policies.

It also became evident that some physician groups would need less restrictive access to NSAIDs, particularly physiatrists and rehabilitation specialists, since many of their patients had already failed trials on the reference products in this category of RDP policy. These specialists were permitted to apply for professional exemptions from the policy.

Questions That Remained

Two significant issues remained to be solved. The first was how to streamline RDP implementation such that notification to stakeholders occurred in sufficient time. This would be aimed at allowing efficient conversion of patients to reference drugs and avoiding the potential of stockpiling of non-reference drugs. Second, and equally important, was how to encourage physicians to try patients on RDP medications before requesting Special Authority.

Anticipating the Bumps

The announcement of the upcoming implementation of RDP for antihypertensives was made on October 15, 1996. To encourage the use of proven, effective antihypertensive therapies, the RDPEAC decided not to include beta blockers and diuretics under RDP, despite major price differences within those categories.

Evidence

The RDPEAC decided that the policy would affect only second-line drugs, specifically the angiotensin-converting enzyme inhibitors (ACEIs) and the dihydropyridine calcium channel blockers (CCBs). It is widely recognized that there are no clinically significant differences within each of these classes in therapeutic or adverse effects when used for uncomplicated hypertension. A meta-analysis of the Collaborative Group of ACE Inhibitor Trials showed some heterogeneity among ACEIs but not enough to conclude that a single substance exerts any effect other than the class effect (Garg and Yusuf 1995).

What Was the Policy?

The RDP policy for antihypertensives became effective on January 1, 1997, and stated:

1. Captopril, ramipril, and quinapril were the reference drugs in the ACE inhibitor class; they would be fully covered in all dosage forms up to Can$27.00/month.
2. Felodipine was the reference drug among the CCBs with full coverage of all dosage forms up to Can$31.00/month.

Cardiologists, nephrologists, and internists were exempt from the policy, as were patients with asthma and diabetes. Sustained-release generic versions of verapamil and diltiazem, which were available at the time, were covered under the government's generic substitution policy that was already in place.

Barriers

The announcement of the upcoming antihypertensive RDP policy caused a surge of opposition. It was spearheaded by the release of a position paper written by the Canadian Cardiovascular Society (CCS 1997). Among many allegations, the paper implied that RDP compromised patient care, endangered the health of British Columbians, and totally ignored individualization of therapy. However, as emphasized in a letter to the editor from three prominent health care and epidemiological researchers, "the paper contains a number of inaccuracies, produces a limited literature review and nowhere names the participants. . . . Furthermore, the background paper published adjacent to the position paper is produced by two employees of the pharmaceutical industry, who have a commercial conflict of interest as evaluators of the RDP policy" (Holbrook, O'Brien, and Grootendorst 1997). An author of the paper subsequently chaired public forums (sponsored by a pharmaceutical manufacturer affected by the antihypertensive RDP policy) further damning the policy as harmful to patients.

A lobby group with connections to the pharmaceutical industry was also formed, calling itself the British Columbia Better Pharmacare Coalition. Its sole objective was to oppose RDP. This organization supported the idea that RDP sacrifices quality care in the name of short-term budget cutting and called for a moratorium on RDP until it was evaluated. This view was solicited through letters to newspapers, radio commentary, and meetings set up between government officials

and member organizations such as the Internal Medicine Specialists of Nanaimo BC, the First Association of Nephrologists of British Columbia, and the British Columbia Pharmacy Association.

Lessons Learned

It was during this phase that we learned the most about how evaluation could defuse criticism. The RDP Evaluation Committee established a peer review process for RDP evaluation proposals submitted by researchers outside the Ministry of Health. We did a great deal of relationship building with researchers and decision makers at this time in order to clearly describe the impact that research would have on the policymaking process and vice versa.

The estimated savings from both classes of drugs was Can$14 million annually (Can$9 million for the CCBs and Can$5 million for the ACE inhibitors). It became evident that as RDP expanded, more pressure was applied by its opponents. The message persisted that the policy was harmful and would not meet its savings estimates. This pressure resulted in more time spent responding to criticism and less time spent improving and developing policy and implementation strategies. Special Authority requests were still coming in at a steady rate of 300–400 per day. One of the main criticisms from physicians was the additional burden of filling out and faxing SA forms, a task for which they were not paid.

Despite the negativity, the policy seemed to gradually gain acceptance by the public and professionals. The BC Pharmacy Association dropped out of the BC Better Pharmacare Coalition and stated publicly that the evaluation procedures employed would answer its questions about the policy's viability. The BC Arthritis Society notified the government that it was not a member of the BC Better Pharmacare Coalition. Media coverage became more supportive of the policy despite the relentless efforts of the pharmaceutical industry and diehard opponents.

Questions That Remained

It is not known whether the RDP policy has had or will have a preventive effect on drug price increases in Canada. Since British Columbia is the only province with an identified reference drug program, the impact on national pricing levels may be minimal. However, there has been an increasing trend for drugs within a therapeutic class to be priced at the same level (e.g., angiotensin antagonists for high blood pressure, and triptans for migraines).

A persisting question that remained after this and previous phases of RDP implementation was how to reassure physicians that the policy was evidence based and would be properly evaluated for patient impact.

A Twist in the Track

The next phase affected drugs used in the treatment of reversible airway diseases like asthma. This began as an RDP policy, was changed to a drug "delisting" policy, and finally ended as a medication conversion policy called the Nebulizer to Inhaler Conversion Program. This evolution occurred in response to the pharmaceutical industry's continued pressure against RDP, which favored the Nebulizer to Inhaler Conversion Program over extending RDP to cover all respiratory drugs.

Evidence

The creation of this policy also reflected our review of evidence that metered-dose inhalers were the drug-delivery devices of choice: "The use of home wet nebulizers in the delivery of asthma medication is rarely, if ever, indicated in the management of asthma in adults and older children. Informed use of metered-dose inhalers (MDIs) with or without a spacer device is less expensive and at least as effective as that with nebulizers in the treatment of mild to moderate asthma" (Ernst, Fitzgerald, and Spier 1996). Numerous randomized controlled trials supported this position (Chou, Cunningham, and Crain 1995; Colacone, Afilalo, Wolkove, et al. 1993; Idris, McDermottt, Raucci, et al. 1993; Levitt, Gambrioli, and Fink 1995). In addition, many local hospitals had implemented nebulizer to MDI conversion programs to facilitate better therapy as well as save money.

What Was the Policy?

The policy, effective March 1, 1999, restricted coverage of nebules and solutions for nebulization. Patients 18 years of age and under were automatically exempt. Pharmacare coverage would be provided under Special Authority only if patients:

- had a cognitive impairment *and* an unsuccessful trial in the use of an MDI and a spacer;
- were living independently and either suffered from severe upper-extremity disability or lacked fine-motor coordination that precluded effective inhaler techniques;
- were residents of long-term care facilities and regularly required the administration of three or more inhaled medications at least three times a day;
- had difficulty in generating adequate inspiratory effort such that they were unable to achieve therapeutic benefit from an inhaler.

Due to the acuity of most of the nebulizer users, there were fears that one failed conversion could result in negative

publicity. It was suggested that providing patients with a spacer device and paying pharmacists to instruct patients on device technique would aid in a smoother conversion. Pharmacies were paid double the customary professional fee for each patient they assisted with the conversion. Free spacer devices were provided to patients through community pharmacies.

Barriers

A change of senior Ministry of Health staff and communications personnel meant that significant momentum was lost in the implementation. We were reminded of the urgency in making the evidence clear to the stakeholders again, as many health care professionals and patients believed that nebulized treatment for asthma was the hallmark, despite evidence to the contrary. Lack of direct communication between the Policy Advisory Committee and the director of Pharmacare occurred as a result of the acceleration of the "roller coaster effect" of the policy cycle during implementation. Unclear communication within the advisory committee led to the unclear wording of one key exemption: "patients who have such difficulty in generating adequate inspiratory effort that they are unable to achieve therapeutic benefit from an inhaler are exempted." This statement should have read, "patients who have difficulty in generating adequate inspiratory effort from dry powdered inhalers such that they are unable to achieve therapeutic benefit *and* have had an unsuccessful trial in the use of an MDI should try use of a spacer and MDI together prior to exemption." This lack of detail resulted in the unnecessary exemption of a large group of patients.

These communication difficulties and resultant policy problems are magnified by the policy cycle's roller coaster effect. Pharmacare is, by design, concerned with more than just the implementation of a single policy. Multiple drug benefit programs were being conducted at the time, and many employees had responsibilities for more than one program.

As with the initial implementation of all previous RDP policies, frustrated and angry physicians, pharmacists, and patients contacted Pharmacare by letter, fax, and telephone demanding changes. Additional complaints of increased workload due to the policy came from some staff at long-term care facilities where the administration of respiratory medications via nebulizer is considered to save time when more than one medication can be administered simultaneously. The policy allowed for the continued use of nebulizers if three or more medications were to be administered together, a practice nursing home staff believes decreases workload.

Consideration was given to an age of exemption lower than 18. The pediatric population accounts for the highest group of nebulizer users in British Columbia, and MDIs are now preferred over nebulizers for routine care of school-age children. Had the policy included school-age children, Pharmacare's savings would have been greater. However, one barrier was Pharmacare's concern that parents would have difficulty converting children to inhalers successfully. Also, children were exempt from earlier phases of RDP because what little financial benefit might have come from including them was offset by the potential risk of a story in the news media of a child coincidentally suffering an adverse event shortly after switching medications because of the policy.

The resistance of and pressure by the pharmaceutical industry experienced previously was noticeably absent during the implementation of this policy. This was likely due to the industry's awareness of the scientific literature clearly stating that respiratory medications delivered via metered-dose inhalers were at least as effective as medications delivered via a nebulizer. Another possibility is that the industry may have profited as much or more from metered-dose inhalers as from nebulizer medications.

Lessons Learned

The Nebulizer to Inhaler Conversion Program saved Pharmacare more than Can$1 million over one year. Researchers' collaboration increased because the policy was initiated with an evaluation component in the form of a randomized controlled trial. About 20 percent of physicians and their patients were randomized to be affected immediately by the policy ("treatment group") or offered a six-month exemption ("control group"). The unit of randomization was physician's office address so group practices would not be split. Physicians at control addresses were told in a letter from the principal investigator (B.C.C.), confirmed by an enclosed letter from Pharmacare, that their six-month exemption was already programmed into the PharmaNet computer.

Preliminary results have shown that the policy did not affect patients' quality of life or health status, in contrast to what opponents had predicted. The study also showed that significant stockpiling occurred before the policy took effect, which was a predictable response to the six-week advance notice to pharmacists and physicians. Pharmacies rarely billed for the fee available to them for the extra counseling required to switch patients from nebulizers to MDIs.

Questions That Remained

Although we have hypotheses, we do not yet know how to use the results of our policy trial to best advantage in building support for future evidence-based changes in drug coverage. This is because the collaboration between researchers and policymakers waned as a result of major turnover in Pharmacare's management and a hiatus in policy development.

EVALUATION

RDP was introduced in a climate of growing interest in outcomes evaluation but declining operational resources within the Ministry of Health. Pharmacare's priority was to develop complex cost-containment policies with limited staff. Few of its human resources could be devoted to evaluation. In this section, we will review the forces that enabled Pharmacare to forge ongoing links with researchers engaged in evaluating its policy impacts.

Initial Surveys of RDP Impact and Research Uptake

The Seniors Drug Focus Project (SDFP) was the original seed for what became a multifaceted research program. Its two aims were to study the impact of drug-substitution policy on seniors, and seniors' (and SDFP's) impact on policy. Initially, SDFP was hampered in pursuing its first aim because permission to contact patients directly affected by the policy was denied because of privacy concerns, until a solution was found in 1997 (Maclure 1997). From May 1995 to July 1996, SDFP conducted focus groups and telephoned 1,699 randomly selected seniors. SDFP found that seniors were more cost-conscious than physicians and generally supported RDP (Brunt et al. 1998; Mullet and Coughlan 1998).

As for its second aim, SDFP found evidence from seniors had little impact on Pharmacare policymakers unless SDFP conducted rapid research. Decision makers were more receptive to studies using focus groups, small telephone surveys, and studies of databases completed in two to eight weeks. As participant-observers in the rushed policy-implementation process, we discovered that the RDP Expert Advisory Committee had time for little more than a decision-oriented summary that encapsulated a study's main finding and was communicated in a sound bite at the time and place a decision was being made. To gain the attention of policymakers, researchers discovered they needed to offer their help with policy implementation: consulting with specialists, testing brochures in patient focus groups, or assembling the evidence base for the policy.

The lesson learned from this project is that there are logistical impediments to bridging research and policymaking, but they can be overcome if the researcher is creative about methods and timing and obtains the trust of the policymakers. Researchers need to take the first steps.

External Funding

Credit for the evaluation of RDP must be given first to agencies that fund health services research initiated by independent investigators. In 1994 the Seniors Independence Research Programme in Ottawa sent a representative across Canada requesting proposals. One of us (M.M.), then manager of Statistical Analysis and Surveys in the Research and Evaluation Branch of the Ministry of Health, heard her presentation and submitted a Can$526,000 proposal that became the SDFP. SDFP began as an initiative outside Pharmacare and ended within Pharmacare, because midway through the study the ministry disbanded the Research and Evaluation Branch and moved Maclure to Pharmacare in 1997.

The hope of funding from external agencies was also an incentive for researchers at Harvard, McMaster University, the University of Washington and the University of British Columbia to propose evaluations in 1996-1997. Based on reviews of their proposals by the RDP Evaluation Subcommittee, Pharmacare provided seed money to help researchers at Harvard, McMaster, and the University of Washington who were interested in conducting retrospective reviews of RDP policies to develop competitive grant proposals for submission to national agencies. Subsequently, approximately Can$1.5 million of external grant support from seven different agencies has been obtained, including the U.S. Agency for Health Care Research and Quality, the Canadian Health Services Research Foundation (CHSRF), the Canadian Health Transition Fund (HTF), and the Drug Information Association. The scientific aspects of the policy trial were funded by grants from CHSRF and HTF. As of early 2001, the evaluations were nearing publication.

The lessons learned about evaluation funding are that research grant agencies should continue or increase their support for policy evaluations, and that agencies like Pharmacare can encourage such support by providing seed money to investigators.

Impact Assessment

What sort of evaluation would have been done in the absence of external funds? It is hard to be certain, because Pharmacare had the assurance that high-quality evaluations were being done externally. However, we do know what evaluation Pharmacare was able to do in the interim. Four months after joining Pharmacare, one of us (M.M.), as manager of Statistical Analysis and Evaluation, was asked to conduct an evaluation of RDP with three data analysts working in other parts of the ministry; this was to be completed in two weeks, just before the presentation of the provincial government's annual budget. The monthly numbers of medical services and hospitalizations for sentinel diagnoses among people who switched drugs after the policy was put into place were plotted for time periods before and after the policy's implementation. These numbers showed fairly constant rates, with seemingly random fluctuations from month to month and no sudden changes after instatement of the policy. That evaluation served its immediate purpose and the information was used by the director of Pharmacare at many public meetings for two years. However, ultimately it was recognized as scientifically flawed, because the cohort of people who switched was defined in the middle of the process rather than at the start of follow-up. This can allow for sequence bias in before-and-after comparisons whereby the outcome of interest—the dependent variable (e.g., hospitalization)—can precede and therefore cause the independent variable (e.g., switching medications).

The lesson here is that there is a large cultural gap between what an administrative organization does for evaluation and what health service researchers do. These functions are complementary, not conflicting. Insiders and outsiders should continue doing what each does well, but should collaborate on each other's components.

Results of Impact Evaluations of RDP

Evaluations by University of Washington and McMaster University researchers were initiated in 1996 and 1997. In 1997 Pharmacare contacted Stephen Soumerai, a recognized expert in health policy evaluation at Harvard, and invited him to participate in the evaluation of RDP. The evaluations were still in progress as of early 2001 because the data sets are massive and the methodology problems proved challenging: two cohorts must be defined in the same way, one in advance of the "before" period, and one before the "after" period. Otherwise, historical controls are not comparable (due to the above-mentioned sequence bias); dozens of patterns of switching between drugs are complicated by many patients who simultaneously take two drugs from the same class; the nonzero before-policy rates of switching, switching back, and stopping drugs must be subtracted from the after-policy rates; the timing of stopping is unknown and must be inferred; and the fact that hospitalizations cause drug switching must be controlled in any analysis of whether switching causes hospitalizations.

Critics Accuse Pharmacare of No Evaluation

After the pharmaceutical industry failed to stop RDP by advertising and court challenges, a small number of RDP critics with industry support created the BC Better Pharmacare Coalition. It advertised that RDP had not been evaluated and should be stopped until evaluation was completed. However, an evaluation subcommittee had already been formed six months after the first phase of RDP had been implemented, and had developed procedures for evaluating RDP impacts on patients and the health system in general. One key document created by this committee was a peer-review process for RDP evaluation proposals. Two key organizations that had signed on to the coalition withdrew when they learned that Pharmacare was assisting the three universities with independent evaluations. At the same time, the industry supported the launch of an evaluation, coordinated at the Fraser Institute (a conservative think tank) by a general practitioner, that had already published articles in BC newspapers strongly criticizing RDP. That evaluation effort was slow to begin, in large part because initially recruited investigators decided not to continue with the project.

Randomized Policy Trial

A third aim of SDFP was to assess feasibility of randomized controls for policy evaluation. We found that physicians considered randomized trials the gold standard for evaluation but considered policy trials infeasible. We also found that seniors were comfortable with the idea of delaying a policy change in a subgroup "as long as it is OK with my doctor." This information helped the RDP Expert Advisory Committee approve a randomized control group, whereas three years earlier a similar committee advising Pharmacare quickly rejected the idea as unworkable and unethical.

The lesson learned from these trials is that if researchers develop a sustained collaborative relationship with policymakers and sensitivity to their concerns, it is feasible to conduct a randomized policy trial with a randomized control group in which the policy is delayed briefly.

PERSONAL REFLECTIONS

Researcher Observations

We discovered major impediments to funding research and evaluation by Pharmacare but substantial interest in evaluation if it were supported by external funds and synchronized with the policy cycle. Researchers inside government can help obtain funds and achieve synchronization, while independent external researchers are needed to persuade reviewers of impartiality. One of the best ways a drug program can foster collaboration is to allow randomized delayed controls, because this demonstrates the policymakers' commitment to rigorous impact evaluation that can inform both the researcher and the funding agency. However, it is difficult for external evaluators to advocate randomized policy trials without appearing self-serving and insensitive to the realities of decision making. This can be avoided by having an internal researcher do much of the bidding and help tailor the proposal to deal with decision makers' concerns.

In our "public-policy laboratory," we learned that the traditional academic process of developing research ideas long in advance of peer review funding and data collection did not work well. It was only by luck that delays in the Nebulizer to Inhaler Conversion Program equaled the delays in peer review of the external grant for the policy trial. We also learned to be amenable to rapid changes and concerned about the impact our research would have on policy staff.

On the other hand, we found that a major opportunity for developing collaboration with policymakers was to offer assistance with the development and implementation of policymakers' ideas. Efforts on behalf of specific policies were rewarded with attempts to understand and accommodate evaluation methods into new policies.

Policymaker Observations

In a review of the Canadian health care system sponsored by the federal government, it was noted that "the probable

effect on drug costs of any public (or private) reimbursement policy can be gauged by the tone and vigour of the industry's response" (Lewis et al. 1997). Since the implementation of this policy was opposed extremely vigorously by the pharmaceutical industry, it can be assumed that it had significant impact on the industry's revenue and on the provincial expenses as well. On a more objective basis, the policy was estimated to have saved Can$44 million annually for the drug program.

Despite this opposition, the RDP policy was introduced successfully. In addition to its solid philosophical foundation and basis in evidence, its success was largely due to the commitment from all levels of the provincial government: the cabinet, the minister of health, the deputy minister, the executive director of Pharmacare, the physician director of the ministry's Clinical Support Unit, and Pharmacare's pharmacists.

Collaboration with researchers enhanced the policy cycle but depended on their direct experience of the roller-coaster dynamics of the process and the constantly changing context. In general, there needs to be a mutual recognition between the researcher and the policymaker of each other's expertise and role in the system. The policymaker needs to recognize and value the researcher's expertise and academic strength, while the researcher must acknowledge the expertise and authority of the policymaker. When this is achieved, there are tremendous opportunities to generate new knowledge that will allow the advancement of health and public policy.

GLOSSARY

BC
British Columbia: The third-largest, westernmost province in Canada.

DBC
Drug Benefit Committee: The Pharmacare committee that recommends to the director of Pharmacare what drugs to cover and with what restrictions, based on the reviews of evidence by the Therapeutics Initiative and by the Pharmacoeconomic Initiative.

Drug class
A group of medications with similar chemical structures that exert their intended effects by the same pharmacologic mechanism.

LCA
Low Cost Alternative Program: The term used by BC Pharmacare for its policy of fully covering the lowest cost drug within a class of chemically identical drugs. The LCA is normally a generic drug with the lowest average Pharmacare-claimed price over a period of months. Patients who wish the brand-name drug or a more expensive generic may pay the difference in price.

Pharmacare
The publicly funded drug insurance program with an annual budget of about Can$700 million, administered by the BC Ministry of Health for all British Columbia residents with different deductibles and co-payments for different subgroups of the population.

PharmaNet
The single provincewide secure pharmacy network linking all retail pharmacies in British Columbia to a central computer with an online record of each patient's prescription medications that the patient filled in British Columbia in the past 13 months. The system became established in September 1995 and enables instantaneous adjudication of patients' drug claims under relatively complex drug coverage rules.

PI
Pharmacoeconomic Initiative: An expert committee, chaired by a health economist, that reviews pharmaceutical manufacturers' economic evaluations of new drugs; such evaluations are required by Pharmacare before a new drug will be covered. The PI advises the Drug Benefits Committee of the potential cost-effectiveness of the new drug. The PI is based at the University of British Columbia and is funded by a contract from the Ministry of Health.

PMAC
Pharmaceutical Manufacturers Association of Canada: The trade association of patented medicine manufacturers, renamed Canada's Research-Based Pharmaceutical Companies (CRPAC).

PMPRB
Patented Medicines Prices Review Board: An independent quasi-judicial body created by the federal government in 1987 to monitor drug prices during their periods of patent protection in Canada, and to establish maximal, nonexcessive prices for all new chemical entities that are patented.

Randomized Policy Trial
The term used in British Columbia for a policy implemented for the majority of patients and physicians, but delayed for six months in a randomized control group of 10 percent of physicians and patients.

RDP
Reference Drug Program: The program in British Columbia that applied the principle of Reference Pricing—similar drug insurance coverage for similar drugs—to the coverage of drugs for the elderly, the poor, and patients with special needs.

RDPEAC
RDP Expert Advisory Committee: A committee charged with providing expert advice to the executive director of Pharmacare on the implementation of the Reference Drug Program in British Columbia. It is composed of physicians, pharmacists, epidemiologists, staff resources, and other experts.

RP
Reference Pricing: An insurance policy by which, in a class of similar drugs, one or more less expensive drugs are fully covered as the "reference" drugs. Patients have the option to pay the difference in price for more expensive drugs in that class if they or their doctors do not want to use one of the reference drugs. In British Columbia, this was initially called Reference Based Pricing and later called the Reference Drug Program. Unlike RP in many other countries, the program in British Columbia allowed full coverage of drugs costing more than the reference drug if the patient had specific clinical needs for the alternative.

SA
Special Authority: The term used by BC Pharmacare for prior authorization of an exemption for a patient from one of Pharmacare's policies, such as RDP.

Stage I Reference Pricing
The term used in Germany for Reference Pricing within a group of chemically identical drugs made by more than one manufacturer. The reference price is usually that of a generic drug. Patients have the option of paying the extra cost of a brand-name drug in that class. (See LCA.)

Stage II Reference Pricing
The term used in Germany for Reference Pricing within a group of chemically slightly different but pharmacologically interchangeable drugs, regarded as therapeutically equivalent.

Stage III Reference Pricing
The term used in Germany for policy encouraging therapeutic substitution across different drug classes. This form of reference pricing was not implemented in British Columbia.

TI
Therapeutics Initiative: Established by the Department of Pharmacology and Therapeutics in cooperation with the Department of Family Practice at the University of British Columbia, the TI provides physicians and pharmacists with up-to-date, evidence-based, practical information on rational drug therapy. It includes a multidisciplinary committee of clinicians, researchers, and others who meet monthly to review published evidence of the comparative effectiveness of prescription medications. This committee sends the results of its reviews to the Drug Benefit Committee. Before Pharmacare covers a new drug, it must be assessed by the TI. The TI is funded by the Ministry of Health but functions at arm's length from the government, pharmaceutical industry, and other vested interests.

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Kaiser Permanente's National Integrated Diabetes Care Management Program

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EXECUTIVE SUMMARY

Kaiser Permanente's investment in a national, evidence-based population care management approach for adults with diabetes has yielded significant improvements in clinical processes and outcomes. In general, this success is based on the strategy of "making the right thing easier to do." Specific success factors include collaborative development and deployment of the policy; rigorous evidence basis; a focus on and adequate support for implementation, including clinical information technology; and comprehensive measurement systems for processes and outcomes.

Barriers

- *Cycle time and measurement issues.* Many improvements in care management are long-term, difficult to achieve, and hard to measure. Improvements in health often take many years to measure in a population, yet

there is ongoing budget pressure to demonstrate the value of our care management investments against competing priorities. The relative lack of good cost data makes it difficult to assess the cost-effectiveness of interventions. True outcomes data are difficult to obtain from administrative data, since they require member self-reporting of functional health status.
- *Incorporation of new evidence.* New clinical evidence in diabetes care emerges continually.
- *Acceptance of guidelines.* Good physicians who feel strongly that we should implement interventions where there is lack of data get frustrated and may drop out of the process when we stick to firm guidelines.
- *Deployment of clinical information technology.* The rapid deployment of clinical information technology remains our single largest challenge *and* opportunity.
- *Member self-management.* Members provide the vast majority of their chronic disease management themselves. Health care system interventions will not be successful if member self-management is not an integral component of the program.
- *Lack of integration.* Some of the most difficult challenges in implementing our diabetes care management program have been in those Regions with significant numbers of members who receive care in contracted, non-KP facilities. Challenges include limitations of automated information systems, non-KP clinicians delivering care without access to our clinical guidelines or implementation support materials, and lack of process and utilization data.
- *Lack of resources.* There is wide variation across and within Regions in capability to accommodate new programs.

Facilitators

- *Collaborative development and deployment of the policy.* To be successful, an improvement initiative needs to be actively and visibly sponsored by key leaders within the organization. Recognized experts need to lead and participate in the work or it will not be successful. Finally, to create a viable program, those responsible for implementation must be included in the development process. While gaining acceptance from key constituencies is time consuming and laborious, Kaiser Permanente's integrated system promotes the kind of cross-functional collaboration that can make an integrated care management program successful. As a group model, the vast majority of Kaiser Permanente physicians belong to the Permanente Medical Groups and are, in essence, "on staff."
- *Evidence basis.* Applying the rigor of evidence-based medicine optimizes the organization's ability to define and achieve desired clinical outcomes. It also dramatically facilitates clinician acceptance and support, enabling more rapid and successful implementation. The national care management program is well suited to quickly incorporating new clinical knowledge.
- *Focus on implementation.* Policy development is the easy part; sustainable improvements require ongoing sponsorship, leadership, and implementation support. The best clinical policy is not of value unless it is put into practice. The optimal pace of sustainable change can be achieved only through active engagement and support of stakeholders.
- *Information technology.* Clinical information technology is the most powerful lever to make the right thing easier to do.
- *Measurement.* "You manage what you measure." Measurement informs and motivates change. Clinical registries are essential for individual and population care management.

Lessons Learned

- *Collaborative development and deployment of the policy* (see "Facilitators," above). This collaboration in development and deployment results ultimately in a much stronger and more flexible program. The objective is to support, not dictate, medical practice.
- *Focus on implementation:* Making the right thing easier to do. We have learned that clinical content and policies (the right things) have no value without effective implementation, and that effective implementation is much more difficult than policy development. Binders with clinical policies and programs sit on the shelf (or worse) and quickly become outdated. Our care management programs focus on implementation and provide implementation support. Information technology—in the form of automated prompts, orders, reminders, documentation, and feedback at the point of care—is a key factor in making the right thing easier to do.

INTRODUCTION

Unlike most developed countries, the United States does not have a national health care system. Instead, our "system" is a patchwork of public and private organizations and services. The United States, with a population of 276.4 million (U.S. Census Bureau Nov. 2000), is governed under the principles of federalism, meaning that any powers not specifically given to the federal government (in the Constitution) are reserved for the 50 states. Two reasons often cited for the failure of the United States to implement a national health care system are: (1) a relatively weak or "decentralized" federal government that often deferred to states to protect the social welfare of citizens (Starr 1983); and (2) the enormous power (particularly in the first half of the 1900s) of the American Medical Association, which opposed any attempt by the government to interfere in physicians' fees or practice.

Responsibility for the provision of health care services to the U.S. population is shared by

- The federal government, through health insurance and health care programs for the poor ("Medicaid"), the elderly ("Medicare"), the military, and federal employees
- State and local governments
- The private sector, mostly via employers offering health insurance as a benefit of employment
- Charitable organizations
- Individuals

While Medicare, Medicaid, private insurance, and direct-pay account for the vast majority of medical expenditures in the United States (83 percent) (Levit, Cown, Lazenby, et al. 2000), there are many people without insurance of any kind; in 1999, 42.5 million people, or 15.5 percent of the population, were uninsured (U.S. Census Bureau Sept. 2000). Such individuals often receive care in hospital emergency rooms or publicly financed health centers and clinics. Funding for such clinics comes from the federal, state, county, and sometimes city governments. Many also receive private charitable funds.

In 1998, the United States (all payers) spent $1.1 trillion, or 13.5 percent of the Gross Domestic Product, on health care (Levit et al. 2000). Because the health care system is made up of so many different payers, health care policymaking is done on a number of different levels and in a multiplicity of ways. Decisions about what to cover and for whom (i.e., implicit "rationing") are not centralized for the nation. The federal government sets policies for Medicare. (Because Medicare is such a large portion of the health care market—18.9 percent—such policies often "spill over" into private-sector activities.) State and local governments also develop policies for the programs over which they have jurisdiction. Finally, private payers also make decisions about coverage and care effectiveness. This is a case study about how one of them, Kaiser Permanente, links research and policy.

INTEGRATION OF CLINICAL RESEARCH, POLICY, AND IMPLEMENTATION AT KAISER PERMANENTE

In the late 1990s, Kaiser Permanente leaders and policymakers faced a problem common to the rest of the health care industry: The literature and best practices within our program suggested huge opportunities to improve health care and outcomes for our members with chronic conditions, but how could we make it happen? How could we bridge the gap between this knowledge, the policy arising from it, and the implementation of the policy?

The Care Management Institute

This thinking spawned the creation of the Care Management Institute (CMI), jointly sponsored by the Kaiser Foundation Health Plan and the Federation of Permanente Medical Groups in 1997. The vision and mission of CMI are:

Vision: *The Care Management Institute, on a national level, will synthesize knowledge about the best clinical approaches and create, implement, and evaluate effective and efficient health care programs*.

Mission: *The Care Management Institute will be a nationally consistent, evidence-based, cost-effective approach to the delivery of health care that improves the health of all Kaiser Permanente members.*

Simply stated, the unifying theme of CMI is "to make the right thing easier to do."

The Right Thing

CMI's objectives feature complementary and integrated efforts to identify the "right" things that will best support the delivery of evidence-based, cost-effective, population-based care. Examples include using the rigor of evidence-based medicine and results from Kaiser Permanente's three major research centers to create and maintain care management programs; identifying and transplanting successful practices; and supporting the identification and maintenance of enterprise-wide content for embedding into Kaiser Permanente's Clinical Information System (CIS).

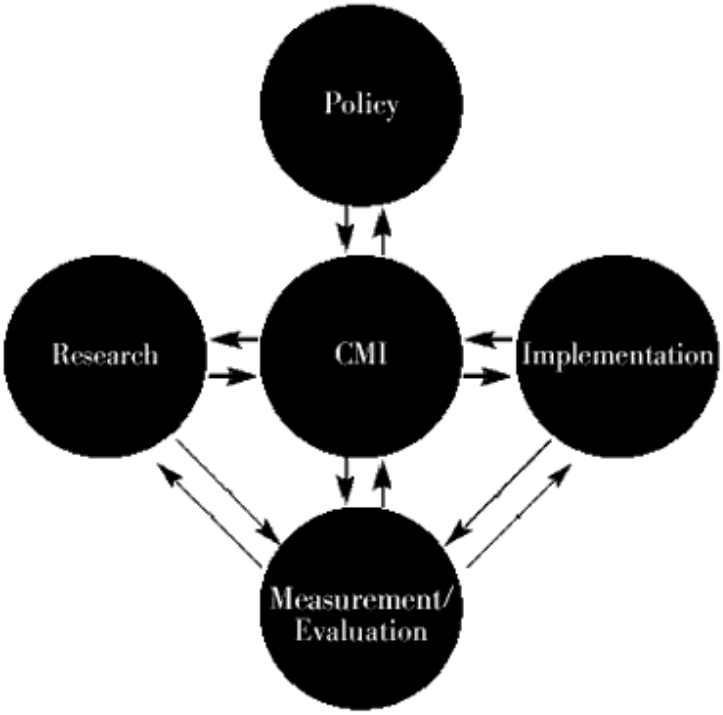
Making It Easier

Making the right thing easier to do includes fostering implementation by engaging and supporting individuals and groups, and by developing and improving systems to support care. Examples include the work of an Implementation Network; collaboration with regional and national leadership; development of a Fund for Implementation Assistance; and the creation and management of a clinical knowledge repository Web site (the Permanente Knowledge Connection). Making the right thing easier also means ensuring that the scope of CMI's work is aligned with emerging technologies, including CIS, our member Web site (KP Online), and technologies to support population care management.

CMI as Nexus

CMI serves as the nexus for coordination between research and policymakers in the development and implementation of evidence-based care management programs, as depicted in Figure 1.

FIGURE 1. CMI SERVES AS THE NEXUS FOR COORDINATION BETWEEN RESEARCH AND POLICYMAKERS



The following sequence of steps outlines the general process for development and implementation of a national care management program through CMI:

1. *Research.* From the evidence in the literature and experience within Kaiser Permanente, CMI staff develops the rationale for a select set of care management programs for priority populations. Kaiser Permanente's three major research centers—the Department of Research in Northern California, the Center for Health Research in the Northwest and Hawaii, and the Research and Evaluation Center in Southern California—are important sources of clinical evidence.
2. *Policy.* The CMI Board of Directors, comprising medical group and health plan leaders from across KP, establishes a subset of priority populations for national care management program development based on the materials presented.
3. *Research.* CMI staff coordinates the development of the care management program with a team of clinical and operational experts and champions from the KP program, based on evidence from the literature and experience within Kaiser Permanente. Evidence is reviewed in two areas: clinical management and successful implementation practices. CMI's biomathematical simulation model, "Archimedes," enables us to test the impact of alternative clinical policies and guidelines prior to implementation and to extrapolate the results from process improvements into longer-term clinical and financial outcomes.
4. *Policy.* The CMI board reviews and approves the care management program.
5. *Implementation.* CMI contracts with each Region to fund implementation and analytic network support to achieve targeted performance improvement in clinical effectiveness and efficiency.
6. *Measurement.* CMI staff coordinates the development of a measurement system, again with a team of clinical and measurement experts from across KP. Elements of the measurement system include common specifications, clinical registries for population-based care management, and national outcomes studies for benchmarking and program evaluation. The CMI Analytic Network, composed of staff in each Region, develops the registries or cohorts for clinician feedback and population care management, as well as providing the data for the national outcomes reports. CMI staff produces the national outcomes reports on an annual basis, providing

comparisons of performance over time and across Regions and the basis for program evaluation of successful practices and the impact of interventions.
7. *Implementation.* The CMI Implementation Network, composed of physicians and project managers in each Region, supports the local implementation of the care management programs.
8. *Implementation.* CMI hosts quarterly national users' group calls to discuss implementation issues and new clinical developments.
9. *Measurement.* The CMI Analytic Network prepares quarterly performance reports of regional progress against targeted performance improvement.
10. *Research and Policy.* CMI staff coordinates the review and update of the care management programs at least biennially, as described in step 3, for review and approval by the CMI Board.

Practical Implementation of Care Management Programs

The rest of this report uses the KP Integrated Diabetes Care (IDC) Management Program as a case study to illustrate the practical implementation of the conceptual approach described above, as well as to show the results achieved and lessons learned.

In summary, in the four years since the inception of the IDC program, we have achieved dramatic improvements in care management performance for our 330,000 members with diabetes. For example:

- From 1996 to 1999, Hemoglobin A1c (HbA1c) screening rose from 71 percent to 80 percent, and the percentage of members with diabetes with good glycemic control (HbA1c <8%) also increased, from 33 percent to 48 percent. This translates into 31,000 more members screened and 51,000 more members in good glycemic control in 1999 compared to 1996. The projected impact of this improvement over a ten-year period includes: 1,000 averted cases of retinopathy, 1,200 averted microvascular events, and 5,000 averted cardiovascular events.
- Lipid testing and control increased from 39 percent in 1996 to 51 percent in 1999 (tested), and from 25 percent in 1998 to 29 percent in 1999 (good control). That means 12,500 more members had good lipid control.
- The combined total rate of recommended eye exams was 75 percent in 1999. This exceeded the Health Plan Employer Data and Information Set (HEDIS) 90th percentile benchmark of 57 percent and the Healthy People 2000 goal of 70 percent.
- There has been dramatic improvement in renal screening and treatment for renal disease, from 59 percent in 1997 to 72 percent in 1999. This means that 47,000 more members were receiving appropriate screening or preventive therapy for renal disease in 1999 than in 1997.

In addition, although Kaiser Permanente's size and integrated financing and delivery system are unique, we have learned a number of lessons along the way that may prove to be instructive to other organizations in their development of care management programs. The key success elements include collaborative development and deployment of the policy, a focus on implementation, and measurement, each of which is described below.

Collaborative Development and Deployment of the Policy

KP's organizational structure is unique and somewhat complex, including the following key elements relevant to the collaboration between research and policymakers:

- Partnership management between the national Health Plan and the Federation (of eight Permanente Medical Groups) as well as between each regional Health Plan and the associated Permanente Medical Group
- Physician partnership in the Permanente Medical Groups
- Salaried physicians, with no fee-for-service incentives

These structural features require collaborative development and deployment of clinical policies and guidelines. The health plan does not and cannot impose such policies and guidelines, and the Federation and individual Permanente Medical Groups choose not to impose them. Examples of collaborative development include:

- Designating a well-regarded KP expert as the "clinical lead" for each care management program
- Convening clinicians and operational managers identified by regional leadership to serve on the development work groups
- Sticking closely to the evidence in the development of our programs
- Providing financial support for implementation and measurement
- Maintaining a network of champions and program "users" across the KP organization

This collaboration in development and deployment results ultimately in a much stronger and more flexible program. The objective is to support, not dictate, the medical practice of Permanente physicians.

Focus on Implementation: Making the Right Thing Easier to Do

We have learned that clinical content and policies (the right things) have no value without effective implementation, and that effective implementation is much more difficult than policy development. Binders with clinical policies and programs

sit on the shelf (or worse) and quickly become outdated. Our care management programs focus on implementation and provide implementation support. Listening to physicians and designing the programs around what they need is important for implementation success. For example, physicians in KP-Southern California felt that requiring members to fast before lipid tests created a barrier, so a nonfasting test was implemented. We find that clinicians are often too overwhelmed to add even minor things to short office visits, but they are more cooperative if they feel that they have been listened to and that their needs and constraints are being taken into account.

Information technology—in the form of automated prompts, orders, reminders, documentation, and feedback at the point of care—is a key factor in making the right thing easier to do. Setting up such systems is difficult, time-consuming, and costly. Also, if the registry information is incorrect, the systems quickly lose credibility and are not used.

Measurement: "You Manage What You Measure"

Measurement systems are essential to the success of our care management programs. Clinical registries and cohorts provide the basis for clinician, care manager, and member feedback and reminders; identify successful practices and common problems; and enable comparisons across Regions and over time.

Key areas for continued development in the future for Kaiser Permanente's care management programs include:

- *Clinical information technology.* This is the key to making the right thing easier, through automated order entry, prompts, reminders, and feedback; a clinical knowledge repository with advanced search-and-retrieval and decision support; and a member Web site, which facilitates self-management.
- *Patient-centered outcomes data.* Our administrative data systems are limited primarily to process measures. We need to establish broad-scale mechanisms to gather functional status and outcomes data directly from our members and to provide better measures of the effectiveness and value of our care management programs.
- *Program evaluation.* Our data reporting systems currently focus primarily on descriptive information about the care management programs, across Regions and over time. While this descriptive information is valuable, we need to invest in research and program evaluation to better understand the relationship between interventions and outcomes, differences in performance across Regions, and cost-effectiveness of alternative approaches. Our "Archimedes" simulation modeling capability will be utilized to test alternative policies and guidelines and to project longer-term health and financial outcomes of process improvements, thus helping to bridge the gaps between research, policy, and implementation.
- *Hospital utilization*. Contrary to expectations from the literature, we have not yet achieved reductions throughout KP in hospital utilization among diabetics as a result of our programs, even though we have achieved substantial process improvements. While a lag is expected between improvements in glucose and lipid control and hospital utilization, a key test of our program's success will be demonstrating utilization improvements as a result of our program. There is some evidence of reduction in hospital utilization in those Regions that have had diabetes care management programs in place the longest. For example, Group Health Cooperative (GHC) of Puget Sound (an affiliated member of KP) recently documented in a retrospective cohort study reductions in utilization and cost as a result of improved glucose control (Wagner, Sandhu, Newton, et al. 2001).

CASE STUDY: KAISER PERMANENTE'S INTEGRATED DIABETES CARE MANAGEMENT PROGRAM

Background Information about the Care Management Institute

Care management, also commonly referred to as "disease management," has been widely acclaimed by forward-looking health care experts as the next major evolutionary step beyond the cost-focused innovations of "managed care." Care management's promised impacts on future health outcomes and on the care delivery system itself are expected to be profound, given its potential to improve the management of chronic diseases, which account for nearly 60 percent of all medical costs in the United States.

Kaiser Permanente, which pioneered the population-based preventive care revolution more than 50 years ago, sees population management as the next level of innovation. In 1997, a national partnership agreement between the Health Plan and the Permanente Federation started the Care Management Institute (CMI), giving it a mandate to drive, fund, and catalyze care management activities throughout our health maintenance organization.

Care management as CMI defines it is *coordinated* health care, for *logical groupings* of members, intended to *prospectively* improve, maintain, or limit the degradation of their functional status. Terms are defined as follows:

- *Coordinated care:* Care that is delivered by a multidisciplinary health care team. Usually, a "care manager" oversees the treatment to ensure that the care is, indeed, coordinated.
- *Logical groupings:* Condition-specific populations of members, such as all those with diabetes, asthma, or depression, or with demographic/physical conditions such as the frail elderly or pregnant women.
- *Prospective and forward-looking prevention and/or health maintenance:* Strategies are aggressively pursued for each individual patient on the basis of customized care plans, with health status monitored longitudinally so that any deterioration can be addressed early.

Through systematic coordination, population grouping, and prevention, care management can improve the health and

functional status of millions of individuals by keeping patients with chronic conditions healthier and more engaged in managing their own care. In addition, prospective, preventive care management can greatly reduce the growing, ever more costly demand for acute care to patients with chronic diseases. According to a 1995 study by the Institute for Health and Aging at the University of California at San Francisco, treatment for chronic disease populations accounts for nearly half of total national health expenditures, including 55 percent of all emergency-room visits and about 80 percent of hospital days. If a significant fraction of those acute-care episodes can be reduced through prospective care management, the savings could translate into better and more affordable care for virtually all people.

The populations that can benefit most from care management are those with conditions that share certain characteristics: high treatment costs, high prevalence in the general population, and the availability of effective, evidence-based treatments. Thus, diseases like diabetes, asthma, depression, heart failure, and coronary artery disease are the initial, major candidates for care management. CMI has developed comprehensive, integrated management programs and annual outcomes studies for each of these populations. These five clinical priority areas affect approximately one million Kaiser Permanente members and account for more than $3 billion in incremental costs (above and beyond the costs for members without these conditions) per year (Care Management Institute 1996–2001; Ray, Collin, Lieu, et al. 2000). Implementing programs based on the most current medical research for these conditions results in improved quality of life for a significant portion of members, greater employee productivity, more affordable health care for all members, and enhanced medical expertise.

CMI, as one of Kaiser Permanente's Program Offices (corporate office) departments, is funded by the Health Plan's Regions. The Institute works through a small national staff in Oakland, California, and an extensive network of implementation physicians, project managers, and analysts/programmers in each of the program's Regions. The current $12.3 million CMI budget is a very small percentage of Kaiser Permanente's overall budget of $17 billion. More than half of CMI's budget is returned to the Regions in implementation and analytic support. The balance of the CMI budget is used to develop care management programs and provide infrastructure support, such as the Kaiser Permanente national clinical Web site, the Permanente Knowledge Connection.

CMI funds Regional implementation and analytic support to achieve performance targets in clinical effectiveness and efficiency for CMI's priority populations. In exchange for funding, Regions target improvements in performance greater in value than the investment, formalized as Memoranda of Understanding agreements (MOUs). The Regions provide quarterly reports of progress against the MOU performance targets. This process:

- Establishes accountability for the CMI investment
- Provides concise documentation of the investment and resulting benefits
- Focuses attention on initiatives with greatest potential benefits
- Provides a framework for regular review of progress
- Is relatively simple and easy to administer

The Market

Purchasers

Purchasers are still quite focused on costs; however, for larger, national purchasers, health plan value has become defined more broadly than by low cost. These purchasers are requiring evidence of customer satisfaction, clinical outcomes, and improved productivity in the workplace.

Consumers

Members of Kaiser Permanente, like other health care consumers, are becoming increasingly interested in participating in decision making regarding their own health and are turning to the Internet for assistance.

Competitors and Other Players

These include other national managed care organizations, for-profit disease management companies, and pharmaceutical companies. They are responding to the increased consumer power in health care by developing systems for them to share in their own health care. However, they are limited in their ability to manage care jointly with consumers due to lack of truly integrated delivery and financing systems.

Accreditors and Government

The National Committee for Quality Assurance (NCQA) is an independent, nonprofit organization whose mission is to evaluate and report on the quality of the nation's managed care organizations. NCQA evaluates health plans through:

- *Accreditation:* A rigorous review of key clinical and administrative systems and of a health plan's performance on several important aspects of care and service
- *Health Plan Employer Data and Information Set (HEDIS):* A set of standardized performance measures
- *Consumer Assessment of Health Plans Survey (CAHPS):* A comprehensive survey of member satisfaction

Although the accreditation program is voluntary and rigorous, more than half the nation's HMOs currently participate. HEDIS scores are now widely used by consumer groups, government agencies, and employers to evaluate the quality of managed care organizations. While HEDIS performance scores are very important for purchasers and consumers, they are necessarily limited to the common denominator of what managed care plans around the country can report. Kaiser Permanente supplements HEDIS clinical performance metrics with CMI measures that are more closely linked to health care outcomes.

The Centers for Medicare & Medicaid Services (CMS, formerly the Health Care Financing Administration, or HCFA) and state governments both purchase care and set regulatory frameworks for providing benefits, including what is covered.

Diabetes Program Overview

The Integrated Diabetes Care (IDC) Program was the first in a portfolio of high-priority care management programs developed by CMI. The planning, development, and implementation of the IDC program has spanned four years. The project-planning phase was launched in the spring of 1996 with the establishment of national sponsorship from Permanente Medical Group and Health Plan leaders. The fall of 1996 marked the beginning of interregional collaboration on program development. In 1997, work groups were established to create the core components of the initial IDC program. In addition, the measurement and evaluation system was launched in 1997, producing the first outcomes report (1996 data) and conducting a patient survey.

The full IDC program was distributed throughout the organization in January 1998. Following the release of the program, efforts focused on dissemination and implementation, as well as ongoing measurement and evaluation work. The second outcomes report was published in January 1999 (1997 data). Also early in 1999, interregional work groups reconvened to revise the IDC program, focusing on grading the evidence basis for each clinical practice recommendation, guidelines, expansion of the model of care (how to organize the delivery system to maximize clinical care and outcomes), and inclusion of change management strategies. The revised program was reviewed in summer 1999 and the final revision was distributed in December 1999. Ongoing measurement and evaluation work resulted in the publication of the third outcomes report in December 1999 (1998 data) and the fourth report in August 2000 (1999 data). The overall focus in 2000 was implementation of the IDC program throughout the Permanente Medical Groups and Health Plan.

To obtain sponsorship from Kaiser Permanente leaders, a business case was made by the department that preceded CMI and initially investigated how best to develop a national initiative in care management. The advantages of an interregional approach were articulated as

- Elimination of duplicate efforts to develop disease management programs in multiple Regions
- Prevention of added *post hoc* work that occurs after Regions have adopted alternative approaches or measurements that then must be reconciled with others in the organization
- Rapid dissemination and transfer of innovations across Regions, leading to increased speed to market
- Availability of similar outcomes data from different practice environments for comparative purposes
- Greater consistency of clinical care across KP
- Enhanced national reputation of Kaiser Permanente
  - –Provides convincing response to purchasers' demand for integrated programs to care for major chronic diseases
  - –Promotes improved results on HEDIS and other outcomes measurements
  - –Enables partnerships with influential national diabetes groups (e.g., American Diabetes Association)

The overriding objective of the IDC is to enhance the health of our members with diabetes, control disease progression, and prevent disability. Supporting objectives include:

- To promote the application of the latest medical evidence and national standards in clinical practice
- To disseminate components of proven diabetes care approaches by integrating them into the IDC program
- To equip our members with diabetes to be effective self-managers of their health and care, in partnership with their health care team
- To recommend proven strategies for successful implementation of diabetes interventions by clinicians
- To measurably demonstrate improvements in care through assessment of key outcomes measures

The IDC program is population based, utilizing economies of scale and intellectual capital. The program addresses the challenges of providing consistent, high-quality care to Kaiser Permanente members with diabetes. The IDC program is strongly grounded in medical evidence for treatment of diabetes. This focus on the evidence extends to many aspects of our comprehensive care management program, including:

- National, evidence-based clinical practice guidelines
- Model of care, including patient registries, stratification methodologies, commitment to a team approach, and evaluation of care
- Clinician resource materials
- Patient resource materials

- A measurement system
- Implementation support, including technology tools

These elements of our diabetes care management program are described in more detail in Appendix A.

Stakeholder Involvement and Communication

Internal

CMI provides overall process facilitation, but involves Kaiser Permanente's many clinical and operational experts to inform the substance of its programs. Development follows an evidence-based approach, particularly in evaluating the available medical literature. Policy is developed by:

- Designating a well-regarded KP clinical expert as the "clinical lead"
- Convening clinicians and operational managers identified by regional leadership to serve on the development work groups
- Sticking closely to the evidence in the development of our content
- Utilizing a broad "review and comment" process before finalizing our products
- Maintaining lots of flexibility in the "how to do" pieces, including first trying to adapt existing local programs to new protocols rather than imposing new ones
- Relying on our "deployed network" to lead implementation

The strength of our diabetes care management program is based in large part on the involvement of a broad spectrum of people and groups across Kaiser Permanente, including:

- *National Health Plan and Federation leadership:* Provides endorsement and funding for CMI
- *CMI Board:* Selects, reviews, approves, and endorses the diabetes program and national outcomes reports
- *CMI national staff:* Develops and updates the program and outcomes reports, negotiates performance improvement targets with the Regions
- *Diabetes program clinical leads:* Provide expertise and lend credibility to the program and outcomes reports
- *Diabetes program national work groups:* Build consensus for clinical guidelines and create acceptance and support by clinicians
- *Diabetes program outcomes advisory group:* Develops and sanctions consistent national measurement specifications and reviews outcomes reports
- *CMI implementation network:*Provides Regional implementation support
- *CMI analytic network:* Develops and maintains registries and cohorts, and uses them to produce feedback reports and regional data for the national outcomes reports
- *Regional leadership:* Funds and endorses care management programs, negotiates performance improvement targets with CMI
- *National users' group:* Clinicians and operating managers implementing care management programs meet regularly to share successful practices and new clinical information
- *Care managers:* Support clinicians in the management of panels of diabetic members through such activities as registry maintenance, in-reach and outreach, health education, and group visits
- *Clinicians:* Deliver diabetes care to members
- *Members:* Ultimately, provide the bulk of their own care, guided by Kaiser Permanente resources, including personal physicians, care managers, self-management tools, the member Web site (KP Online), health education classes, and advice nurses

The diabetes care management program and performance is communicated internally through a variety of mechanisms, including:

- Integrated Diabetes Care Program binder
- National annual outcomes reports
- Web site (Permanente Knowledge Connection)
- Online Continuing Medical Education
- Quarterly reports from Regions on progress against performance targets
- CMI Implementation Network meetings
- National Users' Group quarterly conference calls
- Bimonthly newsletter (CM*Ideas*) and CMI annual reports

External

The primary external stakeholders include major purchasers, the NCQA, CMS, the American Diabetes Association (ADA), the Foundation for Accountability (FACCT), and the Diabetes Quality Improvement Project (DQIP).

- *Major purchasers:* CMI has produced a brochure for national employers that includes general information about our care management programs and processes and inserts about each program, including diabetes, that include outcomes information. Major purchasers are becoming increasingly interested in our care management

programs and their impact on their employees. For example, Pitney Bowes distributes our diabetes program patient resource materials to its employees.

- *NCQA:* A portion of the NCQA accreditation for managed care organizations is determined by their Health Plan Employer Data Information Set (HEDIS) scores. Among the Effectiveness of Care measures in HEDIS 2000 is *Comprehensive Diabetes Care*, which addresses blood sugar, lipids, retinopathy, and nephropathy.
- *CMS:* CMS (formerly HCFA), which oversees federal Medicare funding for older adults, is interested in diabetes care management as both a major purchaser and a regulator. HCFA funded and led the Diabetes Quality Improvement Project (see below).
- *ADA:* The ADA produces clinical guidelines and sponsors a voluntary Provider Recognition Program for physicians, which includes a set of key performance and outcomes measures to assess the care provided to diabetic patients.
- *FACCT:* This not-for-profit organization has focused on the development of consumer/patient perceptions of care, and on making information about quality accessible and more easily used by consumers and purchasers of health care services.
- *DQIP:* A collaboration of HCFA, the ADA, NCQA, FACCT, the American Academy of Physicians, the American College of Physicians, and the Veterans Administration. The intention of DQIP was to develop a single set of measures to relieve health plans of the burden of dealing with different sets of measures for the various regulatory organizations. The measures they developed were the origin of the HEDIS and ADA measures.

Evidence

Evidence for Choosing Diabetes

Diabetes was selected for the inaugural CMI care management program based on a number of factors, including the high prevalence of the disease, the risk of complications and mortality, the cost of treating patients with diabetes, and the opportunity for improving health outcomes through care management.

Diabetes affects a large number of Kaiser Permanente members. In 1999 more than 330,000 adult members, 6.1 percent of our adult membership, were identified as having diabetes. These rates are consistent with the prevalence of diabetes in the United States; the American Diabetes Association estimates that 16 million (5.9 percent) of Americans have diabetes (Harris, Flegel, Cowie, et al. 1998).

In addition to affecting a significant number of our members, the burden of disease for diabetes is very high. Diabetes can involve serious health risks and complications and can affect nearly every organ system of the body. Complications of diabetes can include microvascular disorders such as blindness, kidney disease, and lower-limb amputation. In the United States diabetes is the leading cause of new cases of blindness among adults (CDC 1998). Diabetes is also the leading cause of end-stage renal disease, accounting for 40 percent of new cases (CDC 1998). Although only 6 percent of Americans have diabetes, more than half of lower-limb amputations in the United States occur among people with diabetes (CDC 1998). Diabetes is also associated with an increased risk of macrovascular disorders, such as heart disease and stroke (National Diabetes Data Group 1995). Finally, diabetes entails an increased risk of mortality. In the United States, diabetes is the seventh leading cause of death (CDC 1998).

In addition to the health and quality of life costs associated with diabetes, there are significant economic costs. In the United States the estimated cost of diabetes (direct and indirect costs) totals $98 billion per year. Within Kaiser Permanente, the cost of treating a member with diabetes was estimated at $4,150 per year (Ray, Collin, Lieu, et al. 2000), which represents an excess cost of $3,500 compared to members without diabetes (Selby, Ray, Zhang, et al. 1997). The cost of treating members with diabetes was approximately 2.4 times higher than the cost of caring for matched controls without diabetes (Selby et al. 1997).

Effective treatment of diabetes has been shown to prevent and/or delay the onset of many of the associated complications (Diabetes Control and Complications Trial Research Group 1993). Diabetes represents a key opportunity for care management because there is wide variation in practice and the natural opportunity for a population-based approach, including stratification of the population and coordination of care across care teams. Care management has been shown to be effective in improving outcomes and reducing costs among patients with diabetes.

Evidence for Diabetes Clinical Guidelines

The CMI guidelines are predicated on formal evidence from either evidence-based guidelines (Group Health Cooperative of Puget Sound, Kaiser Permanente-Southern California, Kaiser Permanente-Northern California) or standardized literature reviews (Cochrane Collaboration). When evidence reviews did not include the relevant, most up-to-date literature, CMI conducted evidence reviews to fill the gaps.

The evidence grades for our recommendations are *strong* (A rating), *fair* (B rating), *weak* (C rating), and expert opinion. In cases where multiple studies supported different conclusions, the evidence rating is based upon the strongest studies (i.e., large, well-designed randomized controlled trials).

- *Strong (A rating):* A recommendation needs to be supported by at least two well-designed randomized controlled trials in relevant populations.

- *Fair (B rating):* A recommendation needs to be supported by a single randomized controlled trial or well-designed non-randomized controlled trials (RCT), or well-designed case-control studies.
- *Weak (C rating):* A recommendation needs to be supported by a single non-RCT or multiple small studies using quasi-experimental designs.
- *Expert opinion:* All other recommendations in the guidelines are in this category, which indicates that insufficient evidence is available; the recommendations are guided by diabetes content experts.

The Kaiser Permanente diabetes clinical guidelines and evidence in support of them are presented in Appendix B.

Continuing Impact of Evidence

To maintain an up-to-date evidence basis, our program is reviewed and revised regularly. The program, including clinical guidelines, is reviewed at least biennially. The first edition was produced in 1997; the second edition was issued in 1999. In addition, two new clinical practice recommendations have been added to the guidelines in 2000 based on new evidence from recently published clinical trials. As described above, the outcomes measures are reviewed and revised annually. Outcomes data are also utilized as evidence to identify successful practices, as well as areas requiring a focused improvement effort.

Evaluation: Current Efforts

National Outcomes Reports

The evaluation of the CMI IDC program is conducted through annual National Outcomes Reports. These studies, which began in 1996, identify more than 330,000 Kaiser Permanente members with diabetes (6.1 percent of our adult membership) and report on numerous clinical and process outcomes for these members, including case identification, glycemic screening and control, lipid screening and control, eye examination, renal screening and treatment, and hospital utilization.

For each report, CMI convenes an advisory group of clinical and measurement experts in diabetes from across KP to determine the measures for the outcomes report. CMI analysts in each Region collect data for these measures, which are summarized to calculate Kaiser Permanente totals. One unique aspect of these studies is the consistent use of the same measurement specifications across Regions, yielding a large cohort of members with diabetes with comparably measured outcomes, despite differences in data and care delivery systems across Regions.

CMI recently has completed the fourth diabetes outcomes report (data for 1999), which illustrates the improvement in diabetes care across KP from 1996 to 1999 (see Table 1). For example, HbA1c screening rose from 71 percent in 1996 to 80 percent in 1999, and the percentage of members with diabetes with good glycemic control (HbA1c <8%) also increased, from 33 percent to 48 percent. Lipid testing and control, a primary focus in the IDC program, also increased from 39 percent in 1996 to 51 percent in 1999 (tested), and from 25 percent in 1998 to 29 percent in 1999 (good control). There was also dramatic improvement in renal screening and treatment for renal disease, from 59 percent in 1997 to 72 percent in 1999. Improvements have also been shown in eye exams and hospital discharges and days.

TABLE 1. IMPROVEMENTS IN DIABETES CARE OUTCOMES WITHIN KP, 1996–1999

Measure	1996	1997	1998	1999
HbA1c screening	71.3%	78.3%	79.1%	80.5%
HbA1c <8% (of total)	33.2%	43.9%	43.5%	48.4%
HbA1c <8% (of tested)	46.5%	56.1%	55.0%	60.1%
Lipid testing	38.7%	41.9%	47.8%	50.8%
Good LDL control (of total), ages 18–75	NC*	NC	25.0%	29.4%
Good LDL control (of tested), ages 18–75	NC	NC	52.4%	57.8%
Eye examination	NC	72.3%	74.1%	NC
Renal screening/treatment for renal disease	NC	58.6%	63.7%	72.5%
Hospital discharge rate (per 1,000)	NC	248	266	262
Hospital days rate (per 1,000)	957	983	1109	1020

*NC: Measure not comparable due to changes in specifications.

Between 1996 and 1999, 51,000 more members with diabetes had good glycemic control.[1] Although these are aggregate data that do not include individual-level information on changes in glycemic control or other risk factors, using some simple assumptions based on randomized clinical studies, we can estimate the impact of our diabetes care management programs. The United Kingdom Prospective Diabetes Study (UKPDS) compared intensive metformin treatment for glycemic control to conventional treatment (diet, clinic visits, nonintensive pharmacology) among overweight diabetes patients in the United Kingdom (UK Prospective Diabetes Study 1998). Results from the UKPDS suggest that the number needed to treat (NNT) for intensive glycemic therapy over a ten-year period is 49 for microvascular events, 43 for retinal photocoagulation, and 10 for major coronary events (fatal and nonfatal myocardial infarction, sudden death, heart failure, fatal and nonfatal stroke). The NNT is a powerful conversion to estimate how many patients must receive a therapy to see a result in one patient. An NNT of 50 estimates that 50 patients need to receive treatment to result in one good outcome during a specified time period.

We estimated the effect of better glycemic control in the Kaiser Permanente population based on the UKPDS findings. We assumed the effect of conventional compared to intensive treatment in the UKPDS was equivalent to the change from HbA1c levels >8% to HbA1c levels <8% in our cohort. We also assumed that the improvement in control in our cohort would be maintained over ten years, the duration of the UKPDS. Under these assumptions, we can expect to see 1,000 averted microvascular events, 1,200 averted cases of retinal photocoagulation, and 5,000 averted major coronary events over a decade as a result of this improvement in glycemic control.[2]

Using the results for randomized clinical trials, we can also estimate the impact of our programwide improvement in lipid control among our members with diabetes between 1998 and 1999. Between 1998 and 1999, 12,500 more KP members with diabetes had good lipid control.[3] Results from the West of Scotland Coronary Prevention Study (WOSCPS) (Shepard, Cobb, Ford, et al. 1995) suggest an NNT of 42 for primary prevention of myocardial infarction, stroke, and death over five years.[4] For secondary prevention of myocardial infarction, stroke, and death, the Scandinavian Simvastatin Survival Study (4S) (Pyorala, Pederson, Kjekshus, et al. 1997) subgroup analysis of diabetic patients suggested an NNT of 5 over six years, while the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) (LIPID Study Group 1998) suggested an NNT of 17 over five years.[5]

Our data suggest that 16 percent of our members with diabetes also have coronary artery disease (eligible for secondary prevention of cardiovascular events). If we assume that our improvements in lipid control among our diabetic population were comparable to those attained in the above-noted studies, and that our improvements were to be sustained for five to six years, we can estimate the impact of our improvements in lipid control. Among the 12,500 more members with good lipid control in 1999 compared to 1998, we could expect to see between 260 and 650 averted cardiovascular events (myocardial infarction, stroke, death) over five to six years.[6]

Our significant process improvements, however, have not yet had an impact on hospital utilization rates as the literature suggests. In fact, both the discharge and day rates increased from 1997 to 1999.

These evaluation results help achieve the program objectives described above by focusing on key clinical areas of diabetes care and reflecting CMI's evidence-based clinical guidelines. They promote a national effort and allow for interregional comparisons and lessons, another key objective of the IDC program. The results are used to improve and enhance the intervention by highlighting both successful Regions as well as Regions facing challenges. This enables shared learning and problem solving across Regions. The national outcomes reports also enable identification of common barriers across the organization that may require a national effort or study to address and solve. Finally, successful practices and key clinical focus areas can be built into other KP enterprise-wide initiatives, such as the clinical information system.

Member Survey

In addition to the annual outcomes reports, CMI conducts surveys of our members with chronic conditions. Member surveys complement the outcomes reports by providing information on self-management, satisfaction with care, self-reported health status, and other health measures not easily obtained from administrative sources.

CMI conducted our first survey of a random sample of members with diabetes in 1997 (Roblin, Ni, Solomon, et al. 1998). Overall, 12,075 members were surveyed across 21 member service areas. The overall response rate was approximately 60 percent (7,123 completed surveys). The survey included information on demographic characteristics (age, duration of diabetes, race/ethnicity), health care services (foot care, vaccinations, administration of aspirin, smoking cessation counseling), self-management, satisfaction with care, and self-reported health status (including smoking status).

In 2001 we plan to repeat our survey of members with diabetes. In addition to analyzing the data for distributions and trends, we also intend to link the survey data to our administrative measures to enable a richer exploration and analysis of the health status of our diabetic population.

Memorandum of Understanding Reporting

In addition to the annual diabetes outcomes reports, CMI supports quarterly reporting against selected measures in diabetes care. Reporting of these measures is specified in the Memorandum of Understanding (MOU) between CMI and each Region. The measures are linked to specific investments in care management programs, and reporting is conducted on a quarterly basis.

Case Study of Diabetes Care Management: KP Northwest Region

Beginning in 1988, the Kaiser Permanente–Northwest (KPNW) Region implemented a comprehensive diabetes care management program. Although the KPNW program preceded the creation of the CMI IDC, the programs are very similar in their approach to population-based care management of members with diabetes. Like the IDC program, some key components of the KPNW diabetes care management program include a functioning registry of diabetic patients, evidence-based clinical guidelines, focus on patient self-management, and diabetes "expert teams" composed of clinicians, nurses, and pharmacists (see Brown, Nichols, and Glauber 2000).

The relationship between the CMI IDC and KPNW programs has been mutually beneficial. In the creation of the IDC, CMI built on existing diabetes care management programs within Kaiser Permanente, including KPNW, by incorporating successful practices and lessons into our program. The KPNW program benefited from the CMI work through exposure to successful practices from other Regions as well as financial support and sponsorship for population-based care initiatives from the KP leadership.

The findings from the KPNW experience suggest the potential impact of a comprehensive diabetes care management program within the KP health system. The findings from this study conclude that "this centrally organized program, based in a primary care setting and utilizing a register of patients with diabetes, was associated with substantial improvements in the process and outcomes of care in a large population" (Brown, Nichols, and Glauber 2000). Substantial improvements were found in annual retinal screening, from 50 percent to 68 percent within two years; and in immunizations, from 40 percent to 60 percent within four years. Over the study period (1987 to 1996), significant improvements were also seen in testing for glycemic control, from 22 percent to 83 percent; nephropathy screening, from 1 percent to 43 percent; and lipid testing, from 37 percent to 56 percent (Brown, Nichols, and Glauber 2000).

External Performance Reporting

In addition to the reporting of clinical, process, and health outcomes measures for the annual CMI Diabetes Outcomes Reports, each Region is required to report on measures of diabetes care to the National Committee for Quality Assurance (NCQA) for the Health Plan Employer Data and Information Set (HEDIS). These data, which cover a broad range of health care areas, are used by NCQA for health plan accreditation and performance measurement. HEDIS has required reporting of eye examinations among diabetes patients for several years. In 2000 (for 1999 data), HEDIS also required reporting of a set of comprehensive diabetes measures. These measures included HbA1c testing and control, eye examination, lipid profile and control, and monitoring for diabetic nephropathy. Overall, KP performed well in all of these measures.7 In addition to HEDIS measures, the American Diabetes Association (ADA) has developed target measures for its Provider Recognition Program (PRP). These measures are intended to be applied to the performance of individual physicians to assess their care of diabetic patients (see Table 2).

TABLE 2. KP HEDIS DIABETES CARE RESULTS AND NCQA NATIONAL BENCHMARKS

HEDIS Measure	HEDIS 2000* 1999 Reporting Year KP Commercial Population (best performing Region)	HEDIS 2000* 1999 Reporting Year NCQA benchmarks Commercial Population		ADA PRP Target**
		75th percentile	90th percentile	
HbA1c Testing	80.8% (92.3%)	82.5%	86.6%	93%
HbA1c Poor Control	38.5% (23.2%)	34.8%	26.1%	<21%
Eye Exam	71.3% (83.8%)	54.0%	66.4%	61%
Lipid Profile	74.1% (87.7%)	76.2%	80.0%	85%
Lipid Control	46.5% (55.9%)	43.9%	48.5%	63%
Diabetic Nephropathy Monitoring	65.3% (80.6%)	44.3%	56.0%	73%

* Data obtained from Office of Performance Analysis, Kaiser Permanente, October 2000.

** American Diabetes Association: http://www.diabetes.org/ada

While the CMI diabetes measurement set includes measures that correspond to these HEDIS measures, the specifications for these two sets differ in meaningful ways that make direct comparisons between them impossible. Generally, the CMI measures leverage KP's access to higher-quality data compared to other health plans and/or capture outcomes with more clinical relevance than the HEDIS measures.

Future Evaluation

Archimedes Simulation Modeling

An important component of the evaluation of IDC programs in the future is Archimedes, a biomathematical simulation model developed by Kaiser Permanente that models both disease and care processes. By creating a population with diabetes and simulating the progression of diabetes as well as its complications, this model can estimate the impact of various care management investments and interventions. The estimates produced by Archimedes can be projected over an extended time frame, better capturing the true impact of care management investments. This model can aid in decision making and in evaluating alternative programs and interventions.

Program Evaluation

Following the establishment of case identification criteria and outcomes measures, CMI is now well positioned to expand our program evaluation activities. Four years of outcomes data allow for identification of time-based trends as well as successful practices in the Regions. In addition, CMI is moving toward creating an outcomes information system that includes member-level data. These data will enable testing of risk stratification methodologies, investigation of the impact of interventions on outcomes, correlation analysis between outcomes, and linking to member surveys.

Reflection and Generalization: Success Factors and Challenges

We have demonstrated that investment in an evidence-based population care management approach for adults with diabetes yields improvements in clinical processes and outcomes. The generalized success factors articulated at the beginning of this paper apply specifically to the success of our diabetes care management program.

Process (Collaborative Development and Deployment of the Policy)

To be successful, an improvement initiative needs to be sponsored actively and visibly by key leaders within the organization. Recognized experts need to lead and participate in the work. Finally, to create a viable program, those

responsible for implementation must be included in the development process.

An inclusive, collaborative model has been used in all stages of developing the diabetes care management program. National, interdisciplinary teams have collaborated in the development of the care management program as well as the national outcomes studies. Well-regarded clinical experts have been designated as project leaders.

The clinical guidelines are not mandatory. They are, however, strongly evidence-based and are being incorporated into clinical information systems to make the right thing easier to do.

Policy ("The Right Thing")

Applying the rigor of evidence-based medicine optimizes the organization's ability to define and achieve desired clinical outcomes. It also dramatically facilitates clinician acceptance and support, enabling more rapid and successful implementation.

In the first version of our IDC program (published in 1997), we failed to grade the strength of each clinical practice recommendation for the diabetes guidelines strictly on the basis of the quality of the existing evidence. Having gained additional appreciation for the importance of this rigor after the initial guidelines development effort, we added this information to the diabetes guidelines in the 1999 revision. The current clinical guidelines are strongly evidence-based. As the principles of evidence-based medicine become more ingrained in the fabric of Kaiser Permanente, guidelines based on solid clinical evidence are more readily accepted.

New clinical evidence in diabetes care emerges continually. For example, the Heart Outcomes Prevention Evaluation (HOPE) study was terminated early because of the dramatic reduction in relative risk of cardiovascular events, nephropathy, and retinopathy associated with the use of ramipiril, an ACE (angiotension converting enzyme)-inhibitor. Through the following mechanisms, the national care management program is well suited to quickly incorporating new clinical knowledge as it becomes available:

- Quarterly users' group teleconferences
- Periodic program revisions (the diabetes guidelines group reconvened in fall 2000 to formally incorporate the findings of the HOPE study into clinical practice guidelines)
- Ongoing review of evidence by clinical leaders and project managers
- Clinical information systems

CMI is currently creating a national "content network" of all the Kaiser Permanente groups involved in creating clinical policy, to provide a coordinated pipeline for clinical content to fuel our national clinical information system (see below).

Implementation ("Making the Right Thing Easier")

Program development is the simple part; sustainable improvements require ongoing sponsorship, leadership, and implementation support. The optimal pace of sustainable change can be achieved only through active engagement and support of stakeholders. The integrated diabetes care management program consists of much more than a collection of clinical guidelines. Implementation support materials include feedback reports, in-reach reminders, patient-driven reminders, clinician educational resources, and patient education resources. Financial support is provided to each Region for implementation. A national users' group meets quarterly to discuss implementation strategies and review new developments.

Information technology (IT) is the most powerful lever to make the right thing easier to do. Such support includes automated orders, reminders, feedback, registries, charting, and other decision support. Current IT systems support varies substantially across the KP Regions, and those with greater capabilities demonstrate superior performance.

The best clinical policy is not of value unless it is put into practice. The initial IDC program was published in binders and distributed to clinicians. This distribution method had the obvious shortcomings associated with a static paper system, including getting lost on the shelf and difficulty of updating.

KP is developing a clinical information system (CIS), technology tools to support care management such as a population-care registry (PCR), and an Internet- and Intranet-based clinical information Web site, Permanente Knowledge Connection (PKC). In addition, a Web site for members, KP Online, has been developed. It not only provides health information but also makes it possible to refill prescriptions and make appointments with physicians. This information technology provides the foundation for a powerful suite of clinical decision support tools for our clinicians, as well as for members with diabetes and other chronic conditions.

Publication of CMI's care management programs, including guidelines and tools, on the Permanente Knowledge Connection improved access and enabled efficient updating of content. PKC supports implementation in the following ways:

- Efficient search and retrieval of clinical content for diabetes care
- Rapid electronic search-and-retrieval access to clinical textbooks, journal articles, and news on diabetes care

- Online clinical discussion groups and minutes from diabetes users' group meetings

Currently the national content network is working to embed diabetes care management guidelines into Kaiser Permanente's national clinical information system (CIS). This puts the preferred clinical content into the daily operating practice of our clinicians in the form of automated orders for tests, procedures and prescriptions, outreach and in-reach to members, chart notes, and other decision support. Embedding clinical content into the CIS is ultimately the most powerful lever in making the right thing easier to do.

Kaiser Permanente's national automated population-care registry (PCR) has been implemented in two Regions to date. PCR provides an interface to regional legacy information systems and includes a variety of information on members with chronic illnesses, including diabetes. PCR enables care managers to generate automated feedback and in-reach and outreach reminders to clinicians and members. Compliance with various process measures, such as HbA1c screening, has increased significantly with the implementation of PCR.

KP Online, our national member Web site, allows diabetic members to automate appointment making and prescription refills and to access medical advice. It also is a convenient source of self-management information and tools for members, including reference materials and discussion groups. Tools under development include direct member access to medical record information, messaging between members and clinicians, and home glucose monitors linked to the clinical information system.

The rapid deployment of clinical information technology remains our single largest challenge and opportunity. Other implementation challenges include

- *Problems with centralized implementation support.* While we have a national program and policy, the focus of implementation is local. Our support of implementation at the local level has been successful, but our efforts to date at national implementation support have had mixed success. Currently we are reconfiguring our national implementation resources to support cross-fertilization of successful practices, training programs, mentorships, and development of tools and templates for local use.
- *Member self-management.* In terms of healthy behavior, healthy lifestyles, and shared decision making, members provide the vast majority of their chronic disease management themselves. The health care system interventions will not be successful if member self-management is not an integral component of the program.
- *Difficulties of managing care of members in contracted network facilities.* Some of the most difficult challenges in implementing our diabetes care management program have been in those Regions with significant numbers of members who receive care in contracted, non-KP facilities. Challenges include limitations of automated information systems, non-KP clinicians delivering care without access to our clinical guidelines or implementation support materials, and lack of process and utilization data.
- *Regional capabilities and preferences.* The KP Regions differ from one another greatly in terms of systems support and other care management capabilities and preferences. To recognize these differences, the clinical guidelines are presented typically as minimum standards, which some Regions choose to exceed. For example, for aspirin use, the original guideline indicated that there was not evidence to support use for members without coronorary artery disease (CAD). However, some Regions objected, so the language was modified to include optional aspirin use for members without CAD. Similarly, some Regions have chosen aggressive low-density lipoprotein cholesterol (LDL-C) targets for primary prevention, although there is not strong evidence in support of that strategy. The guideline includes a footnote acknowledging that some consensus-based guidelines recommend such treatment, and that the decision should be made jointly by the provider and patient, taking into account the patient's values and risk factors.

Measurement ("You Manage What You Measure")

Measurement informs and motivates change. Many improvements in care management are long-term, difficult to achieve, and hard to measure. Nevertheless, it is important to quantify improvements in objective measures of performance and clinical outcomes. Outcomes measurement informs progress, identifies issues, builds momentum, and serves as a powerful communication vehicle for clinicians and operational managers as well as senior leadership. The current KP national diabetes measurement system is a resource unique in the health care industry, with multiple applications. Challenges and opportunities remain:

- While registries can be used for patient/population management, comparative Regional outcomes reports, and HEDIS reporting, the different purposes require different emphasis on sensitivity versus specificity of the measurement specifications. Interregional comparisons emphasize specificity—ensuring that those identified with the condition really have it—to facilitate Regional "apples-to-apples" comparisons. However, feedback and reminder systems emphasize sensitivity—ensuring that those with the condition are included—so that they can receive needed health care services. In addition, HEDIS measures require a common denominator of measures across all types of health plans in the country. For example, the national outcomes reports require continuous enrollment for a specified period for individuals in the cohort to ensure consistency across Regions and enable calculation of use rates. However, we would never impose a minimum enrollment period to provide needed care to members. The different measurement specifications for different applications create complexity and additional work. Automation of clinical registries will make the use of alternative measurement specifications and inclusion

criteria less burdensome.

- Cost data, especially in a health care system founded on the principles of prepayment, are difficult to obtain, and therefore it is difficult to assess the cost-effectiveness of interventions. Cost-effectivenss analysis will be facilitated as Regions develop cost-management information systems, coupled with better encounter diagnosis and a member-level national outcomes data base.
- Improvements in health often take many years to measure in a population, yet there is ongoing budget pressure to demonstrate the value of our care management investments against competing priorities. Also, it is difficult to isolate the impact of a single intervention on a specific target and therefore attribute the "credit" to the CMI investment in a complex and dynamic health care system. As CMI has established credibility and demonstrated success, the organization has become more willing to take a longer view of the benefits of care management investments. We are modifying the contracting process with Regions to cover a three-year period for both investments and benefits. In addition, our "Archimedes" simulation modeling capability is being utilized to test alternative policies and guidelines, and to project longer-term health and financial outcomes of process improvements.
- True outcomes data are difficult to obtain from administrative data since they require member self-reporting of functional health status. In addition, member surveys are costly and reach relatively few members. We are working to develop tools to gather member self-reported data on a more regular and routine basis to improve feedback to clinicians and enhance our national outcomes reports.
- Changing performance measures and targets challenge our ability to measure changes in KP performance over time. While we endeavor to maintain consistent inclusion criteria and measures, new evidence, technology, or external standards require changes. For example, when HEDIS adopted an HbA1c target of 9.5, we needed to change our threshold of 10.0 in order to be consistent.

EPILOGUE

In an effort to assist Kaiser Permanente Regions in improving the care provided to members with diabetes, the Care Management Institute has undertaken a number of initiatives to support implementation of the Integrated Diabetes Care Program.

Users' Group Calls

Each quarter, CMI convenes and facilitates a users' group call of diabetes experts and practitioners across the program. In November 2000, the diabetes users' group call focused on reducing hospital admissions and length of stay among members with diabetes. Dr. Resa Levetan from Washington Hospital and Dr. Harry Glauber from Kaiser Permanente Northwest spoke on approaches to this crucial issue in diabetes care. Their presentations covered the rates and costs of hospital admissions, as well as strategies to reduce admissions and length of stay. Specific topics included the use of IV insulin to achieve glycemic control of diabetic patients in the hospital, prevention of admissions through a revised advice nurse protocol, consultation with a diabetes practitioner prior to admission from the emergency department, and prevention of admission through patient and physician outreach on lipid control, smoking cessation, blood pressure control, and aspirin therapy.

During the call, the users' group agreed that there was sufficient evidence to support each KP Region having a program in place to decrease hospital days and/or control in-hospital glucose levels among patients with diabetes. The priorities identified for these programs included:

1. Ability to control glucose <200 mg/dl at discharge is assessed and education provided early if needed.
2. Glucose testing is administered automatically upon entrance to the hospital.
3. If glucose is >200, someone is automatically contacted to correct and implement long-term control (surgical services may be the highest opportunity area in which to start).
4. If the patient is at high risk for CAD/ESRD, the patient is started on ASA, ACE, cholesterol lowering, and smoking cessation where appropriate.
5. A case manager is to be involved to remove barriers to discharge (ensure appropriate discharge medication).
6. Outpatient training/assurance of appropriate medication is provided to prevent readmission.

While the users' group calls have been valuable, we still have less than half of the clinical champions involved, in part due to the constraint that clinicians are not allowed any additional time out of schedule to attend.

Quarterly Reporting of Core Diabetes Measures

Each year, CMI develops a memorandum of understanding (MOU) with each Region specifying the allocation of care management resources and targeted achievement on clinical effectiveness and efficiency goals. The MOU process includes quarterly reporting on progress toward these effectiveness and efficiency goals. For 2001, CMI instituted reporting on core measures in key disease areas, including diabetes. Reporting on core measures will enable improved comparisons across Regions, as well as facilitate identification of both successful and struggling programs across KP. The core measures for diabetes are:

- Glycemic testing and control
- Lipid testing and control

- Retinopathy screening
- Renal screening

Physician-Based Decision Making for Formulary Selection

Kaiser Permanente employs a physician-based decision-making process for the selection of medications for formulary inclusion. Regional- and facility-based pharmacy and therapeutic committees have been established to conduct reviews of FDA-approved drugs for formulary addition or deletion. Drugs are evaluated based on safety, efficacy, quality, member convenience, and, where appropriate, cost.

In Northern California, for example, evaluations may be initiated at the request of any Permanente Medical Group physician, facility, or Regional pharmacy and therapeutic committee, chiefs of service committees, or Drug Information Services, a division of Pharmacy Services. Subsequently, an elaborate assessment and approval process is initiated, including an evidence-based analysis of the drug under consideration in relationship to similar formulary products. A drug monograph is prepared, including a preliminary recommendation regarding formulary inclusion. Subsequently, additional reviews are obtained from Regional chiefs of service committees, task forces, and advisory panels. In addition, the advice of individual subspecialists or selected physician groups may be solicited. Consensus recommendations are obtained from the various clinical expert groups.

The Regional pharmacy and therapeutic committee, after reviewing the many expert opinions and recommendations, votes for inclusion in the formulary. In some instances the Regional pharmacy and therapeutic committee may restrict the drug to physician specialist usage. Typically, these are drugs with a narrow safety margin, significant potential for inappropriate use, or a condition requiring specialty expertise. It should be noted that the voting members of the Regional pharmacy and therapeutic committee are physicians, with the exception of the vice president of pharmacy strategy and operations. Decisions are broadly and rapidly communicated to all physicians, utilizing email, newsletters, and the Kaiser Permanente Intranet site.

Each of the drugs used to treat our diabetic patients has been subject to this process prior to formulary approval. It should be noted, however, that when in the opinion of the treating physician a non-formulary drug is medically necessary, that drug may be prescribed without prior authorization. The intent is clearly not to construct barriers to the provision of optimal medical care.

Award-Winning Diabetes Programs

Three programs in the Kaiser Permanente network—Hawaii, Group Health Cooperative (GHC), and the Northwest—earned the top three spots on the National Committee for Quality Assurance's list of the leading managed care organizations for people with diabetes in 2000. The Programwide IDC also earned the American Association of Health Plans' Exemplary Practice Award for Diabetes in 2000.

GLOSSARY

ADA
American Diabetes Association

Archimedes
CMI's biomathematical simulation model (see CMI, below)

CAD
coronary artery disease

CAHPS
Consumer Assessment of Health Plans Survey

CIS
clinical information system

CME
continuing medical education

CMI
Care Management Institute (of KP)

CMS
Centers for Medicare & Medicaid Services (formerly the Health Care Financing Administration, or HCFA)

DQIP
Diabetes Quality Improvement Project

FACCT
Foundation for Accountability

4S
Scandinavian Simvastatin Survival Study

GHC
Group Health Cooperative (affiliated with KP)

HCFA
Health Care Financing Administration (renamed the Centers for Medicare & Medicaid Services, or CMS)

HEDIS
Health Plan Employer Data and Information Set

HMO
Health Maintenance Organization

HOPE
Heart Outcomes Prevention Evaluation

IDC
Integrated Diabetes Care

IT
information technology

KP
Kaiser Permanente, comprising

KFH (Kaiser Foundation Hospitals), **KFHP** (Kaiser Foundation Health Plan), and
PMGs (Permanente Medical Groups)

KPNW
KP's Northwest Region (encompassing chiefly the Portland, Ore., and Vancouver, Wash., areas of Oregon and Washington states)

KP Online
national KP member Web site

LDL-C
low-density lipoprotein cholesterol

LIPID
Long-term Intervention with Pravastatin in Ischaemic Disease

Medicaid/Medicare
(see Appendix C)

MOU
Memorandum/Memoranda of Understanding

NCQA
National Committee for Quality Assurance

NNT
numbers needed to treat

PCR
population-care registry (of KP)

PKC
Permanente Knowledge Connection (national KP clinical Web site)

PRP
Provider Recognition Program (of the ADA)

RCT
randomized controlled trial

Region
areas of the United States in which KP physicians practice (e.g., see KPNW)

UK
United Kingdom

UKPDS
United Kingdom Prospective Diabetes Study

WOSCPS
West of Scotland Coronary Prevention Study

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APPENDICES

Appendix A. Overview of KP-CMI's Integrated Diabetes Care Program

Evidence-Based Clinical Guidelines

Clinical practice guidelines for adult diabetes care are the core of the IDC program and consist of a series of evidence-based algorithms and protocols to assist in screening, treating, and referring patients depending on their specific circumstances. The guidelines are written in a concise, instructive style designed to enable primary care physicians and other clinicians to use the IDC materials easily. National guidelines also increase the consistency of care across the organization and reduce the need for local guideline development. Key components include recommendations for glycemic screening and control, renal screening, and screening and referral guidelines for retinopathy.

To remain current, new evidence is reviewed and our guidelines are updated and revised biennially. To facilitate our clinicians' ability to incorporate these evidence-based clinical recommendations into practice, our guidelines are widely distributed in paper and electronic form. In addition, guideline recommendations are incorporated into clinical technology tools, including point of service reminders, in-reach and outreach tools, our population care registry, and our clinical information system.

Model of Care

The model of care is the infrastructure and process for managing and delivering patient care. The model of care has four important components: population identification through a registry; stratification of patients; commitment to a team approach; and evaluation of care. In addition to descriptions of key components, our recommendations for models of care include examples of models being used within Kaiser Permanente. The inclusion of a variety of models enables our program managers to select models or combine elements of models to best adapt ideas to their local environment.

Population Identification through a Registry

The main purposes of a diabetes registry are to identify and sort the diabetes cohort, track services, target the patient population whose care is to be coordinated, and evaluate treatment outcomes. A registry can also be used to generate targeted mailings or clinical feedback reports and for other quality improvement projects. Reports also can be generated to show employers the care that their at-risk employees are receiving from Kaiser Permanente.

Stratification of Patients

Stratification is used to identify subgroups of members with common sets of needs and resource requirements and to segment the population into groups most likely to benefit from different levels of intervention. The stratification methodology used for a given population is determined by size of the population, local leadership's program objectives, staffing expectations, and the extent to which enabling technologies can be used to serve larger numbers of patients.

The stratification methodology is intended to be coupled with other aspects of the IDC program (i.e., patient education, group visits, and programs for self-management of chronic disease) that provide direct service to patients. The stratification methodology creates three tiers of patients with diabetes. The patients with the least severe disease are well controlled and usually have no evidence of end-stage organ damage. These patients will continue to receive most services in the usual way from their primary care physician or health care professional. Patients with the most severe disease have major, multiple complications and often require subspecialty services. These patients are potential candidates for "case management." Between these two extremes is a sizable cohort of patients who have clinically significant diabetes care needs but whose care management can be handled well through a care coordination system.

Commitment to a Team Approach

The model of care is a team approach in which specific responsibilities are assigned to different clinicians (e.g., a care coordinator, diabetes educator, primary care physician, or eye-care specialist). The care coordinator's role is particularly noteworthy, as it is central to the management of diabetic members.

Care coordinators rely on treatment algorithms and on feedback from supervising physicians to manage their patient panel. Typically, the care coordinator will follow approximately 1,000 patients, but will actively manage the care of 100 to 150. During the period of active management, patients are interviewed to evaluate their personal barriers to self-management, coached to set and follow up on specific, attainable behavior change goals, have their key clinical parameters actively managed, and are then discharged back to their primary care providers with explicit follow-up instructions.

Care coordination is intended to enhance the primary care for patients with diabetes by addressing the critical aspects of management for those patients most in need. Because it focuses attention on the patients most likely to encounter significant and expensive complications, and because it addresses the aspects of care that are likely to have the greatest impact, care coordination is a cost-effective approach to managing diabetes.

Evaluation of Care

All implementation should be evaluated to determine what is working and what really makes a difference. Evaluation at local sites focuses on

- Determining priorities for patient stratification
- Evaluating the ability of physicians and other health care professionals to interpret and use stratification reports
- Assessing the success of the stratification method at directing at-risk patients to care coordinators for an intensive level of care management
- Measuring the impact on patients' health status, self-confidence in managing their own disease, and satisfaction with care
- Interpreting whether stratification increases process efficiencies, i.e., by reducing the need for physician visits and hospitalizations

Clinician Resources

Clinician resources include pocket cards, screening tools, a risk calculator, and electronic reminders. In addition, to help clinicians remain at the forefront of diabetes care, we also developed an online continuing medical education (CME) module for diabetes care. This is founded on our evidence-based clinical guidelines and allows clinicians to test their knowledge of current diabetes care recommendations while earning CME credit. Our diabetes program also includes a significant section focused on change management. This module of our program is based on behavior change theory and targets enabling and sustaining positive change for both clinicians and patients.

Patient Resources

Patient resources in the IDC include tip sheets, a diabetes action plan, a personal care and testing record, and Web-based tools for self-management. Patient self-management is a critical component of any diabetes care management program. Because diabetes is a complex and lifelong disease, empowering patients and involving them in their own care is critical to achieving and sustaining positive outcomes and quality care. Our patient self-management tools, like our clinical guidelines and models of care, are based on evidence in this field and represent the best tools available.

Another key component of the IDC program is integrated patient education. The patient education component of the IDC encourages members with diabetes to participate in group visits. The groups give members an opportunity to talk with others who face similar problems and to increase the number of educational encounters they have with Kaiser Permanente.

To change the traditional, didactic method of diabetes education, patients are asked to set and pursue specific, attainable goals and to develop individual self-management skills. Educational messages are tailored to each patient's readiness for change and to each clinician so that they are continually reinforced.

Measurement System

The measurement system of the IDC enables demonstration of results achieved, identification of areas for improvement, and evaluation of the success of the program across Kaiser Permanente, in addition to allowing interregional comparison and identification and sharing of successful practices across Regions.

Our measurement work is focused primarily on annual national outcomes reports. These national studies include data from all Regions on clinical, process, and health outcomes among our 330,000 members with diabetes. The measures for these reports are aligned with our clinical guidelines and with evidence in the literature on relevant outcomes for diabetes care. These reports are produced annually, allowing for identification and tracking of trends.

As a component of this process, the measures included in the report are reviewed each year by an interregional advisory group of clinical and measurement experts in diabetes care. Measures are evaluated for their evidence basis, relevance, feasibility, value, and degree to which they can be acted on. For example, measures that cannot be captured through administrative data sources do not meet the "feasibility" criterion and are therefore not included in the measurement set. Likewise, measures can be added to the measurement set based on advances in the field or

advances in our ability to capture data.

In addition, CMI regularly surveys members with diabetes to collect data available only from patients (e.g., self-perceived health) or that cannot be measured reliably from other data sources (e.g., foot examinations by physicians). The patient data survey summarizes measures of medical care interventions, self-care attitudes and behaviors, satisfaction with medical care, and patient perceptions of health status.

Implementation

The primary strategies used to effect successful implementation of the IDC include

1. *Feedback reports.* Provision of clinical and administrative data that help clinicians identify patients with specific risk factors (e.g., LDL>130).
2. *In-reach reminders.* Supplied to clinicians at the moment of care to highlight key variables and desired actions.
3. *Patient-driven reminders.* Preventive health prompts, outreach letters that describe available Kaiser Permanente resources, and self-management tools.
4. *Clinician educational methodologies.* Diabetes management clinician pocket reference guide, academic detailing by physician champions with their peers, online CME, and "expert teams" that mentor primary care clinicians in the care of high-risk diabetic patients.
5. *Patient educational methodologies.* Diabetes tip sheets, group appointments for members with diabetes, and an educational curriculum that emphasizes self-management skills.

Technology is also a key aspect in effective implementation. Technology tools for population management are essential for care coordination. These tools make it possible to quickly identify patients in trouble—for example, those who are not filling prescriptions or whose blood glucose levels are becoming dangerously high—and to remind care coordinators about scheduled follow-up care. Technology tools are also used to send messages to care providers and to patients.

In the absence of technology, other tools can assist in care management. For example, CMI has developed a template for a paper version of "speed charting" for patients with diabetes. The speed-charting template allows clinicians to easily check and record pertinent clinical data at routine scheduled visits. A personal diabetes record is another paper-based way to monitor the health status and treatment history of diabetic patients in the absence of technology tools. Patients are encouraged to use a wallet-size card to record their medical visits and laboratory test results. They take the wallet card with them when they visit their physician or other member of the diabetes care team, using it to discuss aspects of their care.

The IDC provides an opportunity to improve health status and outcomes for thousands of Kaiser Permanente members while assisting physicians and other health care professionals. The program provides tools and templates to help physicians manage their desk work and gives opportunities to focus on care, instead of cure. Over the past four years, the IDC has become a mature national Kaiser Permanente care management program and has served as the model for other successful national care management programs, including cardiovascular care, asthma, depression, and elder care. New programs are under development for chronic pain and cancer care.

Appendix B: CMI Diabetes Guidelines

The guidelines can be accessed via the Permanente Knowledge Connection, KP's clinical information Web site, at http://pkc.kp.org.

Appendix C: Kaiser Permanente: A Legacy Born of Challenges

The ideas that shaped Kaiser Permanente emerged from a series of environmental challenges. While thousands of men sought to meet the challenge of bringing Colorado River water to Los Angeles during the Great Depression with the 240-mile-long aqueduct across the Mojave Desert, a Kaiser Permanente founder wrestled with how to provide these workers with quality health care. As huge numbers of workers tackled the challenge of constructing the Grand Coulee, the largest dam in the history of the world, the organization that would become Kaiser Permanente tackled the challenge of making prepaid health care work to the benefit of these men and their families. When World War II demanded that the shipyards in Richmond, California, and Vancouver, Washington, construct ships in record time, Kaiser Permanente was meeting the demands of caring for the workers and battling for legitimacy among our peers and our critics.

Sidney Garfield, the physician founder of Kaiser Permanente, developed an idea that reversed the economics of medicine and changed American health care financing forever: prepayment for comprehensive medical coverage. Harold Hatch, an engineer-turned-insurance agent, suggested to Garfield that insurance companies agree to pay the doctor 5 cents a day for each worker covered. For a payroll deduction of another 5 cents a day, a worker could receive coverage for non-job-related medical problems. With thousands of workers enrolled, Garfield's health care idea soon became a financial success.

The introduction of prepayment enabled Garfield to encourage safety and health activities rather than just treating the ill and injured. He persuaded contractors to have their men pound down nails, and he inspected tunnels to combat the two

most common injuries—nail punctures through rubber-soled boots and head injuries caused by falling rocks or protruding shoring.

This focus on prevention changed the economics of medicine by focusing on keeping the patient healthy rather than treating the illness. *Prevention, partnership* between medicine and management, *integration* of all of the elements of health care services, provision of *comprehensive benefits*, and *choice* of physicians have remained defining principles for Kaiser Permanente.

Kaiser Permanente continues to be shaped by the challenges confronting the country's health care environment. The birth and continued existence of the Care Management Institute, for example, have coincided with major environmental shifts that are influencing the way medical care will be delivered in the 21st century. The number of people with chronic diseases is growing, with expectations that by 2010, 40 percent of the American population will be living with one or more chronic conditions. New and costly therapeutic interventions are forcing Kaiser Permanente to ensure that there is a sound evidence basis for changes in medical practice. Advances in information technology have fostered members' demand for substantive clinical information and active participation in their medical decisions. The rising cost of providing health care and the corresponding increase in members' dues have challenged Kaiser Permanente to be a better steward of its resources and to develop new ways of delivering high-quality, cost-effective care to populations.

Since its inception in 1997, the Care Management Institute has been committed to responding to these external forces in the context of the principles and practices of Permanente Medicine. CMI's primary focus has been to establish the infrastructure and relationships necessary to support the delivery of high-quality, evidence-based medicine for priority populations in an integrated delivery system. In a practical sense, CMI leverages the resources and intellectual capital possessed by Kaiser Permanente physicians and health care professionals and helps to distribute it throughout the organization. At the same time, CMI serves as a bridge between the Permanente Medical Groups and the Kaiser Foundation Health Plan, catalyzing the types of discussions that ensure alignment between medical values and management realities.

This ability to respond to environmental shifts has made Kaiser Permanente America's oldest and largest private, nonprofit, integrated health care delivery and financing system. Founded in 1945, the group-practice prepayment program has its headquarters in Oakland, California. Today, Kaiser Permanente serves the health care needs of 8.2 million members in 10 states and the District of Columbia. It encompasses Kaiser Foundation Health Plan Inc., Kaiser Foundation Hospitals and their subsidiaries, and the Permanente Medical Groups. Kaiser Permanente also has an affiliation with Group Health Cooperative (GHC), based in Seattle, Washington. Nationwide, Kaiser Permanente includes about 90,000 technical, administrative, and clerical employees and about 11,000 physicians representing all specialties.

Blue Prescriptions: A Program in Transition

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EXECUTIVE SUMMARY

This report describes collaboration between researchers and policymakers and the use of evidence in the process of evaluating new drugs for health care insurance reimbursement in Norway; drugs thus approved are called "blue prescriptions" because they are written on blue paper. The authors studied five controversial decisions taken in the Ministry of Health and Social Affairs through the review of available documents; through discussions among the authors, who were participants to varying degrees; and through review of earlier drafts of this paper by other participants in the processes described, as well as by the authors of other papers in this report and two external referees. The aim was to gain insight into the decision-making procedure and thereby identify possible areas for improvement toward a more rational and explicit process for setting priorities.

The drug reimbursement program has developed in the light of Norwegian welfare policies and consists of a patchwork of regulations. Changes in the program during the 1990s have aimed at a stricter emphasis on cost-effectiveness, but even so, assessments of drugs have been largely informal, with consultation of external experts occurring only on an ad hoc basis. This somewhat unstructured procedure has created an environment sensitive to lobbying efforts by experts and representatives of the pharmaceutical industry to influence policymakers in the Ministry of Health and Social Affairs and politicians in Parliament, resulting in considerable impact on the decisions made in the examples reviewed.

INTRODUCTION

The Norwegian Health Care System

The Norwegian health care system has developed in the context of welfare policy in Norway, where equality and justice have been highly valued. All individuals should have equal access to a decent standard of living, work, a place to live, and coverage of crucial health and social services independent of where they reside or their economic situation.

Following from this welfare policy, a key feature of the health care system is the predominance of tax-financed public provision. The hospitals and the primary health care system have been financed largely through block grants from the central authorities and contributions or reimbursement from the state-owned National Insurance Scheme. Membership in this program is mandatory and universal, and is financed by compulsory contributions by employees and employers. The National Insurance Scheme covers retirement pensions, disablement benefits, sickness benefits, unemployment benefits, and health care, including drugs.

There is a co-payment by patients for ambulatory care and co-payment for reimbursed drugs. The ceiling for the total co-payment by a patient is 1,450 Norwegian kroner (NOK) ($U.S.160) per year.1 Expenses above this amount (for reimbursed drugs and ambulatory care) are covered by the insurance program.

Overall planning of the Norwegian health care system has been relatively centralized at the federal level, whereas responsibility for providing most services has been transferred to the county (for primary care) and municipality (for secondary care), with the aim of providing necessary services locally even in remote areas. Based on health status indicators, such as perinatal deaths or life expectancy at birth, the Norwegian population is relatively healthy compared to other OECD (Organisation for Economic Co-operation and Development) countries (OECD 1998). The health care system has, nonetheless, faced problems of long waiting lists and shortages of health care professionals for many years. One response to this has been changes toward a more output-based system in which hospitals and physicians are paid according to activity, for example, through introducing the use of Diagnosis-Related Groups (DRGs) in the funding of hospitals. Additional changes are currently being implemented. The current government has proposed restructuring the ownership of hospitals so that each hospital will be an independent unit directly organized under the federal government. Partial capitation is being implemented this year (2001) in primary care, which has been predominantly fee-for-service-based. Under the new system general practitioners will have contracts for a list of patients and must fulfill specified obligations for providing service to listed patients. This reform is, in part, intended to increase the gatekeeping role of general practitioners and reallocate physicians to underserviced areas.

Drug Expenditures in Norway

The Norwegian National Insurance program covers approximately half of all drug expenditures; patients pay directly for one third, and hospitals and nursing homes cover the rest. Based on sales figures, a total of approximately 9 billion NOK ($990 million) was spent on prescription drugs in 1999 in Norway for a population of 4.5 million people. During the last 12 years, reimbursement expenditures have grown at an annual rate of 10 to 13 percent (approximately 8 percent in fixed prices). In 1988 the public drug bill was 2.6 billion NOK ($283 million)—0.4 percent of the gross national product (GNP), or 610 NOK ($67) per capita. In 1998 the amount was 6.7 billion NOK ($739 million—0.6 percent of the GNP, or 1,520 NOK ($167) per capita (Table 1).

TABLE 1. PUBLIC SPENDING ON HEALTH CARE AND DRUGS, 1988-1998

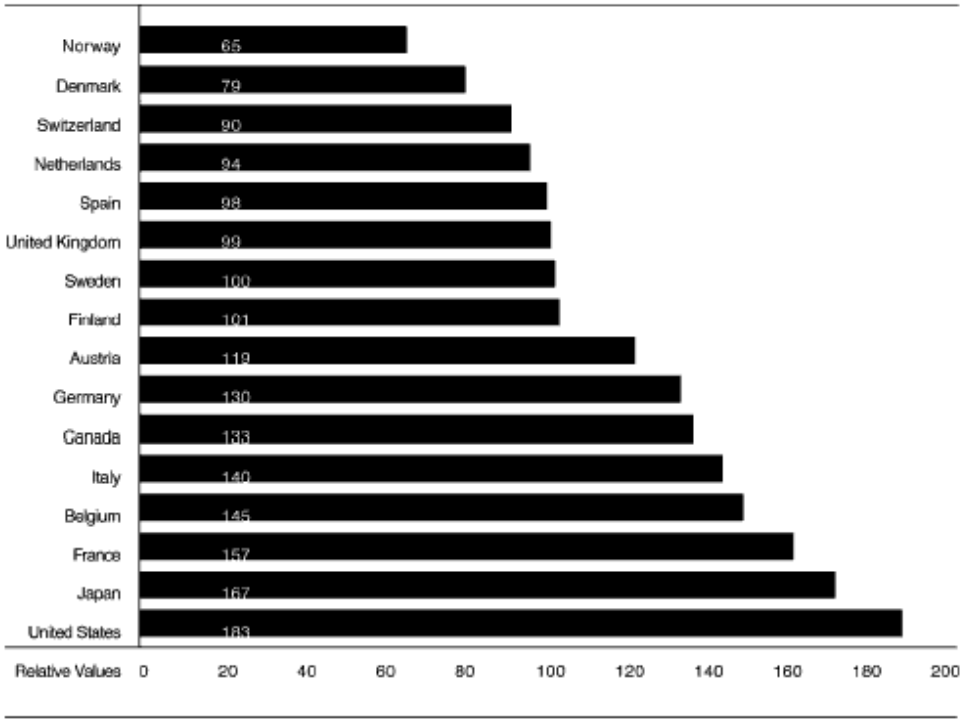
Year	GNP Million NOK	Public Health Care Expenditures		Public Drug Expenditures		Public Drug Expend. per Capita
		Million NOK	% of GNP	Million NOK	% of Health Care Expenditures	
1988	639,591	42,351	6.6	2,573	6.1	610
1989	682,347	43,105	6.3	2,806	6.5	663
1990	722,071	45,675	6.3	3,191	7.0	751
1991	762,774	50,352	6.6	3,582	7.1	838
1992	784,296	52,550	6.7	3,953	7.5	919
1993	823,339	54,036	6.6	4,277	7.9	969
1994	869,742	56,145	6.5	4,585	8.2	1,054
1995	925,866	60,390	6.5	5,053	8.5	1,156
1996	1,017,794	65,850	6.5	5,454	8.3	1,242
1997	1,084,788	71,985	6.6	6,014	8.5	1,383
1998	1,107,082	79,843	7.2	6,715	8.4	1,520

Source: Norweigan Board of Health

There are two main reasons for this growth: increased drug use and increased prescribing of new and more costly drugs. Price increases have not been an important factor behind the increase in drug expenditures.

Several measures to curb the growth in drug expenditures have been launched. In 1992 patient co-payments were raised from 20 to 30 percent of each prescription for people between 16 and 67 years of age. In 1993 a reference price system was introduced, limiting reimbursement to the cost of the cheapest comparable drug available (for example, generic and parallel imports). If a more expensive drug is prescribed, the reimbursement will cover only 70 percent of the cost of the cheapest comparable drug. (The reference price system has been criticized and was ended in January 2001 [*Evaluation* . . . 2000].)

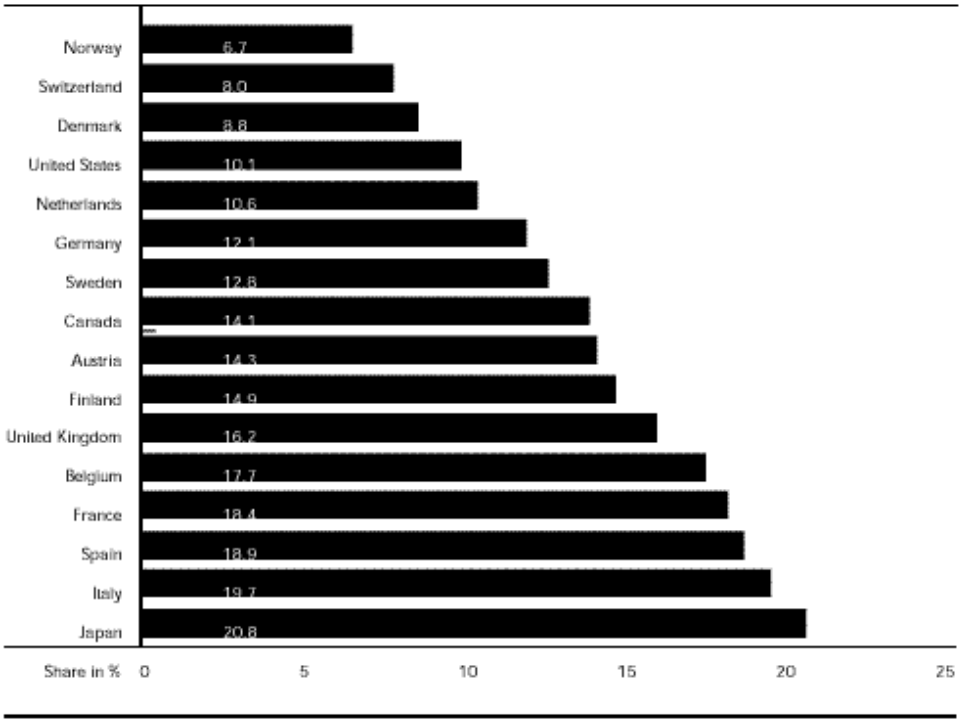
FIGURE 1. PHARMACEUTICAL CONSUMPTION PER CAPITA IN THE OECD, 1997, IN RELATIVE VALUES



Source: OECD 1998.

Despite the growth in drug expenditures, Norway still spends less money on drugs than other OECD countries. Figure 1 shows pharmaceutical consumption in relative values. OECD data demonstrate that in 1997 the United Kingdom spent 6.8 percent of its GNP on health care and 1.1 percent on drugs. The United States spent 13.9 percent of its GNP on health care and 1.4 percent on drugs. Norway, on the other hand, spent 7.5 percent of its GNP on health care and 0.5 percent on drugs. (OECD numbers are slightly different from national data from the Norwegian Board of Health due to different methods of calculation.) Public spending on drugs as a percentage of public health care expenditure in 1997 varied from 6.7 percent in Norway to 20.8 percent in Japan (Figure 2).

FIGURE 2. PUBLIC SPENDING ON DRUGS AS A PERCENTAGE OF PUBLIC HEALTH CARE EXPENDITURES, 1997



Source: OECD 1998.

Because a large proportion of drug expenditures is covered by blue prescriptions, there is an economic incentive for pharmaceutical companies to add new drugs to the reimbursement list in Norway. The consultation process for decisions about adding new drugs to the reimbursement list has been largely informal. Denials to add new medications to the list have been met with heavy criticism from drug companies via the mass media, specialists, and lobbying of Parliament.

OVERVIEW OF THE DRUG REIMBURSEMENT PROGRAM

The first drug reimbursement program was launched in 1953. The main aim was to introduce free prescriptions for drugs that were considered important to the public's health, commonly referred to as blue prescriptions. The blue prescription program, along with other existing programs, was later made a part of the National Insurance Scheme, which is overseen by the National Insurance Administration. In 1981 Parliament introduced co-payment by patients; co-payments are currently set at 36 percent of the amount of each prescription, with a limit of 360 NOK ($40) and a ceiling of 1,450 NOK ($160) per year.

Reimbursement is provided only for "long-term" medication for chronic diseases, defined as more than three months' worth of medication per year. In general the reimbursement program does not cover short-term therapy (for example, antibiotics for pneumonia). The social welfare context in which the program has developed has led to a number of "escape" clauses to ensure that social welfare goals, particularly equity, are achieved. There are four main ways in which drugs can be covered (Box 1). Items A and C require that the drug has been approved for reimbursement. Drugs in groups A and C will, when first approved by the authorities, be reimbursed automatically, while drugs in groups B and D require a formal application for each patient.

BOX 1. WAYS IN WHICH DRUGS CAN BE COVERED

A. Doctors prescribe medication specified on an approved list. The medication must be prescribed for the particular conditions listed in the "disease list" under this paragraph.
Examples: alendronate (Fosamax) for osteoporosis, statins for hypercholesterolemia.

B. Individual application from specialists. Only relevant specialists can apply for reimbursement based on criteria that an individual patient does not respond to first-choice drugs or cannot use first-choice drugs for other reasons. In some cases costly drugs can be reimbursed for diagnoses not included in the diagnosis list.
Examples: montelukast (Singulair) for asthma, interferon b (Betaferon) for multiple sclerosis.

C. Full reimbursement for drugs for specified communicable diseases.
Examples: drugs for syphilis, tuberculosis, HIV/AIDS.

D. Individual claims for support for large expenditures by patients. This covers large expenditures for drugs not covered by the blue prescription program.

The National Insurance Administration operates with two lists: one for approved conditions, and a corresponding one of approved groups of drugs. The groups in the drug list are variably defined; in some cases the chemical compounds are clearly specified (e.g., nitrate compounds), while in others the specifications are very broad (e.g., antidepressants). Drugs approved for general reimbursement (group A) must be licensed to treat one of the listed conditions and belong to an approved drug group. More than 90 percent of total reimbursement expenditures arises from group A. If a drug is not licensed for the listed diagnosis or is not on the "positive list" of reimbursed drugs, it can still be approved for reimbursement based on individual applications (group B). Group C is a remnant from a policy established to eliminate communicable (mainly sexually transmitted) diseases and recently has been revised. Group D fulfills the social intentions of the program; there is no need to document the severity or duration of the disease or of a drug's beneficial treatment effect to apply for coverage in this group. The out-of-pocket expenses are much larger for drugs reimbursed in group D than in the other groups.

Procedures for Assessing Blue Prescription Applications

The Medicines Control Authority is responsible for the licensing of drugs, while the National Insurance Administration has had, until recently, responsibility for approving drugs for reimbursement. To obtain marketing authorization for a particular drug a pharmaceutical company must document the efficacy, safety, and manufacturing quality of its product. The Medicines Control Authority assesses this documentation and makes any licensing decision on the basis of data from clinical trials. To obtain authorization, the effect of the drug must be better than or equal to standard treatment or, if there is no established standard, a placebo. After marketing authorization is granted, the pharmaceutical company must apply to the Medicines Control Authority to set a maximum price, which is usually based on the average of the three lowest prices in Germany, United Kingdom, Ireland, the Netherlands, Belgium, Austria, Denmark, Sweden, and Finland. At this stage there is no assessment of the cost-effectiveness of the drug.

Pharmaceutical companies have up to now applied to the National Insurance Administration for inclusion in the reimbursement program, but recently the responsibility for approving the addition of new drugs to the list of reimbursable medications has been transferred to the Medicines Control Authority, which concurrently has changed its name to the Norwegian Medicines Agency. (However, in this report we refer to the Medicines Control Authority throughout, since the recent administrative and name changes occurred after most of the events reported here.) What follows is a description of the roles of the institutions as they have existed until the present.

Along with the application, the pharmaceutical companies usually provide a selection of relevant publications and sometimes an economic analysis. Until recently the National Insurance Administration has made its own evaluation of a given drug in terms of effectiveness and cost to the reimbursement budget, with consideration given as well to juridical and administrative issues. Implicitly, the efficacy should be documented, but no formal procedure for how to do this has been established; nor has there been a requirement for a systematic review of the evidence. When considered necessary, relevant experts have been consulted for advice.

The Medicines Control Authority, while primarily responsible for licensing drugs, was frequently asked for advice; thus, in keeping with a trend toward growing emphasis on cost-effectiveness, the Pharmacoeconomics Unit was established in 1996 to provide economic analyses and information regarding reimbursement. When considering reimbursement for

a new drug, this unit compares the price and effect of the drug with alternative treatments from a societal perspective. Drug companies are encouraged to perform health economic analyses and submit them with their reimbursement applications. This will become mandatory in 2002 and is described in a formal guideline. Health economists have collaborated with the Ministry of Health, the pharmaceutical industry, and others to develop the guideline, which focuses mainly on economic issues. When appropriate, the cost-effectiveness of a new drug will also be compared to nondrug treatments.

The aims of these comparisons are to provide reliable estimates of the cost of reimbursement, costs if reimbursement is not provided, and the effects of treatment. In this way increasing efforts are being made to improve the use of research evidence in reimbursement decisions. The price of a drug is set when the substance is licensed; the Medicines Control Authority sets prices according to production costs, prices of similar drugs, and prices in other countries.

Making Decisions on Reimbursement

The National Insurance Administration has the mandate to accept a new drug for reimbursement if the diagnosis the new medication is licensed to treat is listed, and if the drug belongs to one of the groups on the list of reimbursable medications for that diagnosis. The Ministry of Health and Social Affairs must approve changes to both the diagnostic list and the list of approved drug groups. The budgetary costs for reimbursed drugs are supplied according to the running expenses generated by the approved drugs.

A new class of antidepressants, the selective serotonin reuptake inhibitors (SSRIs), generated unexpectedly large budgetary costs after being approved for reimbursement in the "antidepressive drug" group. This initiated a change in practice so that if large budgetary expenses are expected, the Ministry of Health and Social Affairs should be contacted even if there is no need to change the list of conditions or the list of drug groups. The Ministry of Health can then choose to present new drugs to Parliament as an attachment to the next budget proposal, or make the decisions itself.

In summary, the final decisions can be made at three different levels: in the National Insurance Administration, the Ministry of Health or Parliament. As described below, initiatives for adding new drugs to the list have also been proposed by Parliament. This somewhat unclear process is open for drug companies and others to influence members of Parliament and thus bypass the regular evaluations made by the National Insurance Administration.

Stakeholders—for example, the Norwegian Medical Association or patient organizations—are not formally heard in the process. There is no plan to change this, following the shift of administrative responsibility from the National Insurance Administration to the Medicines Control Authority.

Rationale for Changes in the Program

Changes in the blue prescription program were initiated by data showing increasing drug expenditures. Research evidence was not taken into consideration with regard to the effectiveness of alternative strategies to control costs while achieving the aims of the program. The government established a committee in 1995 to evaluate the blue prescription program; its report was published as a white paper (Ministry of Health and Social Affairs 1997a). Consisting of members of institutions and organizations with an interest in the program, the committee was given the mandate to define and specify the overall goals of the reimbursement plan and make recommendations in light of anticipated developments in health care. Although not explicitly stated in the mandate, the increasing cost of the program was clearly an important factor behind the evaluation. The committee was asked not only to consider equitable access to medications, but also to suggest basic principles for setting coverage priorities. Because there is almost no drug industry in Norway, no direct attempt was made to incorporate industrial concerns regarding the development of new drugs.

The committee concluded that the reimbursement program functioned in keeping with its intentions in achieving the basic goals of the Norwegian welfare system. By international comparison, the program was considered very generous from the patient's viewpoint

The committee's recommendations for improvements in the program included changing the principles for setting priorities in health care, which were taken from an earlier government document (Ministry of Health and Social Affairs 1997b). It was suggested that new drugs be prioritized according to the severity of the disease and the cost-effectiveness of the treatment, principles that previously had not been explicitly applied to drug policy. Seriousness of disease had been used as an implicit criterion for adding a chronic illness to the list, and any licensed drug used to treat it had been added to the reimbursement list. The committee recommended that economic evaluations should be performed for new drugs being considered for addition to the list.

The committee also recommended developing a prescription register to monitor and control prescribing practices. It advised strengthening the efforts to implement cost-effective prescribing practice by consulting "professional groups" and computer-based guidelines. Specific recommendations were made to expand the program to include rare diseases and serious short-term diseases not previously listed.

A number of organizations and institutions took part in reviewing the report. There was generally agreement regarding the aims of the program, and most of the report was supported by all who reviewed it. Remarks mainly concerned details of how the program was organized. In the subsequent legislation put forward by the Ministry of Health and Social

Affairs based on the report, priority setting was not fully discussed. Parliament recommended a more transparent process for making decisions on reimbursement, but did not state an explicit policy for priority setting. It was suggested that economic evaluation be incorporated in the assessment of new drugs under consideration for addition to the list, but it was stated that these evaluations should be used with caution and that they cannot replace sensible judgment. This view was repeated in Parliament, and some politicians were reluctant to apply a cost-effectiveness approach to these issues (Ministry of Health and Social Affairs 1999–2000). These politicians claimed that decisions should be based on need alone. In the end, cost-effectiveness and the seriousness of a given disease were introduced as criteria for priority setting, but were not explicitly incorporated into subsequent legislation or regulations. Nonetheless, these criteria have been adopted by the National Insurance Administration and the Ministry of Health and Social Affairs, and underlie their recommendations.

IMPLEMENTATION OF CHANGES IN THE PROGRAM: FIVE EXAMPLES

The Medicines Control Authority's Pharmacoeconomics Unit has prepared 19 reports since 1998 (Box 2); here we examine decisions regarding two of these drugs and three additional examples. The main focus is on studying the use of research in making decisions about reimbursement rather than on the implementation of such decisions or their effects on patients. The examples included here represent decisions on drugs that were supposed to have large budgetary consequences, have raised public debate following initial rejection, or have induced changes in legislation to control expenditures (as in the case of sildenafil). They are not necessarily representative of drugs that involve small expenditures or that are approved without controversy.

BOX 2. REPORTS ON SPECIFIC PRODUCTS PREPARED BY THE PHARMACOECONOMICS UNIT NORWEGIAN MEDICINES CONTROL AUTHORITY, 1998-2000

Year 1998

valsartan (Diovan)
testosterone (Atmos Depot)
donepezil (Aricept)
felbamate (Taloxa)
sildenafil (Viagra)

Year 1999

montelukast (Singulair)
donepezil (Aricept)
pramipexole (Sifrol)
megestrol (Megace)
acamprosate (Campral)
repaglinid (Novonorm)
palivizumab (Synagis)

Year 2000

moxonidine (Physiotens)
clopidogrel (Plavix)
omeprazole (Losec MUPS)
raloxifen (Evista)
cisapride (Prepulsid)
rofecoxib (Vioxx)

The descriptions are based on a review of documents and written correspondence archived by the Ministry of Health and Social Affairs regarding reimbursement, the revised national budget, the response to the proposed budget from the Social Affairs and Health Committee of Parliament, and discussions among the authors and key informants. As described previously, only a subset of decisions are taken at the level of the Ministry of Health and Social Affairs. The examples described here represent approximately half of the controversial cases recently assessed in the Ministry of Health.

The use of economic analyses in decisions about reimbursement is a recent development in Norway and is evolving rapidly. Consideration of strategies for promoting cost-effective prescribing of reimbursed drugs is even more recent. This has been prompted by recognition that physicians change prescribing practice after new drugs are added to the reimbursement list (based on sales figures from drug companies) and that these changes sometimes are not cost-effective or consistent with the aims of the program.

A number of research units are occasionally consulted by the National Insurance Administration, the Pharmacoeconomics Unit, and the Ministry of Health and Social Affairs. These include the Pharmacotherapy Institute at the University of Oslo, other university-based researchers in Norway, clinicians, international consultants, and the Department of Population Health Sciences at the National Institute of Public Health. These contacts have mainly been made on an "ad hoc" basis. There is no formal collaboration between research groups and the institutions assessing drugs for reimbursement. The primary focus in this paper is on collaboration between policymakers in the Ministry of Health and Social Affairs, the Pharmacoeconomics Unit, and researchers in the Department of Population Health Sciences at the National Institute of Public Health in assessing drug effectiveness and costs. In addition, contacts with researchers (clinicians, statisticians, or others) filed in the Ministry of Health under the cases are reported here.

Lovastatin (Mevacor) for Hypercholesterolemia (1988)

Lovastatin is a cholesterol-lowering drug and was the first statin introduced in Norway. The manufacturer, Merck Sharp & Dome (MSD), applied for reimbursement for Lovastatin on a general basis before its authorization in 1988. The drug was only accepted for reimbursement on an individual basis. In 1989, after the drug had been authorized, a new application was submitted, along with original papers on efficacy and some documentation on cost-effectiveness. Lovastatin was not approved for reimbursement in group A (on a general basis), but was accepted for reimbursement on individual applications for patients with specified risk factors (group B). The National Insurance Administration argued that easy access to these drugs could initiate a broader prescription practice (to patients without risk factors), and would have large budgetary consequences.

In accordance with the recently stated wish to have health economics analysis to support decisions on reimbursement, the National Insurance Administration asked the National Institute of Public Health to perform an economic evaluation of Lovastatin. Before the evaluation was finished, politicians in Parliament raised the issue of adding all cholesterol-lowering drugs to the list of reimbursed medications. Politicians, patient organizations, MSD, and doctors approached the government, asking it to speed up the process of adding these drugs to the reimbursement list.

The National Insurance Administration's final recommendation built on the National Institute of Public Health's report. It concluded that there was a need for restricting the prescriptions rather than loosening things up. Still, the report recommended adding Lovastatin to the list of approved drugs (Box 1, group A) to decrease the administrative burden, since all individual applications at this stage were accepted. It was recommended that the prescription should be limited to patients with three specified risk factors (as suggested in the cost-effectiveness report), and that only specialists should be allowed to prescribe the drug to ensure proper use. The government followed these recommendations. However, a series of appeals made by doctors, pharmacists, and patient organizations resulted in a change in the prescribing regulations, so that today all doctors can renew a prescription for a cholesterol-lowering drug once it has been prescribed initially by a specialist.

Additional statins have since been added to the reimbursement list based on this assessment. After six years, reimbursement for statins has reached approximately 800 million NOK ($90 million) annually and accounts for roughly 20 percent of the blue prescription program. The National Insurance Administration foresaw this situation and repeatedly informed the government that the cholesterol-lowering drugs might be prescribed for a large population of patients, including those with low risk of cardiovascular diseases. This would result in a lower cost-effectiveness ratio and higher total costs.

The strategy used so far to control drug expenditures seems to be based largely on restricting access to drugs. When this fails (as here, due to political pressure), there seem to be few other strategies to ensure appropriate use. This experience has had an important impact on raising awareness of the need for priority setting and economic evaluations as a basis for making decisions about insurance coverage for new drugs. The Ministry of Health and Social Affairs has recognized the large expenditure for statins and antihypertensive medications and the potential to improve the quality of care and reduce costs by implementing evidence-based guidelines for drug management of hypercholesterolemia and hypertension. The ministry has contracted the National Institute of Public Health to develop and implement practice guidelines using interventions tailored to address identified obstacles to cost-effective prescribing of these drugs, and to evaluate the effects of the implementation strategy in a randomized controlled trial. This project will provide a basis for decision making regarding tailored interventions to improve prescribing of these drugs. In addition, it offers a possible

model for ongoing collaboration between policymakers and researchers to conduct policy-relevant studies and to help ensure that such research will be used appropriately in policy decisions.

Alendronate (Fosamax) for Osteoporosis and the Prevention of Fractures (1996)

Conflict arose between the Medicines Control Authority and the producer of alendronate (MSD) during the licensing process, prior to consideration of reimbursement. The Medicines Control Authority licensed alendronate with a stricter indication than applied for (established osteoporosis with fractures versus osteoporosis), which led to vehement protest from the producer. This was followed by conflict over price setting. The pricing of drugs was intended to be decided in relation to the treatment effect. The Medicines Control Authority concluded that there was not sufficient proof that alendronate was substantially better than other licensed products (such as didronate), and claimed that the drug should be priced similarly. This led to a price level for alendronate that was substantially below that in all other European countries, which was unacceptable to MSD.

Again MSD protested, and appealed for a new price to be set by the Ministry of Health and Social Affairs. The debate that followed was linked to the evaluation of the effect of alendronate versus didronate in the absence of direct comparisons between the drugs. MSD based its arguments on an economic analysis performed by researchers at the National Institute of Public Health with funding from MSD, while the newly established Pharmacoeconomics Unit performed its own analysis. The Ministry of Health ordered three reports to support their decision: one on costs of osteoporosis in Norway by the National Institute of Public Health; another in the form of a statistical analysis by the University of Oslo; and one from an expert at the National Hospital. In addition, the Medicines Control Authority consulted two external experts.

The producer brought in lawyers at an early stage and exerted pressure on the Medicines Control Authority and the ministry to expand the indication and increase the price. There was extensive argumentation and disagreement about which groups would benefit and the importance of different outcome measures. Members of Parliament were brought into the debate and a number of specialists contacted the ministry requesting a higher price to end the conflict and make the drug available to patients. The phrasing in this letter indicates that MSD prompted contact by these specialists. Parliament instructed the ministry to reject the Medicines Control Authority's recommendation. In addition, the ministry was instructed to add alendronate to the list of approved drugs without a formal application.

The Medicines Control Authority had planned to publish its economic evaluation in its regular journal. MSD responded by suing the Medicines Control Authority to prevent publication of the report. The case was taken to court, and in the end the Medicines Control Authority was allowed to publish the report. Following this, researchers from the National Institute of Public Health (not involved in the earlier economic analysis commissioned by MSD) were requested by the Ministry of Health and Social Affairs to critically review the evidence on the efficacy of alendronate. They reached conclusions similar to those of the Medicines Control Authority and published their assessment in the *Journal of the Norwegian Medical Association* (Kopjar and Bjørndal 1998). However, this had no influence on the decision-making process for the drug in question, which occurred at a political level and was heavily influenced by lobbying, lawyers, and coverage by the mass media.

Interferon Beta-1b (Betaferon) for Multiple Sclerosis (1997)

Betaferon, which is produced by Schering AG, was assessed several times, beginning prior to its being licensed and ending with an approval more than two years later. The National Insurance Administration and the Medicines Control Authority reached different conclusions about this drug. The Medicines Control Authority conducted an analysis based on its own assessment of published randomized controlled trials and concluded that it was questionable whether this medication demonstrated any clinically important effects.

Despite the seriousness of the disease and the lack of alternative therapies, the Medicines Control Authority did not recommend reimbursement. The National Insurance Administration consulted an expert on multiple sclerosis and asked for his opinion, which was that interferon did have clinically important effects and should be reimbursed. (This expert supplied a number of references.) There are insufficient details in these two reports to determine the basis for the discrepancies (e.g., whether the same studies were interpreted differently, or the conclusions were based on different studies). However, it appears likely that such discrepancies were due largely to different views on the relation of surrogate outcome measures to clinically important outcomes. (Surrogate outcome measures are those that are not of direct practical importance—such as physiological or biochemical markers—but are believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients, but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attack.)

The Ministry of Health rejected the application for reimbursement. This was followed by a number of responses from patients, patient organizations, politicians, and doctors and reports in the mass media. Members of Parliament raised the issue of reimbursement for interferon, and asked the government to include this in the revised national budget. The politicians put forward the views of the expert on multiple sclerosis and claimed that there was a need to do more for chronically ill patients in general, and multiple sclerosis patients specifically.

The politicians also argued that it was unreasonable that drugs registered by the Medicines Control Authority for treatment of chronic diseases were not immediately approved for reimbursement. Arguments for this view were that

interferon has a statistically significant effect on the progression of the disease and that any effective therapy should be reimbursed without consideration of cost effectiveness.

Following the instructions from Parliament, the Ministry of Health decided to reimburse Betaferon on individual applications by specialists (Box 1, group B). Neither the National Institute of Public Health nor other research institutions were consulted in this assessment.

Sildenafil (Viagra) for Erectile Dysfunction (1998)

Sildenafil was licensed for treatment of erectile dysfunction in November 1998. The producer, Pfizer, never applied to add this drug to the reimbursement list. However, even before it was licensed, the National Insurance Administration received applications from patients asking for coverage for this drug through individual claims for large expenditures not covered by blue prescriptions (Box 1, group D). The Medicines Control Authority conducted an economic analysis of the costs to the reimbursement budget if all patients having this diagnosis applied for individual coverage. This analysis was only a prediction of the number of patients and did not take into account the possible effects, such as improvements in quality of life. Neither the National Institute of Public Health nor other researchers were involved in this assessment.

Based on the assumption that there are 100,000 patients for whom this drug might be useful in Norway, the Medicines Control Authority advised not to cover the expenses of sildenafil through the reimbursement program and specified that it should not be considered for coverage through individual claims. The National Insurance Administration agreed on this conclusion. Although a cost-effectiveness analysis was not performed, it was concluded that the health gain would not outweigh the costs of reimbursement. In response to this recommendation, Pfizer argued that according to the legislation it was not legally possible to exclude any specific drug from coverage. This resulted in a change in the legislation so that the National Insurance Administration could, for "economic or medical reasons," exclude specific drugs from coverage through individual claims for large expenditures.

This was a further restriction of possible ways to cover expensive drugs, driven by concern over massive expenditures from widespread use of sildenafil if it were to be reimbursed. It might have been argued that erectile dysfunction is, generally, not a severe disease and does not qualify for reimbursement on this basis. However, decision making regarding this drug was dominated by concern over the potential costs.

Montelukast (Singulair) for Asthma (1999)

Montelukast, produced by MSD, was licensed in November 1998. The Medicines Control Authority evaluated its efficacy as part of the licensing process, relying primarily on licensure by the European Union, which now is standard. After an application to add montelukast to the reimbursement list, the Pharmacoeconomics Unit conducted an economic analysis. The Medicines Control Authority was reluctant to draw strong conclusions from this, mainly because there was weak background data. Due to the small treatment effect and uncertain role of the drug in managing asthma, the Medicines Control Authority recommended that montelukast should be reimbursed only when the treatment is started by a specialist to ensure correct use. MSD appealed this restriction.

New studies were presented, and MSD claimed that the effect of montelukast was underestimated and that the costs were overestimated. The Medicines Control Authority and the National Insurance Administration critically appraised the new evidence on efficacy and economic data and did not change their previous conclusion. The National Institute of Public Health was asked to make an independent assessment and concluded that the indications should be more rather than less restrictive. There was agreement about the efficacy and the quality of the studies, but there was disagreement about the value of having an alternative to other available treatments that was more expensive and not clearly more effective. In addition, there was disagreement about the importance of equal access, since restricting prescribing to specialists might limit the availability of the drug to patients in rural areas.

The Ministry of Health and Social Affairs proposed to Parliament that reimbursement be restricted based on the effects of the treatment in relation to the costs. MSD and a number of respirologists again approached members of Parliament, questioning the evidence presented by the government and arguing that the experts were not being heard. In addition, patient organizations contacted the Ministry of Health repeatedly, arguing that both the need and the treatment effect were large. The additional information presented was mainly anecdotal experience of doctors and patients. Some of the stakeholders referred to a Nordic consensus guideline that gave montelukast an important role in drug treatment of asthma. In spite of very active engagement by some members of Parliament, the Ministry's recommendation was followed.

Additional studies on the efficacy of montelukast were brought in at almost every stage of the evaluation and appeal process, but assessment of these studies did not bring new information. MSD actively contacted different stakeholders and involved them in lobbying efforts. MSD complained to Parliament about the speed of the process and the confidentiality of documents in the case. One of the most involved respirologists was the principal investigator of one of the montelukast studies and editor of the Nordic consensus report on asthma management to which many of the stakeholders referred.

Montelukast is now reimbursed after individual application, and it has to be prescribed by a specialist. A working group consisting of representatives from the National Insurance Administration, the Medicines Control Authority, the Ministry of

Health, the National Institute of Public Health, and respirologists has developed criteria for how this should be practiced. Some respirologists were reluctant to participate in this process due to the consequence it might have for further funding from MSD and potential pressure MSD might put on them.

The group recommended N of 1 trials2 to ensure that patients receiving montelukast benefit from the drug, since a major published study has shown that one-third of the patients do not benefit from treatment. As N of 1 trials have not been used on a large scale before, the group recommended testing this concept on a small scale and comparing patient outcomes and costs with ordinary practice (prescription by a specialist). The report was sent to MSD and the Norwegian Medical Association for comments. They questioned the scientific basis of the report and did not support a linkage between reimbursement and an individual documented effect demonstrated by an N of 1 trial.

Even before this report was finished, articles appeared in the media criticizing the evaluation by the National Institute of Public Health with regard to general reimbursement of montelukast, and Parliament requested a new assessment of the documentation if new evidence was available. This case has not yet been resolved.

EVALUATION OF CHANGES IN THE PROGRAM

The National Insurance Administration is a large administrative organization. The interest in evaluation varies in different departments and depends on the interest of individuals employed at any particular time. The changes in the blue prescription program described above are recent and are still developing. Submission of economic evaluations with applications to add new drugs to the reimbursement list will not become mandatory until 2002. There has not been any external formal evaluation of the use of economic evaluations in the decision-making process or of other changes in the process, with the exception of a review of the reference price system (*Evaluation* . . . 2000). At this point no formal evaluation has been planned.

Funds for Research and Evaluation

The Pharmacoeconomics Unit of the Medicines Control Authority has limited funds for hiring external consultants on a case-by-case basis (80,000 NOK/$9,000 for 2000). Consultants are contacted in cases that are considered especially important. One problem with using international experts has been that most documentation and reports are written in Norwegian. On the other hand, it can be difficult to find consultants with the appropriate skills and expertise in Norway. Consideration is being given to producing documents and reports in English to allow for more extensive use of international expertise when needed.

The Ministry of Health and Social Affairs does not have funds earmarked for research and evaluation in relation to the blue prescription program, but it does have some general resources available that can be used for this purpose. For example, 2 million NOK ($220,000) was allocated in 2000 to developing effective strategies for improving prescribing of cholesterol-lowering and antihypertensive agents. The National Institute of Public Health does not have any fixed positions allocated for supporting research and evaluation in relation to the blue prescription program, but is able to allocate some staff time to this.

Current Status of the Program

Within the Ministry of Health and Social Affairs the need for prioritizing and using economic evaluations in making decisions about adding new drugs to the reimbursement list is well recognized, and there is firm support for changes in this direction. Currently, efforts are being focused on developing explicit criteria upon which to base such decisions. The Medicines Control Authority has developed guidelines for economic evaluations, but these do not include rules regarding what evidence to include or how to synthesize that evidence; procedural direction of this kind is not specified elsewhere in the existing legislation or regulations. Further, no guiding principles exist on how to deal with differences in opinion and conflicting judgments; nor is there a process for consulting stakeholders, experts, or researchers. Efforts to support interventions to improve rational prescribing for drugs that are already reimbursed, such as cholesterol-lowering and antihypertensive agents, and to ensure appropriate use of new drugs added to the list, such as montelukast, are recent and are limited to a few projects.

The pharmaceutical industry has been highly critical of the application procedures and has complained about the lack of transparency and communication during the process. Most heavily criticized has been the long time spent on assessing applications for general reimbursement, in particular for innovative drugs. The Norwegian Association of Pharmaceutical Manufacturers complained about this to the European Free Trade Association Surveillance Authority (ESA) in 1998. A report made by the association in October 2000 concluded that during the last two years, only 45 percent of the applications met the 90-day standard set by the European Union.

REFLECTION AND GENERALIZATION

Barriers

Key factors that limit better use of evidence in making decisions about adding new drugs to the blue prescription program in Norway are

- a shortage of people with appropriate training in clinical epidemiology, health economics, and clinical pharmacology
- lobbying and intervening in the process at a political level, particularly by companies with a commercial interest in a decision
- the patchwork nature of the legislation and regulation
- lack of explicit criteria for making decisions

Facilitators

In addition to addressing the factors listed above (for example, by recruiting and training more people), elements facilitating better use of evidence in decision making are

- better communication between policymakers and politicians
- establishing a system to collect prescribing data to monitor practice
- establishing treatment goals (clinically important endpoints) early in the process so that subsequent analyses and discussion can be focused on these
- transparent and explicit processes
- involvement of independent organizations, limiting the potential of stakeholders to derail the process through political lobbying

Lessons Learned

Licensure of new drugs in Norway is now based mainly on a common European evaluation. Evaluations and decisions regarding reimbursement are, on the other hand, made at a national level. Changes in the blue prescription program in Norway largely reflect changes in Europe and elsewhere, and have been driven by increasing costs, the need to set priorities, and the evolving role of economic evaluations in informing decisions about insurance coverage. Also as in many other countries, rigorous use of evidence in economic analyses has been limited by a lack of available data and a lack of people with training in clinical epidemiology, health economics, and clinical pharmacology.

The result has been variable quality in the assessments of applications for drug reimbursement. The perceived legitimacy of the assessments also varies among doctors, patient organizations, politicians, and others. In the cases reviewed here, all experts or specialist physicians, no matter how the contacts were initiated, were supportive of the drugs in question. Only one expert stated a conflict of interest.

There are no clearly defined roles for the various stakeholders in the process of making decisions about drug reimbursement. This might result in a general suspicion toward the body assessing applications for reimbursement and lead to the use of alternative channels, such as the media or appealing directly to members of Parliament, to influence the final decisions.

Another important consideration concerns the implementation of decisions once they have been made. Critical statements by experts in the examples reviewed in this report indicate doubts about the legitimacy of some recommendations and decisions. This could inhibit effective implementation, which is necessary in a system where there is little surveillance of physician practice and no clear delegation of responsibility for developing and implementing guidelines for prescribing drugs.

The use of evidence, critical evaluation and economic evaluations now seems to be valued by policymakers and advisers in the Ministry of Health, the Medicines Control Authority, and the National Insurance Administration. Politicians, however, may value these changes less and, in the cases reviewed in this paper, seem to be more influenced by anecdotes, the opinions of specialists, reports in the mass media, and lobbying efforts. In several of the cases described, politicians have played a decisive role in adding new drugs to the reimbursement list.

The Norwegian drug reimbursement program offers the possibility for cost-effective prescribing, targeting "the right drug to the right patient." However, this potential has not been developed because strategies for implementation and control are lacking. A system for collecting national data on prescribing is now under development and will provide information about individual prescribing practices. Two cases presented here—the one involving cholesterol-lowering and antihypertensive drugs, and the one on montelukast—are examples of possible approaches that could be used to promote cost-effective prescribing.

Changes in the bureaucracy have developed slowly over the past five years and have depended on the initiative of a few individuals within the Ministry of Health, the Medicines Control Authority, and the National Insurance Administration. Although the drug reimbursement decision-making process has been criticized in the past for lacking organization and coordination, recent improvements will, it is hoped, provide a more systematic and explicit approach. The examples described here illustrate several challenges. There is still a need to develop a more transparent and explicit process for assessing drug reimbursement applications as well as for ensuring appropriate use of blue prescriptions. In addition, a better understanding by the public and politicians of how priorities in this area are set might improve the perceived legitimacy and acceptance of decisions.

GLOSSARY

EFTA
European Free Trade Association

ESA
EFTA Surveillance Authority

GNP
gross national product

Medicines Control Authority
The government agency responsible for licensing drugs in Norway, more recently given responsibility for providing advice on which drugs should be added to the list of medications that are reimbursed by the National Insurance Adiministration; now called the Norwegian Medicines Agency and given additional responsibilities.

Ministry of Health and Social Affairs
The government department responsible for health and human services; in this report, sometimes abbreviated as Ministry of Health.

MSD
Merck Sharp & Dome, a pharmaceutical company

National Insurance Administration
The government agency responsible for administering the public insurance system, which covers retirement pensions, disablement benefits, sickness benefits, unemployment benefits, and health care, including drugs.

NOK
Norwegian kroner (crowns), the national currency.

Norwegian Medicines Agency
The new name given in late 2000 to the Medicines Control Authority, along with extended responsibilities.

OECD
Organisation for Economic Co-operation and Development

SSRI
selective serotonin reuptake inhibitors

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The National Institute for Clinical Excellence and Coverage of Relenza by the NHS

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EXECUTIVE SUMMARY

In April 1999 the British government established the National Institute for Clinical Excellence (NICE) with the aim of identifying best practice and advising health professionals on which treatments work best for patients and are cost-effective. Between 30 and 50 technologies a year will be appraised by NICE, which will have a permanent staff of 30 and a budget in its first year of about £10 million ($14.3 million).

The government hopes that NICE will ensure that the latest treatments are available equally to all patients. It is meant to answer the criticism of uneven access in different geographical areas, commonly referred to as "rationing by postcode." The National Health Service (NHS) cannot provide a fully comprehensive, high-quality service that is free at the time of delivery for everyone. Rationing is inevitable, but governments have found it very difficult to acknowledge this and to ration sensibly.

The aim of this case study is to examine how NICE works and the degree to which it offers an opportunity for policymakers and researchers to collaborate in ways that increase the use of research evidence in policymaking. This study focuses in particular on the first assessment carried out by NICE with regard to the new influenza drug zanamivir (Relenza).

In October 1999 NICE ruled against the NHS in using zanamivir on the basis that the available evidence from clinical trials suggested only a moderate benefit of the drug to otherwise healthy individuals. In the absence of clear evidence of its effectiveness in high-risk patients, NICE advised general practitioners (GPs) not to prescribe zanamivir during the 1999–2000 flu season. This decision was changed in November 2000 in the light of some new evidence in high-risk groups.

This first ruling by the new institute raised important questions about the criteria for decision making, the role of costs, and the degree to which decisions of NICE and the secretary of state would be binding on clinicians.

Since then NICE has made recommendations about a range of drugs, devices, and other health technologies. These are systematically reviewed by academics under contract, whose reviews are then used to develop an appraisal by a NICE committee made up of researchers, practitioners, policymakers, and lay representatives. After peer review and consultation a final appraisal is produced, on the basis of which a recommendation to the NHS is made about drug coverage and indications for use.

The case study illustrates the potential depth and extent of the impact NICE could have both inside and outside the United Kingdom. As a result, NICE has dedicated considerable efforts to making the "rules of the game" clear and explicit so that all parties know what is expected. It is clear that the process of review and appraisal needs to be carried out at a high level of scientific rigor, with time for peer review and consultation with key stakeholders, including user groups.

The pharmaceutical industry learned that Phase III studies would not satisfy NICE requirements and that it would be necessary to have a clear understanding of the kind of economic information needed and methodology for handling them (e.g., how to handle uncertainty, especially in the impact on the health service regarding configuration of services, skill mix, and the like). It was obvious that affordability is a factor in NICE's decision making.

It is not likely that NICE guidance on drug choices will be welcomed when it comes to rationing guidance for a treatment relevant to an identifiable and high-profile, well-organized patient or client group such as people with multiple sclerosis. It is not clear to what degree NICE will be willing and able to make deeply unpopular recommendations even with a strong evidence base. This will have an impact on the institute's credibility and on the potential for collaboration with researchers.

The establishment of NICE has provided a major instrument by which the NHS Research and Development (R&D) program in general, and its health technology assessment program in particular, can influence practice. In this sense NICE is not only an arm of regulation but also a facility for knowledge management and transfer.

Barriers

- *Different objectives.* Researchers seek knowledge and academic recognition. Policymakers are looking to inform or justify a decision. Thus, NICE may find that it is increasingly difficult to get academic researchers to carry out appraisals of health technologies unless there is "traditional" academic spin off.

- *Different types of questions and ways of using research evidence.* Policymakers have relatively specific questions and are interested mainly in the implications for action (normative). Researchers want to know what the evidence is (positive). Research evidence rarely speaks for itself; policy requires judgments under conditions of uncertainty, influenced by values, resources, and politics. Researchers are more closely wedded to the research, are less prepared to extrapolate beyond the data, and have higher thresholds of certainty and evidence.
- *Different time frames.* Policymakers in the UK increasingly work to very tight time frames. Researchers prefer to work to longer time frames. There is concern in the research community about the pace at which technology assessments are expected and the possibility that errors will be made and decisions based on substandard evidence. A related issue is the lack of research capacity to handle with speed the volume of rigorous technology assessments commissioned by the NHS Health Technology Assessment Programme on behalf of NICE, and the drug industry's demand for researchers to prepare cases for submission to NICE.
- *Publicity versus confidentiality.* Researchers like to share emerging ideas, but policy research is confidential and cannot easily be published. In the case of NICE, limitations have been placed on reviewers' ability to communicate directly with company scientists, potentially reducing the quality of the research.

Facilitators

- *Shared interest in using research to answer questions.* The establishment of NICE is a way for researchers to influence or have a direct impact on policy and get research into practice. For some researchers, the idea of their work being influential is a big incentive. In the case of the UK, the link between NICE, other elements of the national quality framework, such as the National Service Frameworks, and the NHS R&D Program provides a unique infrastructure for researcher-policymaker collaboration. For others, however, insufficient trust that the work will be used in the "right" way can be a disincentive to collaborate.
- *Resources.* Policy-relevant research can be an important source of relatively protected income for research groups. It also helps demonstrate to ministers and other policymakers the potential value and impact of research, thus raising its profile.
- *Clear rules of engagement.* Collaboration is aided by use of a clear and agreed-upon framework.

Lessons Learned

- There is considerable suspicion of NICE by the pharmaceutical and medical equipment industries. Some of this is fear of the unknown, which will diminish as the rules by which NICE makes recommendations become clearer.
- A well-defined and transparent decision-making process is needed so that all stakeholders know the ground rules.
- Good communication between all parties involved is needed continuously.
- Maintaining the confidentiality of emerging thinking during the process has proved nearly impossible and has now been abandoned.
- The impact of NICE appraisals (at least on drug manufacturers) is potentially as great internationally as it is nationally.

INTRODUCTION

The UK Health Care System

The United Kingdom is a stable parliamentary democracy in which there is devolution of central government powers to varying degrees to Wales and Northern Ireland, and to Scotland, which has its own parliament.

The National Health Service (NHS) was established in 1948 by a Labour (left of center) government; since then it has been the principal public finance provider of health care services to the population, providing universal health coverage free (with some exceptions) at the point of delivery. Funding in England is mainly from non-earmarked general taxation and national insurance contributions. The remainder is raised from user co-payments for NHS dental and ophthalmic services and flat-rate charges for items such as prescriptions (although the majority of users qualify for exemption from prescription charges).

There has been a political consensus on the benefits of a universally available health care system funded through taxation, although there are different views (essentially left of center versus right of center) about how the service should be organized and the role of privately funded and delivered health care. The private health care sector in the UK is small; approximately 11 percent of the population has some form of private health care insurance. Private health care expenditure accounts for about 15 percent of the total expenditure on health care in the UK, mainly for acute elective procedures in secondary care.

The Department of Health (DoH), with a budget in 1998–1999 of more than £37 billion, is responsible for overall policy on all heath and personal social services, including public health and safety issues. Following referenda on devolution, responsibility for determining health care services and budgets since July 1999 has been devolved to the Welsh Assembly and Scottish Parliament.

All political parties agree that the NHS needs to evolve rapidly to meet consumer demands and expectations. The

current (Labour) government has indicated that the health service should become "modern and dependable." It wants rapid reform of attitudes toward the patient/provider relationship and in the service culture, which it sees as tending to organize service around the needs of staff rather than of patients. In 2000 it was announced that there would be a significant program of investment in the NHS over the next three years, which will increase the percentage of gross domestic product (GDP) spent on the NHS from around 6.5 percent to around 8 percent over five years.

In England, primary health care is delivered by general practices, which are owned by self-employed, independent practitioners who have contracts with the NHS to deliver services. Their income is derived principally from a capitation based on the number of people who register with them. More than 95 percent of the population is registered with a GP, who may work alone or in group practices. The practice income is also supplemented by a Basic Practice Allowance, some payments based on hitting targets for vaccination and screening and some fee-for-service elements.

Hospital care is delivered by NHS trusts. Staff, including the doctors, are salaried workers. The hospital budget is derived from commissions from Health Authorities or from Primary Care Groups and Primary Care Trusts, which are allocated central health service funds according to measures of relative need. All health care services can be accessed free at the time of delivery except for prescriptions (see below).

In the UK, doctors' practice decisions traditionally have not been controlled by the central government or even locally. Instead, there has been a strong tradition of clinical autonomy. While this has been changing gradually over the last few years, NICE is the first major attempt to regulate clinical practice and the diffusion of health technologies at a national level.

Financing and Cost Issues

As with other health care systems, the NHS is under considerable inflationary pressure, a significant part of which results from the development of new health technologies, particularly expensive drugs (Stevens, Milne, Lilford, et al. 1999). Pharmaceuticals prescribed in the NHS are subject to a fixed-sum co-payment per prescription of around £6.00 (the prescription charge collected by the pharmacist at the time of dispensing) unless prescribed while a patient is in the hospital or when the patient can take advantage of one or more exemptions (related to employment status, age, certain medical conditions, or receipt of certain social security benefits, for example). The majority of both patients and prescriptions are exempt from this co-payment. The NHS spends more than 12 percent of its budget on pharmaceuticals each year. Though not high by European standards, this has been rising over the years and is a source of concern to policymakers. The perceived fiscal crisis of the NHS has led to calls both for increased funding (to an extent heeded by government) and for alternative methods of health care financing.

The pricing of prescription drugs in the UK has been affected by the Pharmaceutical Price Regulation Scheme (PPRS), a voluntary agreement between Britain's Department of Health and the Association of the British Pharmaceutical Industry by which companies negotiate target profit rates from sales of drugs to the NHS (around 17–21 percent rate of return on investment in research and development). The program's objectives are to secure the provision of safe and effective medicines to the NHS at reasonable prices; to promote a strong pharmaceutical industry in Britain; and to encourage the efficient and competitive development and supply of medicines worldwide. Although the program has been successful in helping to maintain the British pharmaceutical industry, which plays an important part in the economy and science R&D base, its objectives can conflict with other health policy objectives.

In particular, there is a conflict between the DoH's attempts to control NHS expenditure and the program's implicit subsidy of the industry's research and development. Drug prices in Britain are higher than those in several other countries. If cost-containment measures, such as encouraging the use of generic drugs, provision of prescribing data, and other policies aimed at general practitioners' prescribing threaten profits, the price regulation program may allow companies to increase prices. Finally, there was no attempt to link prescribing with cost-effectiveness: products that are cost-effective and those that are not are treated equally under the plan (Maynard and Bloor 1997).

As a result of the rising expenditure on drugs, people have called for comparative cost-effectiveness to be proven before the NHS agrees to pay for new drugs and other health technologies, similar to the systems operating in Australia and parts of Canada (Bloor, Maynard, and Freemantle 1996). This would establish what has been termed a "fourth hurdle" that health technologies would need to go over to be covered—so called because of the Phase I, II, and III trials which drugs need to pass to be licensed. "Under such a scheme assessment of incremental cost effectiveness would be needed to determine whether a product represents value for money at the price sought. The implementation of this type of hurdle in Britain would require restriction of publicly reimbursed drugs by a positive list. At the moment in Britain licensed drugs can be publicly prescribed unless a decision has been made to remove it (negative listing). In addition to facilitating national prioritisation of drug treatments, it could also reduce the problems of differential access to new products. . ." (Maynard and Bloor 1997).

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE (NICE)

Rationale for the Policy

The policy to establish the National Institute for Clinical Excellence was the product of three main forces: increasing pressure of costs, inconsistent health care rationing decisions in the past, and the desire to improve the quality of care.

In addition, there was some pressure to make better use of the evidence base that was being generated nationally through the NHS R&D program and internationally in health technology assessment; this is considered in more detail in the next section.

The first factor in favor of the policy, and probably the most important one, was the (continuing) pressure of costs posed by new and potentially expensive (in terms of price and volume) health technologies, particularly pharmaceuticals, discussed above.

Second, there was considerable disquiet about the way "rationing" decisions had been made in the past about how new drugs would be funded. Where such decision-making had been delegated to Health Authorities, it had resulted in considerable geographical variation in access to the drugs in question, which conflicts with the strong principle of equity within the NHS. This has been described as "postcode rationing." Where decisions were made centrally, there was considerable concern about the rather ad hoc and opaque fashion in which it was done. These issues are discussed in two short case studies presented here on the use of beta interferon for treating multiple sclerosis and Viagra for erectile dysfunction (see Case Study 1 and Case Study 2, boxed text).

CASE STUDY 1. POSTCODE RATIONING

Interferon beta 1b (beta interferon) was licensed in the UK for patients with relapsing-remitting multiple sclerosis (MS) in December 1995. The NHS Executive chose beta interferon in 1995 as the first drug for which to issue specific guidance on prescription. It was recommended that treatment be made available only after patients had been judged appropriate by a consulting neurologist. The interpretation of this guidance has differed widely among health authorities, as ultimately the NHS Executive made clear that its intention was not to make prescribing decisions, but simply to provide more information to medical professionals in the decision-making process.

These guidelines were challenged in a test case in the High Court that found an MS sufferer had been unfairly denied funding for beta interferon treatment by his local authority (given that a neurologist had made an assessment of appropriateness). In the ruling the judge stated that "A blanket ban was the very antithesis of national policy, whose aim was to target the drug at patients who could most benefit from the treatment" (Dyer 1997). Nevertheless, beta interferon is a classic example of "postcode" medicine rationing, with some health authorities refusing to fund what they claim is an unproven and non-cost-effective therapy.

Initial guidance on the use of beta interferon did not specifically take into account the need for cost-effectiveness information (which at the time was rather limited). The treatment is expensive, costing approximately £10,000 per year per patient. If out of the estimated 85,000 people in the UK with MS in 1995, 45 percent had relapse-remitting MS and were treated with beta interferon, the cost would be some £380 million, or 10 percent of the drug budget. However, the situation with regard to access to beta interferon remains confusing, with some Health Authorities refusing to prescribe the drug outside clinical trials.

As a result, beta interferon was referred to NICE for appraisal. While the initial recommendation was that it should not be covered by the NHS, NICE considered an appeal, then commissioned more research, and, at the time of writing, a decision has been delayed.

CASE STUDY 2. POOR APPROACH TO CENTRAL RATIONING

Viagra (sildenfil) was licensed in Europe for erectile dysfunction in September 1998 by the European Medicines Evaluation Agency. Amid a blaze of publicity and the fear of widespread use and associated costs, the DoH told British doctors not to prescribe Viagra until definitive guidance had been prepared. This decision was made by the Standing Medical Advisory Committee of the DoH and was the first time the NHS had refused to fund a licensed drug with proven benefits to a significant number of people principally on the basis of cost. The action was criticized not only by those wishing to prescribe or use Viagra, but also by those who, though generally supportive of the principle of rationing, were concerned about the way decisions had been made—behind closed doors and according to unknown criteria. Subsequently (June 1999) the High Court ruled the NHS's refusal to fund the drug to have been unlawful under English law because it "deterred doctors from exercising their duty to use their clinical judgement." It was also ruled unlawful under European law because it contravened the so-called transparency directive on medicines, which lays down the principle that any decision to blacklist a medicine from a member state's national health service must state reasons "based upon objective and verifiable criteria."

Draft guidelines subsequently issued in January 1999 allowed prescribing for patients with one or more of a very limited set of indications. This marked a clear move to explicit rationing. However, the guidance was severely criticized for its lack of obvious logical basis. For example, it made apparently arbitrary distinctions between different causes of erectile dysfunction (e.g., if associated with prostatectomy, the drug could be prescribed, but if associated with arterial disease, it could not). In May 1999, after a long period of consultation and deliberation, final guidelines were issued that slightly increased the range of indications.

Viagra marked a sea change in that rationing was now on the open agenda; however, the poor way in which the matter was handled raised the stakes for the National Institute for Clinical Excellence (NICE), which was established in April 1999.

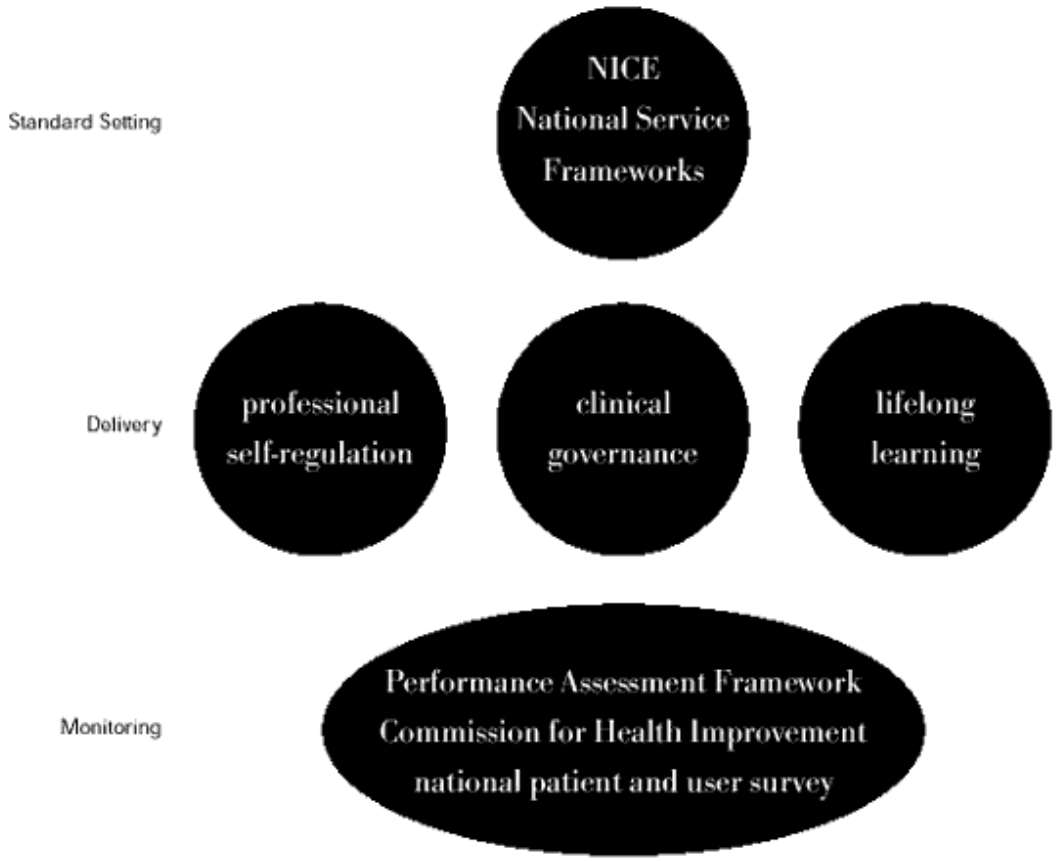
The third rationale for the policy came from the NHS's need to focus more consistently on improving the quality of care. The government has indicated that it is placing the quality of care delivered by the NHS at the heart of its agenda for the service. This policy has been reinforced and accelerated by a series of high-profile cases of bad medical practice, most notably the pediatric heart surgery scandal in Bristol (Smith 1998).

This agenda, as laid out in *A First Class Service: Quality and the New NHS* (NHS Executive 1998), comprises several separate but connected elements, including

- patient and public involvement (including surveys)
- National Institute for Clinical Excellence
- national service frameworks
- clinical governance
- continuing professional development and lifelong learning
- professional self-regulation
- Commission for Health Improvement
- Performance Assessment Framework (high-level performance indicators and clinical indicators)

This can be thought of as a series of mechanisms for achieving three distinct but related functions: the setting of standards, delivering or implementing these standards, and finally, monitoring their implementation and the effect of quality (see Figure 1). These functions are carried out in a combination of external activities (such as standard setting and external review, which make demands on health care organizations) and those internal ones under more local control (which aim to create a culture of quality either at the level of the local organization or among individual clinicians). Elements of the quality initiative, such as clinical governance, represent novel arrangements that have not been applied before in England. The whole constellation of quality interventions that make up the initiative is probably unique in the world.

FIGURE 1. FRAMEWORK FOR HEALTH CARE QUALITY



One key element of the quality strategy is the government's desire for the NHS to establish clear standards that will be pursued by provider agencies through a system of "clinical governance." Professional self-regulation remains but is under pressure to deal more effectively with poor practice, and NHS organizations will be subject to regular inspection. NICE, which was established in April 1999, uses evidence of clinical and cost-effectiveness to provide guidance to health professionals and patients on best practice. A key task of NICE is to provide rapid appraisal of new drugs and other technologies. New products may be accepted or refused NHS reimbursement, or they may be allocated "continuing research" status.

A Knowledge-Based Health Service—Building on and Extending Collaboration with Researchers

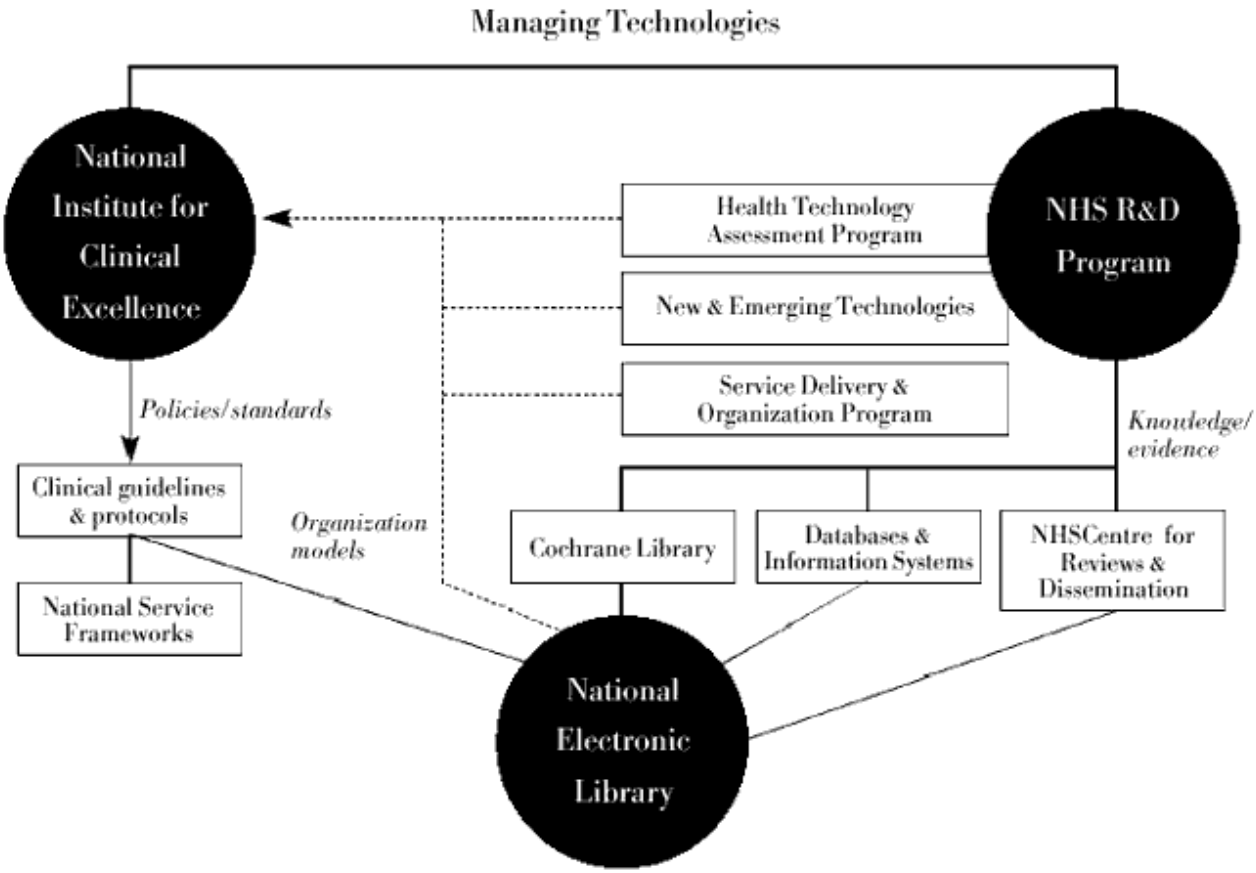
Still another reason NICE came about—or at least a factor in the way it was established—is the existence and influence of the NHS R&D program, mentioned above. Acquiring high-quality research-based evidence to support decision making has been an important feature of the NHS in recent years. In 1991, following a 1988 report from the House of Lords Select Committee on Science and Technology, the DoH developed and published a research-and-development strategy for the NHS. The objective was to support a knowledge-based health service in which clinical, managerial, and policy decisions would be based on sound information about research findings and scientific developments. The NHS R&D programs, therefore, focus on the needs of the health service.

A key part of the NHS R&D strategy is the Health Technology Assessment (HTA) program. Its purpose is to ensure that high-quality research information on the costs, effectiveness, and broader impact of health technologies is produced for those who use, manage, and provide care in the NHS. Every year the HTA program and its panels decide which of the many suggestions received from the NHS and its users should become research priorities. The program then issues calls for proposals and commissions research to answer the questions emerging from those research priorities. Research results are published as reports in the HTA monograph series (http://www.ncchta.org/htapubs.htm).

The existence of the HTA program, and the strength of the NHS R&D program and the culture it helped develop, played a significant role in the structuring of NICE and its methods of operation, particularly the process of summarizing information on health technologies being considered. The National Institute for Clinical Excellence commissions the HTA program to carry out evaluations on its behalf; these are used by the NICE Appraisal Committee (responsible for reviewing research evidence on clinical efficacy and cost-effectiveness). In other words, the HTA program must, among other things, ensure that NICE has access to the requisite evidence, knowledge, and methodologies to inform the advice it gives to the NHS. Other evidence to support the work of the Appraisal Committee is sought by NICE from the pharmaceutical industry, health professionals, and interest groups.

The R&D program and NHS Executive hoped that incorporating the results of research more explicitly into national recommendations and guidelines would increase the likelihood that research might inform clinical practice. Closer links between health care research and the NHS R&D program in particular, and the work of NICE and other elements of the quality initiative, such as the National Service Frameworks, offer the potential to establish a strong and, in international terms, unique collaboration between policy and research (see Figure 2).

FIGURE 2. RELATION BETWEEN THE NHS R&D PROGRAM AND NICE



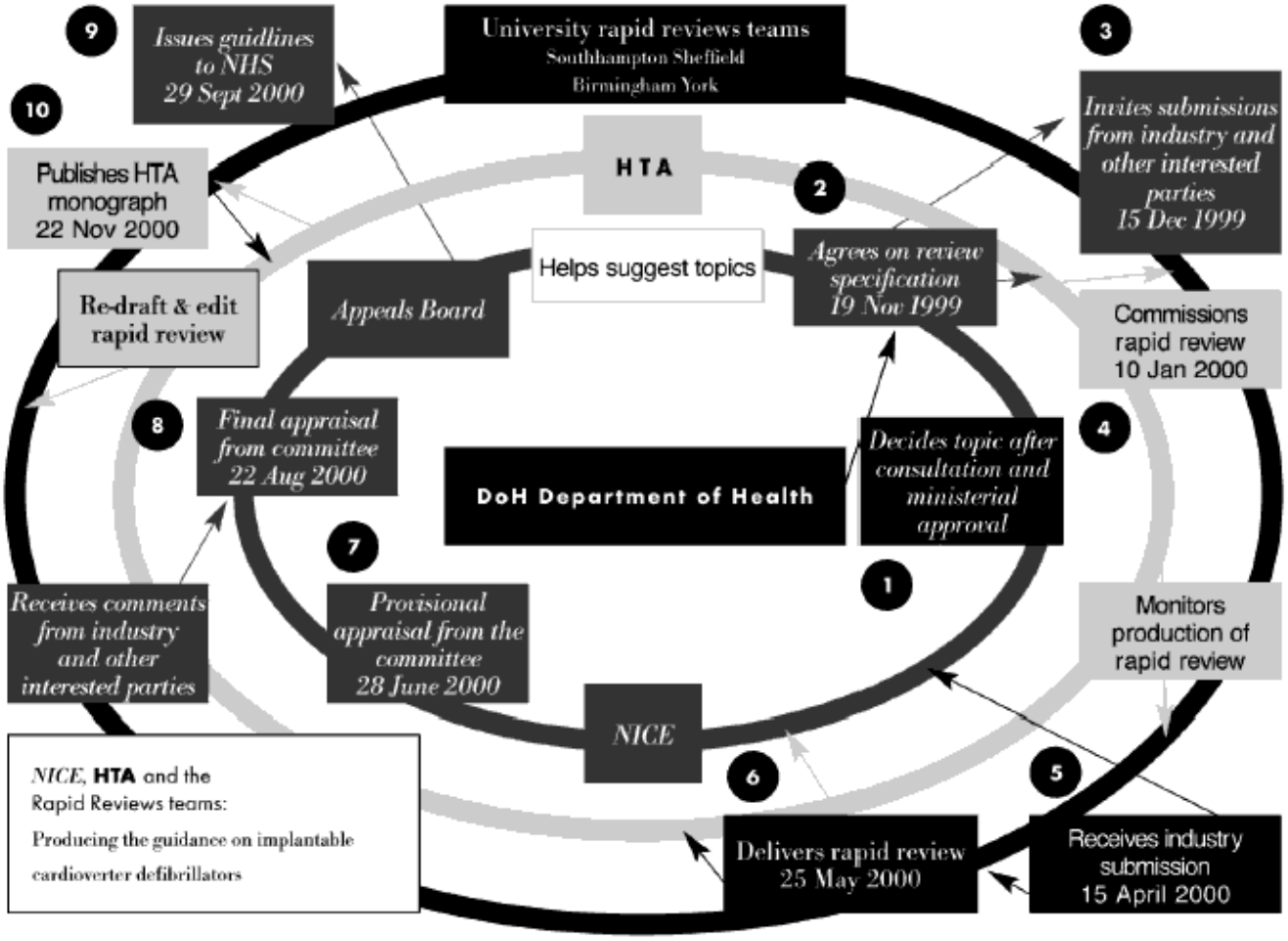
Once NICE has identified the technologies it wishes to appraise and agreed on a timetable leading to the publication of its guidelines, the HTA program becomes the interface between NICE and the review groups contracted to produce the assessment reports. The HTA program establishes liaison with both NICE and the review groups to

- identify the groups most suited to produce each assessment report
- formally commission the work on behalf of NICE
- develop and review documentation to enable the groups to make a declaration of competing interests

In the first year, a national network of academic centers was established involving the Universities if Birmingham,

Sheffield, Southampton, and York; these were under contract to the HTA program to produce up to 40 urgent assessments per year on technologies of high priority to the NHS (see http://www.ncchta.org/nice.htm). Rapid reviews on these specified topics are prepared within an agreed-upon format and a short time frame of three to six months (significantly shorter than most health technology assessments hitherto). Figure 3 shows how collaboration with the universities worked in the assessment of implantable cardioverter defribilators.

FIGURE 3. THE LINKS BETWEEN UNIVERSITIES, THE HTA PROGRAM, AND NICE



Around 40 "rapid reviews" are required annually to meet the needs of the NICE agenda. Examples of these include indications for removal of wisdom teeth; hip prostheses; taxanes for ovarian cancer and breast cancer; liquid-based cytology for cervical screening; Riluzole for motor neuron disease; autologous cartilage transplantation; Glycoprotein IIb/IIIa receptors for unstable angina and coronary syndromes; beta interferon for multiple sclerosis; donepezil, rivastigmine, and galantamine for Alzheimer's disease; and Cox-II inhibitors for arthritis. Following submission to NICE, the HTA program publishes the review groups' assessment reports in the HTA monograph series. Publication of these reports cannot take place before the relevant NICE guidance has been released.

The opportunities for collaboration between researchers and policymakers have increased due to the establishment of NICE. The HTAs carried out by universities are being used directly by NICE appraisal panels as the basis of their decision making. This relatively direct link between research and policy is quite uncommon. However, there are some associated problems. First, the tight schedules required by NICE cause researchers concern about the quality of their output. Second, the focus on individual technologies rather than on sets of interventions for a condition, along with the tight schedules and the need for early confidentiality, mean that there are fewer opportunities for publishing the results in high-quality journals. Publication is vital for researchers' academic careers, and unless opportunities for publication are encouraged, it is likely that the best researchers will not continue to be involved in the HTA program. Finally, there is

a relatively small pool of researchers with the proper training and ability to carry out health technology assessments to a high standard. The sudden rise in the demand for rapid assessments by NICE, matched, of course, by demand from pharmaceutical companies for researchers capable of helping them prepare their cases for submission to NICE, has exposed the shortage of research capacity. This is not something that can be addressed quickly, and has further increased the workload of already busy researchers. The implications of limited research capacity were not well anticipated with the introduction of NICE and need to be addressed.

In summary, the policy reasons for establishing NICE include:

- *Objectivity.* A process for making decisions that could be seen to be free from political interference was needed. This, it was hoped, would "insulate" the political decision makers from at least some of the adverse consequences of difficult decisions and at the same time win them respect and support from health professionals.
- *Uniform implementation.* Health professionals and NHS organizations "consented" to NICE's making decisions for them about the rational use of technologies, based on the latest evidence and taking account of cost-effectiveness as well as clinical effectiveness.
- *Linkage with the R&D program.* This served as a "front end" to the existing HTA program, which had suffered from the lack of a clear dissemination strategy and structural links to policy and practice. NICE guidelines and recommendations, along with the guidance of the National Service Frameworks (see above), were seen as a way to get this research evidence into practice.
- *Securing more resources for the NHS.* The ability to demonstrate to the Treasury that additional resources would be used in clinically efficacious and cost-effective ways was seen as a strong card to play in the competition between government departments for public sector funding (called the PES—Public Expenditure Survey—round). Most of the resources made available to NICE (including about half those required for the technology appraisal program, that is, the costs of the systematic reviews and economic evaluations) were already budgeted. NICE was seen as a mechanism through which greater effect could be secured for this investment.

Establishing NICE Policy and Mode of Operation

NICE, serving the NHS in England and Wales, was established as a special health authority on April 1, 1999, with an overall budget of £10.6 million for 1999–2000. This budget will be increased to £12.6 million for 2001–2002, mainly to reflect the additional costs of dissemination of their recommendations and guidance but also to take into account the resources needed to expand the technology appraisal and clinical guideline programs. The institute's role is to provide guidance to health professionals in the NHS in England and Wales on the management of diseases and conditions, on the organization of care, and on the use of specific new and existing health technologies. The institute is required to provide a version of its guidelines for patients and caregivers.

Only a small proportion of the institute's budget (around £1 million) is for the national assessment of new technology, with the remainder directed toward other forms of guidance and meeting operating costs.

Michael Rawlins, chairman of NICE, has stated that "NICE aims to improve the quality of clinical services across the NHS. It will do this in three ways: by evaluating new drugs and technologies to see if they have a cost effective role in the NHS; by formulating and disseminating guidelines on numerous conditions for doctors, carers, and patients and by developing and promoting clinical audit" (Rawlins 1999). Put more bluntly by the then secretary of state for health, Frank Dobson, NICE will "sort out the wheat from the chaff by protecting patients from outdated and inefficient treatment, and so enable the NHS to do a better job for patients." Another stated objective of NICE is to assist in reducing geographical variations in access to health care treatments, which have developed through different interpretations of quality and cost.

A consultation paper, "Faster Access to Modern Treatment: How NICE Appraisal Will Work" (NHS Executive 1999), sets out in detail how NICE will evaluate interventions and develop guidance on clinical efficacy and cost-effectiveness. NICE guidelines require manufacturers/sponsors of technology to make detailed submissions on the purpose, price, and clinical and cost-effectiveness of the intervention within 12 weeks of NICE's request for information. New drugs present particular difficulties; they usually have been evaluated in relatively few clinical efficacy trials, and there is often uncertainty about their value to patients (Freemantle and Mason 1999). Trial results are often published after the drugs have been introduced, and may not include enough data on all the outcomes. Thus it is important to request that companies provide unpublished data.

Data for the reviews are obtained from the public domain as well as the company submissions. The institute asks that companies disclose all relevant data. They are encouraged to confirm in writing that they have done so by providing in exchange, for example, a guarantee that NICE will not disclose any confidential commercial data to third parties. NICE has no legal powers to compel companies to release relevant (to an appraisal or guideline) data. In this respect, it differs from the Medicines Control Agency, which operates within a legal framework that requires disclosure of all relevant information to allow a judgment to be made about a compound's safety, efficacy, and quality.

In most appraisals, NICE has been able to access the data it needs (although it does not know whether all the available data have been made available). In one or two cases, NICE has requested, for example, anonymous individual patient

data, but has been denied. It is not likely that NICE will operate in a situation that requires companies to release information with the threat of legal sanction to back up requests.

The final decision on referrals of topics that NICE will assess rests with the secretary of state for health and the Welsh Assembly, a situation that threatens to reduce the independence of NICE from government and so may affect its credibility with the NHS and the public. Twenty-two topics were announced for referral to NICE, of which 11 were pharmaceutical interventions, including both new drugs for influenza and beta interferon for patients with relapse-remitting MS. The first appraisal was of the anti-influenza drug zanamivir (Relenza).

It should be stressed that the appraisal process conducted by NICE is distinct from and takes place generally after the licensing process, which is the responsibility of the Committee of Safety in Medicines. Licensing decisions in general are based on judgments about safety and efficacy. Decisions about whether or not to publicly fund a drug, however, are based on clinical effectiveness and cost-effectiveness—the likely impact a drug will have on patients' quality of life and at what cost relative to alternatives available.

Why Was the Policy Initiated? The Relenza Appraisal

Relenza was the first health technology referred to NICE. Zanamivir (Relenza) is a medicine licensed to alleviate the symptoms of influenza and hasten recovery (Wenzel 2000). Because of the need to prepare for possible action within the NHS prior to the advance of winter and the onset of increased incidence of influenza, NICE was asked to carry out a special fast-track appraisal and report the results to health ministers. The fast-track appraisal process, which took about three months, was both different in approach and time frame from current arrangements (for details of the rapid appraisal process, see http://www.nice.org.uk/nice-web/Cat.asp?c=426). Typically, appraisals take about 10 to 12 months to complete (for details, see http://www.nice.org.uk/).

The use of the rapid appraisal mechanism mentioned in "Faster Access to Modern Treatment" (NHS Executive 1999) was an option open to NICE. The Relenza appraisal was an opportunity to test some of the principles underpinning NICE's approach to technology evaluations and to establish the organization while doing something useful for the NHS.

NICE set up a special rapid assessment committee chaired by its chief executive, Andrew Dillon, to produce preliminary guidance on the drug before a possible autumn or winter flu epidemic. The committee met twice in September 1999 and invited representatives from the drug's manufacturer, Glaxo Wellcome, to attend its second meeting. In October 1999 NICE ruled against the NHS's using Relenza. NICE believed that the current evidence from the manufacturer's clinical trials by the manufacturer suggested only a moderate benefit of the drug to otherwise healthy individuals: reducing flu symptoms by about one day with uncertain costs to the NHS. The crux of the argument over zanamivir hinged on whether trials proved that the drug is effective in high-risk patients, such as elderly people, those with asthma, or those with chronic respiratory disease, and saves lives. In the absence of clear evidence of its effectiveness in high-risk patients, NICE advised GPs not to prescribe zanamivir during the 1999–2000 flu season (see Appendices 1 and 2).

Under the institute's rules, the manufacturer of any drug being assessed has the right to appeal to the institute's board before any interim guidance is submitted to the secretary of state. Glaxo Wellcome did appeal but failed to reverse the decision.

This was the first recommendation by the new institute and raised important questions about the criteria for decision making, the role of costs, and the degree to which decisions by NICE and the secretary of state would be binding on clinicians. In fact, NICE's recommendations have no legal standing. Nonetheless, it is anticipated that health professionals will act on these recommendations because of NICE's moral and intellectual authority and the subsequent legally binding decisions on coverage made by the secretary of state for health.

The secretary of state for health and the secretary of the Welsh Assembly agreed to accept NICE's advice and asked it to issue guidance to clinicians in the NHS. This was not the same as a "ban" on prescription. Clinicians remained responsible for applying their own clinical judgment to the circumstances of individual patients. However, in making such judgments, clinicians were expected to take NICE guidance into account. NICE also advised that flu immunization remains the most effective intervention in preventing complications. Rates of vaccine uptake remain low, but beginning in autumn 2000, GPs now receive a fee per vaccination of people over 65 and those at high risk.

NICE recommended that the NHS give practical assistance to Glaxo Wellcome in pursuing further trials needed to obtain improved evidence of zanamivir's clinical efficacy and cost-effectiveness in high-risk groups. The Department of Health agreed to assist Glaxo Wellcome by providing access to GP research networks and infrastructure.

NICE reviewed its guidance ahead of the flu season in the winter of 2000–2001. It had committed itself to doing so at the end of the rapid review, in October 1999, on the basis that the manufacturer had indicated it had initiated further clinical trials and also wished to undertake additional study of the impact on primary-care workloads of the drug's availability. The institute treated the review as a completely new appraisal, initially receiving a revised submission from the manufacturer that reviewed existing data, followed by a supplementary submission containing an analysis of a new trial. This new trial looked at the effects of the medicine on specific at-risk populations (trial reference NAI30008).

The new trial data were not available to the Appraisal Committee until after its initial (one of two) meetings to consider

Relenza. Its provisional determination, which involved consultation with the manufacturer and interested patient and professional groups, did not propose a change to the existing (October 1999) guidance. This is significant, since the composition of the Rapid Review Committee and the Appraisal Committee differ, with few members of the former appointed to the latter. The Appraisal Committee effectively "validated" the Rapid Review Committee's conclusions. At its second meeting, the Appraisal Committee was able to consider a review, prepared by an independent academic team at the University of Birmingham (UK), of the NAI30008 trial as well as an integrated analysis with high-risk patients from previous studies. This review concluded that although of borderline significance, there was evidence that Relenza, by reducing complications in specific at-risk groups, would reduce hospital admissions and deaths. The Appraisal Committee concurred and advised the institute to issue revised guidance with the following key elements:

- For otherwise healthy adults with influenza, the use of zanamivir is not recommended.
- Zanamivir is recommended, when influenza is circulating in the community, for the treatment of at-risk adults who present within 36 hours of the onset of influenza-like illness (ILI) and who are able to commence treatment within 48 hours of the onset of these symptoms.

Based on the evidence from clinical trials, at-risk adults are individuals falling into one or more of the following categories:

- age 65 years or over
- chronic respiratory disease (including chronic obstructive pulmonary disease and asthma) requiring regular medication
- significant cardiovascular disease (excluding individuals with hypertension)
- immunocompromised
- diabetes mellitus

Community-based virological surveillance programs should be used to indicate when influenza is circulating in the community.

Effective targeting of zanamivir for the at-risk adult population with a high incidence of true influenza is essential to maximize both the clinical and cost-effectiveness of this therapy.

This revised guidance was issued by the institute in November 2000 and will be reviewed in November 2002.

Who Was for the Policy, and Who Opposed It?

NICE as Policy

Overall, there was little opposition to the creation of NICE. Many in the NHS had long held a desire for national leadership and guidance on the use of health technologies; the idea was also supported because it was part of a larger strategy to tackle NHS quality issues (NHS Executive 1998). The research community, in particular those involved in health technology assessment, was especially supportive of NICE, viewing it as providing a useful link between evaluation work, policy, and practice. However, researchers expressed anxieties about the methodology to be employed and the quality of the appraisal process (Freemantle and Mason 1999).

The pharmaceutical industry did convey considerable suspicion about what its role would be, how decisions would be made, and the status of NICE's recommendations. Manufacturing professionals and researchers saw it as simply a cost-control mechanism rather than a tool for increasing rational health care provision.

Relenza as Policy

Both the manufacturer of the drug, Glaxo Wellcome, and the DoH agreed to the appraisal, although the evaluation would have gone ahead anyway. The manufacturer was also assured that its application would be viewed pragmatically, and with an understanding of the limits of the fast-track review.

History of Implementing the Policy on Relenza

The initial policy was well received by general practitioners and their representatives. Data from the Prescription Pricing Authority (PPA) on prescribing of Relenza in the winter of 1999–2000 show how little was prescribed and thus adherence to the recommendations. However, there was deeply adverse comment from the manufacturer, which expressed concerns about:

- the accelerated review process and appeal;
- the ad hoc choice of experts to review the data;
- the absence of guidelines on what information should be provided to the Appraisal Committee;
- the apparent lack of interest in societal benefits, for example, productivity gain in comparison to the extra workload and costs that the new technology would generate for the NHS;
- the focus on subgroup analyses, for which the trial program had not been designed.

The last point is of particular interest because the crux of the argument over NHS coverage of zanamivir hinges on the effectiveness of the drug in high-risk patients such as the elderly and those with chronic respiratory disease. The trial data, however, included only very few people at high risk. Ideally, trials should have been conducted in as wide a range of patients as possible, and in this case in those at high risk, since this is where the drug, if effective, would be most cost-effective and of value to the NHS. This raises more general issues about the way decisions are made in drug evaluations; it is possible that those involved in R&D and marketing are not sufficiently conscious of or sensitive to the information needs of regulators and health services that are adopting an "evidence-based" approach. It is likely that NICE processes and similar ones in other countries will elevate the importance of cost-effectiveness, affordability, and population impact in ways that will affect the design of Phase III trials.

The concern felt by the drug's manufacturer was heightened because the adverse publicity led to a negative impact on sales of Relenza outside the UK. For example, interest was expressed in the decision globally, from managed care groups in the United States to regulatory groups in Japan. Under the intense public spotlight, the manufacturer expressed misgivings about the long-term repercussions NICE would have on R&D investment decisions in the UK, such that the pharmaceutical industry would turn to other countries to evaluate and launch innovative products. These concerns were key factors in the prime minister's sponsoring establishment of the Pharmaceutical Industry Competitive Taskforce.

The publication of the revised guidelines for Relenza a year later, however, elicited the reverse response. The manufacturer indicated that it was broadly content with the guidance and did not exercise its right to appeal. However, the response of general practitioners—the doctors most likely to prescribe the drug—was different. Although their national representatives did not appeal the guidance, they did indicate doubts about the Appraisal Committee's interpretation of the new trial evidence, arguing that it was insubstantial. However, the GPs' principal worry was that it would result in unacceptable demands on their time, diverting them from attending to more urgent conditions during the winter period. To deal with this concern, the Department of Health encouraged health authorities to use Patient Group Directions (PGD), which allow community nurses and pharmacists to prescribe named medicines to specific groups of patients—in this case, those in the at-risk categories identified in the institute's guidelines. Nevertheless, GPs have generally been less welcoming to the revised guidance than to the original.

Evaluation of the Policy as Implemented

NICE

No evaluation of the NHS quality initiative has been conducted as yet, but invitations to tender for research into the dissemination and impact of NICE guidance were announced in June 2001. The Commission for Health Improvement and the Medical Royal Colleges are charged with monitoring the implementation of NICE guidance, but there are no data as yet.

Relenza

There has been no published evaluation of the initial Relenza guidance, although the rates of prescribing of Relenza were low over the winter period, with a total of only 212 NHS prescriptions being issued at a total cost of only £5,544.

One of the medical profession's criticisms of implementation was that NICE's decision should have been given legislative force. The failure to "blacklist" the drug was thought not to have protected GPs from potentially significant demand from patients. It remains to be seen how NICE will ensure that the advice it issues will have a greater impact than that of other guidelines (such as those from professional organizations and the DoH), and how it will react to contradictory guidance issued by different organizations or by the NHS in Scotland and Northern Ireland. Guidelines will not be mandatory and local discretion will still be the ultimate arbiter of access to health care services. While clinical discretion will not be challenged, guidance is expected to be adopted universally. It is unclear how any conflicts will be resolved.

The influence of the pharmaceutical industry (which is expected to bear the costs of assessment) on the introduction of guidance cannot be ignored. The legal position on guidance may well be challenged, particularly if access to the market is heavily restricted. As has been seen with Viagra, successful legal challenges can be raised to edicts issued by the DoH. Even an unsuccessful legal action may serve to create long-term uncertainty and hamper the effectiveness of NICE. The new assessment procedures may be perceived as reducing the commercial viability of products, and industry may not consider it worthwhile to submit products for assessment in the UK. This is perhaps one reason to create a NICE type of body at European Union level.

Issues of Communication between Policymakers and Researchers

Communication was very good between Glaxo Wellcome and NICE. The company gave NICE all of its data, doing so being seen as in its best interest. Glaxo Wellcome had concerns about the evaluation process, especially the time frame and the short time it was given to prepare its appeal. The company was shown the draft guidance for comment, and was given the opportunity to present its views to the Rapid Appraisal Committee.

However, the manufacturer felt rather "let down" and that it had been given false reassurance. Some of this possibly

stems from the pharmaceutical sector's not quite realizing that the rules of the game had changed, and that this was not the old sort of process that relied on negotiation and behind-doors agreements. For example, the company discussed and agreed on the content of its fast-track submission with members of the institute; however, in the final analysis the Appraisal Committee had significant misgivings about the company's approach to the whole exercise, and the fact that the process had been agreed upon in advance did not have any impact.

Second, the speed of the fast-track appraisal process made it extremely difficult for both sides. For example, it is hard to be sure that the appraisal committee was able to take all the information available into account, given the extremely short time frame involved (although the appeal board's view was that this had been possible).

In addition, Glaxo Wellcome was asked with little explanation to provide further information, which put enormous pressure on individuals within the company. However, it was unclear whether or not this information was essential to the outcome of the process. Glaxo Wellcome was given the opportunity to present its views in person to the Appraisal Committee (which was not permitted for subsequent reviews), but this did not enable the company to fully understand the critical issues involved in review of the submission.

Sources of Funds

The original research (and the subsequent research) has all been funded by the manufacturer. NICE funded the assessment and the appraisal. NICE is funded directly by the DoH/National Assembly for Wales.

Current Status of NICE

The institute's program of assessments is now fully developed. (For details see http://www.nice.org.uk/.) As of January 2001, nine appraisals have been produced, with the intention to produce 50 per year, along with around 18 clinical guidelines.

REFLECTION AND GENERALIZATION

What Was Expected?

NICE appears to have had a genuinely open mind about the outcome of its Relenza appraisal. The strength and unanimity of the Rapid Appraisal Committee's conclusions was impressive. NICE felt confident that the guidance was robust. On the other hand, the manufacturer was genuinely surprised and frustrated by the outcome. Glaxo Wellcome felt that it had been reassured by the dialogue with NICE that the decision would be "pragmatic" and would take into account the fact that this was a fast-track submission. In reality, however, the company's submission was judged purely on the information about the drug available. While this makes sense from the perspective of researchers and the experience of other countries with "fourth hurdle"–type regulations, it was clearly a departure from previous approaches in the UK and took industry by surprise. It appears in retrospect that Glaxo Wellcome's representatives thought that because this was the first "trial run" of the NICE process, and that NICE had been open and discussed the process with them, the company would be given an easy ride. Possibly NICE saw this as an opportunity to flex its muscles and announce in a clear way that it had "arrived" with a drug for which there was unlikely to be great professional or public support. The expectations of NICE and Glaxo Wellcome were clearly different.

Industry is concerned that NICE and its focus on costs and the burden on primary care could stifle the introduction of new medicines in therapeutic areas where currently there are no satisfactory therapies. How to establish appropriate regulation without at the same time harming genuine innovation is a difficult issue that needs more research.

What Was Learned?

NICE learned much about the process of assessment, appraisal, and dissemination of its guidance, as well as from its direct exposure to the pharmaceutical industry. The institute was perhaps surprised by the potential depth and extent of the impact it could have both inside and outside the UK. It was exposed to intense media and political scrutiny. All of this was formative and positive for the four people who at the time were the only ones employed by the institute. As a result NICE has dedicated considerable efforts toward making the "rules of the game" clear and explicit so that all parties know what is expected. The institute has come pretty much to the conclusion that the fast-track process is not desirable and that a more thorough and extended appraisal process should be adopted.

It was also clearly a huge learning experience for the industry as its first undertaking with NICE. The industry's principal learning points with regard to process were as follows:

- Current Phase III studies would not satisfy NICE requirements; the need for studies in specific subgroups, integrated analysis, and comparator data means that the cost of drug development is likely to be increased.
- The drug industry needs to have a clear understanding of the requirements for economic information and methodology, and how to handle uncertainty, especially in difficult areas such as potential impact on the service.
- Although affordability was not a spoken objective of the review, it was clearly a factor in decision making.
- There is a need for confidentiality during the decision-making process. The premature "leaking" to the press and the public of preliminary and final decisions and the subsequent political manipulation and media coverage made

it extremely difficult to conduct subsequent discussions with NICE, and present an ultimate appeal, in a balanced way. This has occurred with at least one other appraisal (beta interferon).

What Has Made the Policy Succeed or Fail?

NICE is of the view that the Relenza policy has been a success in that the institute produced guidance that has been widely supported and comprehensively implemented. It was needed and wanted, produced at the right time, and disseminated effectively. This is probably the general view of the NHS. However, from the pharmaceutical industry's perspective, there remains debate about whether it was the validity of the guidance itself or the media coverage surrounding it that made the policy successful. Some people took home the message that Relenza didn't work and that it was banned—neither of which was true or what the guidelines indicated.

It is doubtful that NICE guidance on treatments relevant to better-defined, high-profile, well-organized patient or client groups such as those whose members have MS or some cancers will be as well received or easily accepted. After all, there is less of a lobby for influenza sufferers! NICE has tended to recommend the use of cancer drugs, such as taxanes for the treatment of ovarian and breast cancer. However, it initially advised against prescribing beta interferon for MS, a decision that has resulted in much debate in the press, an appeal, and several delays in reaching a final ruling because of additional time needed to review evidence and model cost-effectiveness.

At the time this report has been in preparation, it is not clear to what degree NICE will be willing and able to make deeply unpopular recommendations, even when they have a strong evidence base. A recent editorial by the editor of the *British Medical Journal* criticized NICE for failing to ration health care effectively because it has not said no to most technologies considered (Smith 2000). This negative commentary will have an impact on the institute's credibility and the potential for its future collaboration with researchers.

The establishment of NICE and its processes has had one other effect on the research community in England. The ambitious appraisal timetable the institute has set will result in a significant increase in research activity, and thus the country's need for research capacity. NICE, with a budget of approximately £10 million in 1999-2000, will increase its requirement of systematic reviews of research and of economic analysis and modeling. This demand will come not only from NICE but also from the pharmaceutical companies, which increasingly realize that they need high-quality methodological input to prepare convincing submissions to NICE.

The effect of increasing demand in this sector could be negative in the short term if the UK's fixed and relatively limited research capacity is pulled into NICE-related activity, and thus possibly away from other innovative research areas that might be seen as too risky for NICE submissions. This diversion of research resources may also have a distorting effect on the agenda of the NHS R&D program. In the longer run, however, it will probably stimulate the development of more robust but flexible methods for assessing the cost-effectiveness and impact of new technologies.

GLOSSARY

DoH
Department of Health

GDP
Gross Domestic Product

GP
general practitioner

HTA
health technology assessment

ILI
influenza-like illness

MS
multiple sclerosis

NHS
National Health Service

NICE
National Institute for Clinical Excellence

NSF
National Service Framework

PES
Public Expenditure Survey

PGD
Patient Group Directions

PPA
Prescription Pricing Authority

PPRS
Pharmaceutical Price Regulation Scheme

R&D
research and development

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APPENDIX I. EXTRACT OF FIRST GUIDANCE: ZANAMIVIR

12 October 1999

Issued to

Health Authority Chief Executives
NHS Trust Chief Executives
PCG Chief Executives
Local Health Group General Managers
Special Health Authority Chief Executives
NHSE Regional Directors

Chief Officers of Community Health Councils

Issue date: October 1999

Review date: September 2000

1.

The National Institute for Clinical Excellence has been asked, by the Department of Health and the National Assembly for Wales, to prepare guidance for use within the NHS of zanamivir (Relenza) for the treatment of influenza, during the forthcoming winter. This guidance will be reviewed, in advance of the 2000/2001 influenza season. New guidance will then be issued to cover both zanamivir (Relenza) and oseltamivir (Tamiflu), which is expected to be licensed next year.

2. The Status of This Guidance

2.1

Zanamivir (Relenza) is authorised in the United Kingdom as a prescription-only medicine for the treatment of influenza A and B in adults and adolescents, 12 years of age and over, who present with symptoms typical of influenza when influenza is circulating in the community.

2.2

Zanamivir (Relenza) is accordingly now available for prescribing on the NHS. Individual health professionals have a responsibility to exercise their clinical judgement in determining what treatments are appropriate and necessary for patients with influenza-like symptoms. This guidance does not override that individual responsibility. It is intended to assist health professionals with advice on the appropriate use of zanamivir (Relenza) alongside current best practice. The guidance represents the view of the Institute's Rapid Appraisal Committee (the membership of which is set out in Annex A), arrived at after careful consideration of the available evidence. Health professionals are expected to take it fully into account when exercising their clinical judgement.

3. Summary

3.1

Influenza is an acute respiratory illness caused by infection with influenza viruses A, B and C. Although the primary site of infection is unclear, the virus replicates through the respiratory tract. Influenza is associated with the sudden onset of pyrexia associated with general aches and pains, anorexia, nausea, vomiting and usually a harsh unproductive cough. Most patients do not develop complications and acute symptoms subside within 3-5 days. Patients with underlying morbidity are exposed to complications, which may result in serious illness and death

3.2

The combined evidence from the relevant clinical trials indicates that the use of zanamivir (Relenza), within 48 hours of the onset of symptoms of influenza, reduces the duration of the illness, by one day, from a median of 6 to 5 days.

3.3

Due to the limited numbers of "high risk" patients (particularly the elderly and those with cardiovascular disease, asthma, chronic obstructive pulmonary disease, or immunosuppression) that have been treated with zanamivir (Relenza) in clinical trials, the Institute has not found it possible to conclude that the product reduces the frequency of serious secondary complications in these groups of patients.

3.4

On the basis of its findings and conclusions, the Institute advises that health professionals should not prescribe zanamivir (Relenza) during the 1999/2000 influenza season. The NHS should encourage, and where possible, support the manufacturer in the conduct of the four additional clinical trials which are currently underway.

. . .

6.8

The Institute's guidance applies only to the 1999/2000 influenza season. It is anticipated that zanamivir (Relenza) will be the subject of a further appraisal by the Institute next year. New guidance will then be offered for the 2000/2001 influenza season.

7. Further Information

A summary of the evidence used by the Rapid Assessment Committee can be found on the Institute's web site at www.nice.org.uk.

Yours sincerely,

Andrew Dillon
Chief Executive
12 October 1999

APPENDIX 2. SUMMARY OF EVIDENCE 2001: FAST-TRACK APPRAISAL OF ZANAMIVIR (RELENZA)

This contains extracts of the document summarising the evidence used in the fast-track appraisal of zanamivir (Relenza) undertaken by the National Institute of Clinical Excellence. This document supports the Interim Guidance provided to the Secretary of State for Health and the National Assembly for Wales.

1.0. Introduction

1.1. Background

1.2. Epidemiology

1.3. Current service provision

The mainstay of current influenza management is symptomatic treatment and bed rest. The majority of patients who develop influenza rely on treatment with drugs that target troublesome symptoms. This usually represents self-medication with over-the-counter cold and flu remedies.

Two general measures are currently used within the NHS to reduce the impact of flu: immunisation by vaccines and antiviral prophylaxis/therapy with amantadine. . . .

1.4. Zanamivir

Zanamivir is the first of a new class of selective influenza virus neuraminidase inhibitors. It is marketed by Glaxo Wellcome under the trade name Relenza. Zanamivir is a selective inhibitor of both Influenza A and B virus neuraminidases, essential for viral replication. Its inhibits the viral cleavage of sialic acid from cell surface glyconjugates. Consequently, it prevents infection by stopping the release of newly formed viruses from the surface of infected cells and preventing viral spread across the mucus lining of the respiratory tract. Zanamivir has been approved by the European Licensing Authorities and was launched in UK in September 1999. Its licensed indication is in the treatment of both influenza A and B, in adults and adolescents (=>12 years) who present with symptoms typical of influenza when influenza in circulating in the community. Its pharmaceutical form is a pre-dispensed inhalation powder product delivered by a breath-activated device (Diskhaler). The recommended dose is two inhalations per day for 5 days, providing a total of 20mg daily. It is recommended that treatment should be initiated within 48 hrs of the onset of symptoms.

2.0. Methods

2.1. Identification of evidence

Electronic bibliographic searches (Cochrane Library, HealthStar, PharmLine, Medline, Embase, and National Research Register) were undertaken to identify studies that address the clinical effectiveness and cost effectiveness of zanamivir as a treatment for influenza. As part of a Fast Track Appraisal procedure, the Institute formally sought a submission on zanamivir from its manufacturer, Glaxo Wellcome, according to the format outlined in the Institute's guidance to manufacturers and sponsors. This submission is referred in the remainder of this report as the "industry submission."

2.2. Selection of evidence

Studies were included if they were of randomised controlled trial design and compared zanamivir treatment to placebo or current therapy in adult patients with influenza A or B infections. Studies were excluded if they: (1) addressed the use of zanamivir in influenza prophylaxis; (2) did not use the zanamivir's license dosing and formulation regime; (3) examined zanamivir in experimentally induced influenza.

2.3. Assessment of the quality of evidence

The quality of the identified studies of zanamivir were assessed on the basis of the: (1) clarity of randomisation

procedure; (2) thoroughness of blinding; (3) use of intention to treat analysis; and (4) clarity of description of patients lost to follow up.

3.0. Results

3.1. Excluded trials

Eleven randomised controlled trials were identified; one of which were unpublished. Seven of these trials were excluded, four because they did not assess the recommended dosing regime, and three because they were prophylactic trials, one of which involved experimentally induced flu.

3.2. Included trials

Three trials of zanamivir met the inclusion and exclusion criteria of this review. These were all Glaxo Wellcome phase III trials, each conducted in three different continents: (1) NAIB3001 - Southern Hemisphere; (2) NAIA3002 - North America; (3) NAIB3002 - Europe. All trials are randomised, double blind, and placebo-controlled. The Southern Hemisphere trial [NAIB3001] has been published in full the North American [NAIA3002] and European trial [NAIB3002] published as conference abstracts. A pooled ("integrated") analysis of all three trials was also reported in the industry submission. The pooled analysis was unpublished at the time of this report, although a publication of this pooled analysis has been accepted for publication. The primary outcome in all trials was time to alleviation of symptoms. Secondary outcomes included complications, antibiotic usage, and time to return to normal activities.

3.3. Economic evaluations

No published economic evaluations of zanamivir were identified. A model for the cost effectiveness and budget impact of zanamivir was presented in the industry submission.

3.4. Details of selected studies

The details of the three selected trials for inclusion in this report are summarised in Table 1. All the trials were well conducted—clearly described randomisation procedure, patients/healthcare staff/assessors blinded to treatment allocation, and analysis undertaken by intention to treat.

TABLE 1. SUMMARY OF INCLUDED TRIALS

	NAIB3001 Southern Hemisphere (SH)	NAIA3002 North America (NA)	NAIB3002 Europe (EUR)	Total
Intervention (placebo control)	10mg IH 2 x daily for 5 days	10mg IH 2 x daily for 5 days	10mg IH 2 x daily for 5 days	
Trial Duration	28 days	208 days	28 days	
Participants Male no. (%)	241 (53)	374 (48)	165 (46)	780 (49)
Age: mean yrs (range)	37 (12–82)	35 (12–84)	37.5 (12–81)	
Onset of symptoms	<=36hrs	1–2 days	1–2 days	
Inclusion	1. Fever (i.e., temp =>37.8°C) and/or 2. Feverish 3. at least 2 of headache, myalgia, cough, sore throat	1. Fever (i.e., temp =>37.8°C) 2. at least 2 of headache, myalgia, cough, sore throat	1. Fever (i.e., temp =>37.8°C) 2. at least 2 of headache, myalgia, cough, sore throat	
Total no. of Patients	455 Placebo = 228 Active = 227	777 Placebo = 365 Active = 412	356 Placebo = 182 Active = 174	1,588 Placebo = 775 Active = 813
High risk no. (%)	76 (16.7)	109 (14.0)	32 (9.0)	217 (13.7)
=>65 years no. (%)	14 (3.0)	44 (5.7)	13 (3.7)	71 (4.5)
Other no.	62 (13.6)	65 (8.4)	19 (5.3)	146 (9.2)
Primary Outcome	Time to alleviation of clinically significant symptoms	Time to alleviation of clinically significant symptoms	Time to alleviation of clinically significant symptoms	
Lab-confirmed Influenza	Culture Serology Immuno fluorescent Rapid diagnostic test	Culture Serology PCR	Culture Serology PCR	
Influenza Positive no. (%)	321 (71)	569(73)	277(78)	1,167 (73)

3.5. Clinical effectiveness

Results were evaluated in the intention to treat population (i.e. all patients randomised & the analysis by which clinical effectiveness can be assessed); influenza positive population and high risk population (i.e. patients with chronic respiratory, cardiovascular (excluding hypertension) or metabolic disorders, and immunocompromised and elderly (=>65 years) patients).

3.5.1. Symptom relief

A median reduction of 1.0 day (95%CI: 0.5 to 1.5 days) in the time to alleviation of symptoms with zanamivir was reported in pooled intention to treat population (see Table 2).

TABLE 2. TIME TO ALLEVIATION OF SYMPTOMS

	Intention to Treat Population				Influenza Positive Population				High Risk Population			
	Patient No.	Median No. of days placebo	Median No. of days active	Difference (95% CI)	Patient No.	Median No. of days placebo	Median No. of days active	Difference (95% CI)	Patient No.	Median No. of days placebo	Median No. of days active	Difference (95% CI)
NAIB3001 SH	455	6.5	5.0	1.5 (0.5 to 2.25) p=0.011	321	6.0	4.5	1.5 (0.5 to 2.25) p=0.004	76	8.0	5.5	2.5 (-1.0 to 8.0) p=0.048
NAIA3002 NA	777	6.0	5.5	0.5 (-0.5 to 1.0) p=0.228	569	6.0	5.0	1.0 (0.5 to 1.5) p=0.078	109	6.5	7.5	+1 (CI not given) p=0.710
NAIB3002 EUR	356	7.5	5.0	2.5 (0.75 to 3.5) p<0.0001	277	7.5	5.0	2.5 (1.0 to 4.0) p	32	11.5	9.0	2.5 (CI not given) p=0.178
Total	1,588	6.0	5.0	1.0 (0.5 to 1.5) p<0.001	1,167	6.5	5.0	1.5 (1.0 to 2.0) p<0.001	217	8.0	6.0	2 (95% CI -0.5 to 4.25) p=0.127

TABLE 3. RESULTS: COMPLICATIONS

	Intention to Treat Population			Influenza Positive Population			High Risk Population		
	Placebo N(%)	Active N (%)	Absolute difference % (95% CI)	Placebo N(%)	Active N (%)	Absolute difference % (95% CI)	Placebo N(%)	Active N (%)	Absolute difference % (95% CI)
NAIB3001 SH	64/228 (28%) (28%)	49/227 (22%)	6% (-2% to 15%) p=0.135	48/160 (30%)	38/161 (24%)	6% (-4% to 17%) p=0.243	18/39 (46%)	5/37 (14%)	32% (11% to 54%) p=0.004
NAIA3002 NA	86/365 (24%)	74/412 (18%)	6% (0% to 12%) p=0.066	57/257 (22%)	48/312 (15%)	7% (0% to 14%) p=0.049	17/60 (28%)	17/49 (35%)	+6% (CI not given) p=0.612
NAIB3002 EUR	61/182 (34%)	40/174 (23%)	11% (1% to 20%) p=0.037	47/141 (33%)	33/136 (24%)	9% (-2% to 20%) p=0.125	11/19 (58%)	4/13 (31%)	27% (CI not given) p=0.250
Total	211/775 (27%)	163/813 (20%)	7% (3% to 11%) p<0.001	152/558 (27%)	119/609 (20%)	8% (3% to 13%) p=0.002	46/118 (39%)	26/99 (26%)	13% (CI -1% to 26%) p=0.065

In both the intention to treat, influenza positive and high risk populations, the reduction in symptom alleviation with zanamivir varied across the trials. There was no significant reduction in the time to symptom alleviation in the North American trial.

3.5.2. Complications

Overall, there was absolute reduction in complications with zanamivir of 7% (95% CI: 3% to 11%) in the intention to treat population (see Table 3). In the high risk population, there was, overall, an absolute reduction in complications of 13%,

although in the North American trial, the level of complications increased by 9% (No CI given) in the zanamivir group. This pattern of results was associated with a pooled absolute reduction in antibiotic usage of 4%(0% to 8%, p=0.047), 5% (0% to 9%, p=0.037), and 7% (CI not available, p=0.33) in the intention to treat, influenza positive, and high risk population respectively.

3.5.3. Cost and savings

The anticipated cost of zanamivir in UK will be £24 per 5-day course of treatment. The industry submission presents a detailed economic analysis that indicates that the direct costs to the health service of zanamivir will be less than this figure (i.e., £18.52). This latter cost, as stated in the industry submission, was the result of a reduction in antibiotic costs, GP consultation costs and inpatient cost through re-hospitalisations. This analysis was based on economic modelling using a number of assumptions. For example, re-hospitalisation was not directly assessed in the three phase trials, but predicted from complication rates.

The indirect costs associated with early return to work were also modelled. It was reported that enhancement of productivity with zanamivir would result in an overall cost saving to society of £21.51 per patient.

3.5.4. Cost effectiveness and cost utility

The industry submission reported a direct cost of zanamivir of £18.52 and a reduction in the duration of influenza symptoms by 1.0 day. The cost effectiveness ratio was an incremental cost of £18.52 per day of symptom alleviation associated with zanamivir. This ratio would increase to £24.00 if the direct cost of zanamivir of £24 were used.

4.0. Discussion

4.1. Conclusions

Zanamivir for treatment of influenza has now been evaluated in its proposed license form in three randomised double blind multi-centre controlled trials enrolling approximately 1500 patients. Fully published data is available at present on one of these trials.

There was evidence from the three trials of the benefit of zanamivir in terms of reduction in time to alleviation of symptoms and complications. There was no significant reduction in the time to alleviation of symptoms in the North American study, which was the largest trial. There was evidence from the clinical study report that the mean number of paracetamol tablets and cough mixture usage were higher in the North American trial than in either of the other two trials. However, there was little evidence for differential patient preference for symptomatic relief medication when comparing the zanamivir and placebo arms of the North American trial. In the interpretation of these findings, it is important to recognise that use of symptomatic medications is an accepted element of patient's current management of influenza in the UK.

Although a cost effectiveness ratio (based on the incremental cost per symptom day prevented with zanamivir) is presented within the Industry submission, such analysis was considered questionable given the inconsistency described above in the time to symptom alleviation across trials and the large number of assumptions upon which the calculation of cost are based.

4.2. Implication for the NHS

4.4. Current and planned research

Glaxo Wellcome has identified four randomised, double blinded, placebo-controlled trials of zanamivir treatment, either ongoing or about to begin. These have been designed to address the effectiveness of zanamivir in high risk, elderly, and paediatric groups and on work productivity. The company states that recruitment to these trials has so far been slow. Glaxo Wellcome state that the earliest the final trial results will be available (assuming full recruitment this winter) is October 2000.

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Reducing Mother-to-Child Transmission of HIV Infection in South Africa

Jimmy Volmink, Patrice Matchaba, and Merrick Zwarenstein

EXECUTIVE SUMMARY

The South African government is under intense pressure from a range of different stakeholders to introduce national policy on the use of antiretroviral therapy for pregnant women with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) to reduce perinatal mother-to-child transmission (MTCT) of the virus. Concerns about the lack of efficacy and potential toxicity of antiretroviral drugs have repeatedly been cited as reasons for the government's position. Yet scientific evidence indicates that antiretrovirals are highly effective for reducing perinatal HIV transmission, and, at least in the short term, the benefits of using these drugs appear to outweigh the risks. There is also clear evidence that a policy favoring the use of antiretrovirals for limiting MTCT is a cost-effective strategy that would lead to a net saving to the health service.

In November 1999 the South African Cochrane Centre, based at the Medical Research Council, was commissioned by South Africa's Minister of Health, Manto Tshabalala-Msimang, to report on the risk-benefit profiles of interventions for curtailing vertical HIV transmission. The minister was particularly interested in information on antiretroviral agents, and the drug zidovudine (AZT, ZDV, Retrovir) was of primary concern.

The researchers (J.V. and P.M.) carried out the literature review that formed the basis of the report. They found strong evidence that both an intensive regimen (AIDS Clinical Trial Group, or ACTG 076, protocol) and shorter courses of zidovudine are effective for decreasing the transmission risk, and that this benefit appeared to be sustained even in breast-fed populations. The most important adverse effect identified was anemia in early life, especially with the use of the ACTG 076 regimen, but this effect resolved on stopping treatment. They found no evidence concerning the long-term effects in children exposed to zidovudine in utero and the neonatal period. The researchers also found limited evidence that nevirapine (Viramune), a less expensive drug, was effective and safe.

The findings, which were reported to the minister of health in December 1999, did not initially appear to have changed the government's stance on offering antiretrovirals during pregnancy. The Ministry of Health did not respond to a written request by the researchers for a meeting with health officials to discuss the contents of the report. Furthermore, repeated attempts by the researchers to contact the director-general for health by telephone in this regard proved unsuccessful.

This study examines the interaction between researchers and policymakers on the issue of antiretroviral therapy for the prevention of MTCT, providing background information about the political and epidemiological context of this interaction and summarizing key lessons learned about communication between policymakers and researchers. In the case of antiretrovirals in pregnancy, it seems that scientific evidence is not yet a powerful force in government decision making in South Africa. It appears to be eclipsed by political agendas and entrenched prior views that give undue weight to unsubstantiated opinion. Policymakers may have to ignore those who provide evidence or undermine their public standing in order to justify their action or inaction. Those who produce evidence are prevented from engaging further with policymakers once it is clear that their conclusions will not bolster the previously planned policy. We recommend thorough stakeholder analysis before preparing detailed evidence summaries.

Although a provincial-level policymaker initially agreed to participate in this policy/research collaboration, he did not comment on the contents of this document and, after reading the initial version of the paper drafted by the researchers, requested (without giving reasons) that his name be removed as coauthor. He also did not attend the workshop at which the paper was discussed, citing work pressure as the reason for his absence. We speculate that policymakers in South Africa do not feel at liberty to express their personal opinions on politically sensitive issues, fearing that doing so might be construed as criticism of their superiors. This report therefore reflects the views of the researchers only.

Barriers

- Lack of appreciation on researchers' part of the complexity of the issues influencing health care decision making
- Failure of highest-level national policymakers to provide feedback on the work undertaken by the researchers
- Reluctance of highest-level national policymakers to engage with researchers following the release of their apparently unwelcome findings
- Reluctance of middle-level provincial policymaker to take part in this policy research collaboration, following high-level politicization of the topic

Facilitators

- Personal communication between highest-level policymakers and researchers early in the project
- Lawsuit to prevent the South African government from importing generic versions of patented AIDS drugs

Lessons Learned

- Evidence is not yet a powerful force in government decision making about health-related issues in South Africa. It appears to be eclipsed by political agendas and entrenched prior views.
- Unsubstantiated opinion seems to hold more sway than well-founded scientific evidence when the former agrees with governmental policy and the latter disagrees.
- Policymakers cannot predict or control the evidence they will receive and, in order to justify their own action or inaction, may have to ignore those who provide evidence or undermine their public standing.
- Those who produce scientific evidence are prevented from engaging further with policymakers once it is clear that their conclusions will not bolster the previously planned policy.

- It is important that researchers tailor the amount of their efforts according to the likely use to which the evidence will be put. If it seems likely that initial evidence assessment is producing unwelcome results, little point is to be served in delving deeper.
- Thorough stakeholder analysis should be conducted prior to developing detailed evidence summaries.

INTRODUCTION

Health Care in South Africa

South Africa is a middle-income sub-Saharan country with a population of approximately 40 million. It has recently emerged from 350 years of colonialism into a globally celebrated democratic constitution, but remains among the world's most inequitable societies along racial and class lines. The state is a declining contributor to and user of gross domestic product (GDP), with recent government commitment to private enterprise and a classic market economy. The health system is ineffective for the amount expended on it, ranking 180th of 191 in the World Health Organization's recent performance rating in relation to health status, and 175th in relation to health system performance (WHO 2000a). These rankings are well below those of many poorer countries.

South Africa has both a public and a private health care system. Private health care consumes about 70 percent of the total national health care expenditure. Of the country's approximately 40 million people, only 7 million have private health insurance and funding; the rest depend on government support. Until 1999, private health care fund managers were allowed to select who could apply and participate in their plans. As a result, they typically recruited healthy, low-risk people, and when risk was a factor, they charged more. Unemployed people and ill patients who could not afford the increased premiums were left to be looked after by the state. This "cherry picking," as it is now called, was put to a halt by an act of Parliament in 1999, as the state believes that the risk and cost of health care must be shared.

Because drug costs are a significant factor in the national health care budget, only medications that have been put on an essential drug list are paid for by the state and generic prescribing is encouraged to keep costs down, a situation that in part explains the current crisis regarding the proposed parallel importation of cheaper generic antiretrovirals (offer from Cipla in India) and pharmaceutical manufacturers' insistence that their patents be respected. When no generics are available, the state orders drugs from the pharmaceutical industry via a tender system, typically resulting in prices that are at least 20 percent lower than in the private market.

According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), 5.4 million people (620,000 children among them) were newly infected with HIV during 1999, bringing the total number of people living with HIV/AIDS to 34.3 million (including 1.3 million children) (UNAIDS 2000). Of these, an estimated 18.8 million AIDS deaths (including 3.8 million children) have already occurred since the start of the epidemic.

Sub-Saharan Africa has a disproportionate burden of HIV/AIDS cases, with 24.5 million (>70 percent) of the world's infected population concentrated in the region. UNAIDS figures suggest that South Africa has the largest number of people with HIV/AIDS in the world, and that in this country the proportion of adults infected with HIV has grown rapidly, from 12.9 percent in 1997 to 19.9 percent in 1999 (UNAIDS 2000). AIDS is already killing more people in sub-Saharan Africa than war: in 1998, 2 million compared to 200,000 (UNAIDS 2000).

The health, social, and economic implications of the disease for the region are considerable. Of particular concern is the increase in the number of AIDS orphans and the impact this will have, not only on them as children without parents, but also on the demand for social and financial services from the state. Furthermore, infected babies who go on to develop AIDS will be expensive to treat, as they require frequent admission to the hospital.

Consequently, AIDS has been recognized as an issue for human security in Africa, and in 2000 it was chosen as the theme for the United Nations Security Council meeting (see http://www.hivnet.ch:8000/global/intaids/viewR?562). Almost everyone agrees that urgent steps are necessary to control the epidemic, concentrating particularly on the African continent.

Reducing Mother-to-Child Transmission of HIV Infection

Vertical transmission of HIV infection occurs mainly in late pregnancy, during labor, or through breast-feeding (John and Kreiss 1996). In Africa the overall risk of vertical transmission is estimated to be between 25 and 35 percent (Working Group 1995). This relatively high number, combined with high fertility rates, accounts for the fact that more than 90 percent of the cases of pediatric infections are found in sub-Saharan Africa (UNAIDS 2000). The region therefore stands to gain much from wide-scale introduction of efficacious and cost-effective medical interventions for reducing mother-to-child transmission. Conversely, the health, social, and economic costs of failing to implement such measures, where available, are likely to be enormous. It is with this in mind that the researchers engaged to prepare this report eagerly responded to the South African government's request for information on antiretrovirals.

POLITICAL CONTEXT

South Africa does not yet have a comprehensive, evidence-based, national policy to deal with the HIV/AIDS epidemic. Policy decisions on what interventions do or do not work are not arrived at using a systematic, evidence-based

approach. A system similar to the UK's National Institute for Clinical Excellence (NICE) would be advantageous in South Africa, more so in the face of limited resources available.

Governmental Response to the Epidemic

Under the previous National Party government little was done, as HIV/AIDS was not seen as a priority issue, perhaps because it was perceived to affect mainly gays and black people. During the early 1990s, when the epidemic was beginning to gather momentum, the country was in a period of political transition and no effective government existed to deal with the problem. However, hope for a coordinated, rational approach to HIV/AIDS surfaced when the African National Congress (ANC) came into power in 1994.

The new government appeared keen to act promptly and decisively on the issue, appointing a ministerial task force against HIV/AIDS (initially chaired by President Thabo Mbeki when he was deputy president). Awareness campaigns and government support for an HIV vaccine initiative soon followed. These encouraging signs unfortunately gave way to a series of controversies that are widely believed to have hindered control efforts. Against this background, the epidemic has escalated rapidly. Below are some of the more highly publicized reponses from the Department of Health.

Sarafina II

Sarafina II was intended to be a high-profile theatrical production aimed at educating people about reducing the spread of HIV among African youth. It was produced by a popular South African playwright, who was contracted at a cost of 14 million rands. However, a public outcry soon ensued as a result of a growing feeling that this was not a cost-effective intervention strategy. There were also some concerns about possible irregularities in the funding of the project. *Sarafina II* was terminated halfway through the production, amid criticisms against the Health Department for misusing donor (European Union) money. This scandal resulted in a loss of trust and goodwill between the government and AIDS activists and the donor community.

Virodene

Around 1997 some academics from the University of Pretoria reported that they had found a drug cure for AIDS. This drug, named Virodene, contained the industrial solvent dimethylformamide. Several politicians publicly embraced this substance as an inexpensive alternative for treating HIV infection despite the lack of supporting scientific evidence. Before long the government became embroiled in a clash with its drug regulatory authority, the Medicines Control Council (MCC), which refused to approve clinical trials of the drug because of the lack of evidence of efficacy and concerns about toxicity in animal and early human studies. Following this dispute, the chairman of the MCC was dismissed from his position.

The government was later embarrassed by the findings of an independent review panel, led by the South African Medical Research Council, that the "promising" results of preliminary Virodene reseach were largely fraudulent. An opposition party later claimed the government decision to support the development of Virodene had been corrupt (Gazi 2000).

SANAC

The third controversy arose from the replacement of the AIDS Advisory Council with the South African National AIDS Council (SANAC). A number of the country's leading HIV experts and key nongovernmental organizations (NGOs) were excluded from this new body established to advise government on matters relating to HIV/AIDS. A public uproar ensued because it was perceived that this action had been taken as an attempt by the government to marginalize its critics.

AIDS Dissidents

Most recently, President Mbeki caused international concern when he sent an open letter to heads of state, including then President Clinton, that raised questions about whether factors other than HIV could account for AIDS in Africa and called for a uniquely "African solution" to the problem. For advice on this issue Mbeki appointed an international panel of AIDS experts, controversially including a large number of AIDS dissidents led by Peter Duesberg, a professor of molecular and cell biology at the University of California, Berkeley. Duesberg's pseudoscientific thinking on the issue had previously been exposed in the scientific literature (Maclure 1998). The presidential AIDS panel met in May and July 2000 and a report of their discussions has been submitted to the president. This report simply restates the two positions, orthodox and dissident, with no resolution.

Government and the Reduction of Mother-to-Child Transmission of HIV

The South African Ministry of Health has not yet adopted a national policy of providing antiretroviral therapy to pregnant women with HIV or AIDS. However, in the light of growing evidence from local and international research that antiretrovirals are both efficacious and cost-effective for reducing vertical transmission of the virus, the government's position seems increasingly untenable. Critics have consistently interpreted this stance as a sign of political unwillingness to address the HIV epidemic sweeping the country.

When President Mbeki agreed to open the AIDS 2000 international conference in Durban, it was widely anticipated that he would use the occasion to remove all doubt about the government's commitment to implementing an effective and comprehensive AIDS control program in South Africa. It was also anticipated that such a program would include the introduction of antiretrovirals for the reduction of vertical transmission. These expectations were not fulfilled. Instead, the Department of Health released an HIV/AIDS & STD (sexually transmitted disease) Strategic Plan for 2000-2005 at that time, which did not mention the use of antiretroviral drugs in pregnant women with HIV infection (Department of Health 2000).

The Department of Health (DOH) Strategic Plan lists reduction of mother to child transmission of HIV as goal 3 under Priority Area 1 (Prevention). The objectives associated with this goal are: (1) improve access to HIV testing and counseling in prenatal care clinics by developing counseling guidelines and training counselors; (2) improve family-planning services to known HIV-positive women by training reproductive-health providers in HIV/AIDS counseling, and by ensuring better access to comprehensive reproductive-health services for HIV-positive women; and (3) implement clinical guidelines to reduce the transmission of HIV during childbirth and labor by training all relevant medical practitioners and midwives.

Government and Multinational Drug Companies

Private pharmaceutical companies own patents on HIV drugs that are protected by intellectual property rights policed by the World Trade Organization (WTO). Such patents prevent countries from manufacturing or importing cheaper generic versions of these drugs. Industry's view is that high prices are necessary to recoup research and development costs.

Since coming into power the ANC has worked toward making essential drugs less expensive and more affordable in South Africa. This has led to clashes with pharmaceutical companies and a protracted trade dispute with the United States and several European countries (see http://www.cptech.org/ip/health/sa/). Central to this dispute is South Africa's Medicines and Related Substance Control Amendment Act, and in particular, a new Section 15c of the act that provides authority for fast-track compulsory licensing of medicines and parallel importation of medicines.

The government has argued that this step is in keeping with the WTO's Trade-Related Intellectual Property Rights (TRIPS) agreement, which provides certain exceptions to normally strict commercial intellectual property rights so that poor countries in health emergencies are allowed to circumvent patent laws in various ways in order to produce their own inexpensive generic versions of necessary drugs. Compulsory licensing enables a country to manufacture a drug in emergency situations without the permission of the patent holder provided that "adequate remuneration" is given to the company concerned. Parallel importing permits a country to buy a drug from the lowest bidder without the consent of the patent holder.

Despite these allowances, there is considerable resistance to the introduction of the above measures. Countries have been threatened in the past with trade sanctions by the United States in an attempt to protect its drug industry. South Africa was put on the U.S. government's "301 Watch List" of potentially offending countries some years ago. Although this is no longer the case (in response to U.S. domestic protests), the United States has made it clear that it continues to monitor South Africa's policies.

In addition, direct pressure on the South African government was until recently being applied by pharmaceutical companies themselves. Thirty-nine companies (under the banner of the Pharmaceutical Manufacturers' Association of South Africa) were suing in the South African courts to prevent the Medicines Act from becoming law. However, the companies recently withdrew their suit, paying defendant's costs, under global public pressure. Glaxo Wellcome (now GlaxoSmithKline), the manufacturer of zidovudine, appeared to be the target of the most intense opprobrium, as illustrated by a public exchange of letters between President Mbeki and Tony Leon, leader of the official opposition party.

There is widespread recognition that the cost of antiretroviral drugs is a key obstacle to curbing the AIDS epidemic, and a number of groups, including UNAIDS, have criticized laws that keep AIDS drugs out of reach of the poor. Médecins sans Frontières (MSF) has drawn attention to the fact that public research institutions have heavily funded the development of antiretroviral drugs, and that the time to approval of AIDS drugs is, on average, half the usual industrywide average of 87 months (Chirac, von Schoen-Angerer, and Ford 2000). Both of these factors have reduced research and development costs borne by pharmaceutical manufacturers, thus weakening their argument for high drug costs in the case of antiretrovirals. MSF further points out that one such antiretroviral (zidovudine) was first synthesized in 1964, and studies evaluating its efficacy against HIV were mainly funded by the U.S. National Institutes of Health (Chirac, von Schoen-Angerer, and Ford 2000). Yet having obtained the patent for zidovudine for the treatment of HIV/AIDS, Glaxo Wellcome brought the drug onto the market in 1987 as one of the most expensive ever sold (Chirac, von Schoen-Angerer, and Ford 2000).

Fortunately, there have been some important developments recently in relation to the costs of antiretrovirals. In 2000, the U.S. government dubbed AIDS a threat to its national security, which allowed then President Clinton to issue an executive order stating that the United States would allow countries in sub-Saharan Africa to pursue legal means to make AIDS-related drugs more affordable. This announcement came at around the same time the United Nations made it known that it had successfully negotiated a deal with five multinational pharmaceutical companies to reduce the price

of HIV drugs in the developing world (see http://www.hivnet.ch:8000/africa/af-aids/viewR?783). The South African government's response to these announcements has not been enthusiastic. A possible reason for this is that the government believes price reductions negotiated with pharmaceutical manufacturers are not a permanent or substantive solution to the cost of drugs, and that prices can be reduced much further and more sustainably if a country obtains these drugs through local generic production, or by parallel importation from countries such as Brazil, Thailand, or India, which successfully produce generics at a fraction of the price of branded products.

RATIONALE FOR THE POLICY

Stakeholders and Their Involvement in the Process

On November 21, 1999, following preliminary telephone discussions with the director-general for health (DG), one of us (J.V.) received a written request from the national minister of health for a "thorough assessment and analysis" of the "risk-benefit profile" of interventions to reduce mother-to-child transmission of HIV. (Although a unitary and not a federal state, South Africa operates a national ministry of health that makes health and health care policy decisions for the country; these decisions, however, are implemented through the provincial departments of health, which provide tax-funded medical care for the poor. Each province has its own health minister, the limits of whose autonomy in relation to national decisions is still being tested.) The DG stressed that this information was urgent, as the government was being threatened with court action over its failure to introduce a policy on antiretrovirals.

The researchers (J.V. and P.M.) completed the review and prepared a report, which was faxed to the minister and DG on December 24, 1999, and mailed on January 4, 2000. A cover letter accompanying the report asked for a meeting with the recipients and others whom they wished to include to discuss the evidence provided. No response to this request was received.

Following the submission of the report, however, the researchers were contacted on two occasions. A telephone call and a letter dated February 8, 2000, from the DG requested information on "other studies on nevirapine." None could be identified other than a trial conducted in Uganda and the ongoing South African Intrapartum Nevirapine Trial (SAINT), which had already been mentioned in our report. A preliminary analysis of resistance patterns in the Ugandan nevirapine trial that had become available since our report was then sent to the DG. One of the researchers (J.V.) subsequently received a further letter from the minister on February 29, 2000, stating, "I wish to thank you for the report on *zidovudine* [italics added]. We are currently assessing it. We shall revert to you in due course." She has not done so to date.

Why the Policy Was Initiated

It appears that the government had initially made a decision not to develop any detailed policy on antiretrovirals for HIV infection and was applying the general "no antiretrovirals" policy to the prevention of MTCT as well. The reasoning behind this is not clear and is the subject of various theories. Drug safety and cost appeared to be the main concerns, although no official cost-effectiveness study had been done or referred to by the Department of Health.

Critics concluded that the government was in a state of denial because of the immense challenge of managing the AIDS epidemic. Some believe this might be behind the government's flirtation with AIDS dissidents and pseudoscience (Makgoba 2000).

Government critics have also suggested that the policy is being driven by the need to contain the number of orphans left behind by the rapidly growing number of adults dying of AIDS. It has been claimed that some government officials hold the view that preventing mother-to-child transmission of HIV is best avoided because the care of AIDS orphans will add to the financial burden on the state (see http://www.hivnet.ch:8000/africa/ad-aids/).

Although the government has not mentioned the indirect costs of manpower, infrastructure development, laboratory services, counseling, and social services support, it is possible that this is playing a major part in the current impasse. Like other African governments, that of South Africa has put in place economic policies that have been encouraged by the World Bank and International Monetary Fund. Such policies have resulted in the freezing of jobs in the health and education sectors as a means of cost containment. Meeting the AIDS challenge head-on would mean the recruitment of more staff in health and social services. Unfortunately the government has not articulated this argument in public—which is understandable since doing so would not be received warmly by the people who elected its members into power.

Another plausible reason for the government's stance is its dispute with drug companies that have held up the passing of a new law allowing compulsory licensing, generic production, and importation of patent-protected pharmaceuticals. This law would affect all drugs, not only those related to HIV treatment and prevention. Now that the companies have withdrawn their lawsuit, this law will go onto the statute books.

The dispute started when Nkosazana Zuma was the minister of health and may be the underlying reason for her pronouncement in 1998 (and the president's subsequent reiteration) that there would be no national funding for perinatal zidovudine. The offer by Glaxo Wellcome to reduce the price of zidovudine to South Africa to 30 percent of the world average price, and by the pharmaceutical company Boehringer Ingelheim to offer its drug nevirapine at no cost for

a limited period, have not been sufficient to persuade the government to change its policy on antiretrovirals. The reason for this might be that the government views the HIV treatment issue as simply the first of many tough battles it will need to fight to implement its chosen strategy for reducing the total cost of pharmaceuticals and is unwilling to lose this first battle, lest it jeopardize the whole campaign.

Opposition to the Policy

The government has come under heavy fire from opposition parties for its policy on antiretrovirals in pregnancy. Costa Gazi, spokesperson on health for the Pan Africanist Congress Party, laid a charge of human rights abuse with South Africa's Human Rights Commission against Minister of Health Manto Tshabalala-Msimang for the decision not to provide zidovudine to HIV-positive women. The government responded by laying five charges of misconduct against Dr. Gazi (who is also a senior health official in the Eastern Cape Health Department), accusing him of contravening the Public Service Act by openly criticizing the government and bringing the Department of Health into disrepute.

Further opposition has come from AIDS activists, who picketed the opening of Parliament in 2000 to protest against the government's decision not to provide free antiretroviral drugs to pregnant women with HIV. One group, the Treatment Action Campaign, believes it is "immoral, uneconomical and unlawful" to delay such a provision any longer and has undertaken court action to force the government to act on this matter.

As evidence of the efficacy of antiretroviral therapy has grown, so has criticism from a range of stakeholders, including health care professionals and the pharmaceutical industry. The government appears to be responding to such criticism by seeking allies in the scientific community who will help bolster its chosen position.

First, the government turned to the MCC—its drug regulatory authority—with a request for evidence on zidovudine. The MCC report, submitted in October 1999, favored the use of zidovudine but was rejected by the minister of health on the grounds that the review process had not been sufficiently rigorous. Next, the assistance of the South African Cochrane Centre was sought; this experience is documented in this report. (The South African Cochrane Centre is part of a global network of individuals and institutions that prepares systematic reviews of existing evidence on health care interventions. The Center is funded and housed by the Medical Research Council of South Africa.) Finally, the presidential AIDS panel was convened and charged to advise on, among other topics, the role of antiretroviral therapy.

OUR REPORT

The purpose of our report to the government was to summarize the most reliable information concerning the effects of antiretroviral therapy for the prevention of vertical, mother-to-child transmission of HIV. Issues of cost-effectiveness, feasibility, and acceptability did not factor into our mandate. A shortened version of our findings follows.

Zidovudine

The most widely studied antiretroviral drug, zidovudine (azido-deoxythymidine, or AZT), is a synthetic analogue of the naturally occurring nucleoside thymidine. Zidovudine acts by inhibiting HIV-1 reverse transcriptase, the enzyme needed for the synthesis of proviral, double-stranded DNA from the RNA template. Treatment with zidovudine reduces plasma viremia but does not lower the amount of virus in lymphocytes or tissue. The drug crosses the placenta, reaching therapeutic levels in the cord blood, and is present in breast milk.

Efficacy

The AIDS Clinical Trials Group (ACTG 076) report published in 1994 provided the first reliable evidence that zidovudine was effective for reducing vertical transmission of HIV (Connor, Sperling, Gelber, et al. 1994).

Due to the complexity and cost of the ACTG 076 regimen, shorter courses of zidovudine administered during late pregnancy and labor were assessed in randomized, placebo-controlled trials in Bangkok, Thailand (Shaffer, Chuachoowong, Mock, et al. 1999); Ivory Coast (Wiktor, Ekpini, Karon, et al. 1999); and Ivory Coast and Bukina Faso (Dabis, Msellati, Meda, et al. 1999). The reduction in the risk of transmission reported in these three "short course" trials were, respectively, 50, 37, and 38 percent.

A meta-analysis of all four of the trials mentioned above shows that zidovudine monotherapy is a highly efficacious means for reducing MTCT of HIV, halving the risk of HIV transmission (pooled relative risk reduction [RRR] 0.47, 95 percent CI 0.32 to 0.59) (Brocklehurst 2000).

Safety in Pregnancy

Follow-up of the children included in the ACTG 076 trial provides reassurance that there are no major adverse effects attributable to zidovudine in uninfected children up to the age of four years (Culnane, Fowler, Lee, et al. 1999). Furthermore, an Antiretroviral Pregnancy Registry, supported by the pharmaceutical industry, reported no increase in the incidence of congenital abnormalities in 300 children exposed to zidovudine in pregnancy, including 89 children exposed during the first trimester.

Summary of Effects of Zidovudine Use in Pregnancy

Current evidence thus suggests that zidovudine is an effective drug for reducing the rate of vertical HIV transmission. The most severe adverse effect documented to date is anemia, and this appears to be transient, disappearing by 12 weeks of age. Based on the estimated rates of transmission in the randomized trials available, we calculated that for every 1,000 cases treated using the ACTG 076 regimen, 167 babies would be protected from HIV infection and 91 babies would develop anemia, representing a benefit-risk ratio of 1.8. By comparison, for every 1,000 cases treated with short-course zidovudine, 100 will be saved from infection and 11 will develop anemia, a benefit-risk ratio of 9.

Nevirapine

Nevirapine is a non-nucleoside reverse transcriptase inhibitor with potent antiviral activity. It is rapidly absorbed when taken orally and readily crosses the placenta. These properties, combined with the long half-life of the drug in pregnant women and infants, makes it attractive as an intervention during labor.

Efficacy

The efficacy and safety of short-course nevirapine was compared to zidovudine given to women during labor and to babies during the first week of life in the HIVNET 012 trial (Guay, Musoke, Fleming, et al. 1999). This was an open-label (nonblind) randomized trial carried out in a predominantly breastfeeding population in Uganda. Compared with zidovudine, nevirapine reduced the risk of HIV infection in babies at 14 to 16 weeks by 48 percent (95 percent CI 17 to 60 percent). While these results are encouraging, it is important to note that the zidovudine regimen used had not been tested in previous trials and that there was a high transmission risk in this arm (i.e., the group receiving zidovudine). It is therefore not possible to determine the efficacy of nevirapine in relation to the established short-course zidovudine regimens.

Safety

There are few data on the safety of nevirapine. The main adverse effect with chronic treatment appears to be Stephens Johnson Syndrome, which occurs in 0.3 percent of exposed people. Other side effects are rash, granulocytopenia, and hepatic dysfunction. In the HIVNET 012 trial there was no difference between nevirapine and zidovudine in terms of hematological toxicity in mothers or babies, neonatal mortality, or maternal mortality. By December 1999 more than 700 women worldwide had received nevirapine for the prevention of MTCT and there had been no reported problems with safety.

Combination Antiretroviral Therapy

One trial of combination therapy (Clinical Studies on Prevention of Perinatal HIV Infection, known as PETRA) assessed the effects of a fixed combination of two nucleoside reverse trancriptase inhibitors, zidovudine and lamivudine (3TC) (Brocklehurst 2000). Only preliminary findings on the risk of transmission by six weeks of age were available at the time our report was completed.

Efficacy

Preliminary results of the PETRA trial suggest a reduction in the risk of transmission compared to placebo when zidovudine and lamivudine are given from 36 weeks until delivery (the risk was halved; RRR 0.48, 95 percent CI 0.24 to 0.65) or from the start of labor until one week after delivery to mother and baby (risk was reduced by one-third; RRR 0.34, 95 percent CI 0.06 to 0.54). There is no evidence that combination therapy with these drugs in the intrapartum period alone decreases the risk of transmission (the effect was equivalent to that of placebo; RR 1.01, 95 percent CI 0.74 to 1.38). Combination therapy was not compared to zidovudine alone, and the additional benefit of lamivudine (3TC) therefore cannot be assessed.

Safety

A recent unpublished WHO report mentions a French study in which two uninfected children of women who had received zidovudine and 3TC died from a rare mitochondrial disorder leading to neurological disease (WHO 2000b). Since then the Centers for Disease Control and Prevention (CDC) and National Institutes of Health (NIH) in the United States have reviewed case records of 14,000 uninfected children. None of the 33 deaths recorded suggest a mitochondrial cause. The PETRA study organizers identified five cases with neurological symptoms or signs possibly caused by mitochondrial dysfunction. One was in the placebo arm.

Cost-Effectiveness

Our report did not include a discussion of cost-effectiveness, but there have been a number of evaluations of this issue with regard to antiretrovirals for reducing MTCT. These studies take into account not only drug costs but also the costs of providing prenatal services, counseling, testing, and training. At the time of our report, a study using South African data suggested that zidovudine would reduce total cost to the health service while saving many thousands of lives per year (Soderlund, Zwi, Kinghorn, et al. 1999). It achieves this largely through reduced health service use by the children

who would otherwise have been born HIV-positive and would be heavy users of care. The savings are likely to be greater with nevirapine, a cheaper and more effective drug, especially in view of its manufacturer's willingness to distribute it free.

Implementation Issues

A policy change in South Africa to one favoring antiretroviral therapy for pregnant women with HIV infection will require the necessary political will. Attention would also have to be given to several feasibility issues. Prenatal services are not uniformly accessible, and this problem would have to be addressed. Counseling facilities and testing kits are often lacking, but merely providing these would be insufficient. In many cases, women resist being tested for HIV due to stigma and fear that they will not receive the social and medical support they need. Those who are tested often do not return to obtain the test results. Thus, optimal implementation will demand consideration of several factors apart from drug costs.

REFLECTION AND GENERALIZATION

In South Africa as elsewhere, health care policies are generated by proponents with the credibility and degree of organization needed to formulate courses of action according to their values, and the power to put the proposed policy on the agenda for consideration and decision. These proponents could be governing parties, well-organized opposition blocs in Parliament, or influential civil society groups, such as organized commercial, environmental, special-interest, or labor groups. A policy decision is often determined by the outcome of a political struggle, with allies marshaled, favors called in, and compromises made. Scientific evidence has little impact; although evidence of clinical ineffectiveness of a medical treatment may be used to argue against its implementation, the most influential of all factors might well be financial cost to the taxpayer, rather than therapeutic efficacy.

In responding to the request for a review of the benefit-risk profile of antiretrovirals in pregnancy, we had assumed that the Department of Health would implement interventions if they could be shown to be clinically effective and cost-effective. With the benefit of hindsight we realize that this was naïve. However, we learned during the process that this issue was being dealt with by extremely high-level policymakers and elected politicians, whose framework of decision making was primarily a political one, and not one in which efficacy or even cost-effectiveness was likely to carry much weight. Clearly, we should have taken more seriously the impact of the political and socioeconomic factors that are associated with AIDS.

While accepting that scientific evidence is only one ingredient needed for formulating rational policy, and that the government may have had its reasons for deciding on a particular stance, it would have been of great assistance if the Department of Health had engaged the researchers in discussing the findings (as had been suggested).

Lessons Learned

In the case of perinatal antiretroviral therapy, evidence is not yet a sufficiently powerful force to change government policy. For this reason, researchers' engagement with politicians under the current climate is likely to be unsatisfactory. Policymakers cannot predict or control the evidence they receive, and may have to ignore it if it goes counter to the other social and political factors that determine policy. The challenge, however, is to find a way for researchers and policymakers in South Africa to maintain dialogue over such health care issues. Appreciation on the part of researchers for the constraints under which policymakers operate would help to promote such dialogue. Policymakers, on the other hand, would assist by discussing their concerns with researchers more openly.

Our experience suggests that it is important to tailor the amount of effort expended in evaluating scientific evidence according to how such evidence is likely to be used. If it seems that the initial evidence assessment is producing unwelcome results, little point is to be served in delving deeper. Thorough stakeholder analysis should be conducted prior to developing detailed evidence summaries to see if this can be predicted. Reluctance of the provincial policymaker to take part in our policy research collaboration may suggest that middle-level policymakers in South Africa do not feel at liberty to express their personal opinion on politically sensitive issues, fearing this might be construed as criticism of their superiors.

Reasons for Failure

Why has the South African government failed to respond to the evidence and refused to adopt a policy in favor of using antiretrovirals for interruption of MTCT? This has not been answered satisfactorily in public statements by the government. Speculation among activists and the media is wide ranging. The following are possible explanations that have been suggested.

- The state cannot afford to look after the orphans.
- South Africa cannot afford to establish programs to deliver antiretrovirals successfully.
- The government's struggle against the pharmaceutical industry needs to be won to achieve the ultimate goal of lowering the cost of all essential drugs.

There is "unspoken" concern within government circles that money spent on drugs would do little to alter the main

reasons the South African black population is vulnerable to AIDS and other infectious diseases. It is suggested that perhaps in the long term, resources would be better utilized by creating jobs, educating the people, and fighting poverty and malnutrition.

In attempting to comprehend this confused and conflict-ridden situation, we should be aware that South Africa has a new government that, having democratically won power and accountability after a long and difficult struggle, finds the cup of freedom poisoned. Faced with the prospect of massive population loss, suffering on a scale greater than any previous holocaust, famine, or war, is denial not an understandable response? Great wisdom and further research are needed in finding a way to contribute constructively to this difficult situation.

Afterword

Recently there have been some encouraging moves on the part of the government in relation to antiretrovirals. Following the release of the positive findings of the locally conducted SAINT trial evaluating nevirapine, the Department of Health has directed that pilot studies be undertaken in the country's nine provinces. While it is not clear what the precise purpose of the pilot studies will be, or the way in which the resulting information will be used to modify policies, this decision is the first official acknowledgment that antiretrovirals are worthy of being considered as part of a national strategy to reduce MTCT of HIV.

GLOSSARY

ACTG 076
AIDS Clinical Trials Group 076

AIDS
acquired immunodeficiency syndrom

ANC
African National Congress

CDC
Centers for Disease Control and Prevention

DG
Director-General for Health

DOH
Department of Health

GDP
gross domestic product

HIV
human immunodeficiency virus

MCC
Medicines Control Council

MSF
Médecins sans Frontières

MTCT
mother-to-child transmission

NGO
nongovernmental organization

NICE
National Institute for Clinical Evidence (UK)

NIH
National Institutes of Health (U.S.)

PETRA

Clinical Studies on Prevention of Perinatal HIV Infection

PMA
Pharmaceutical Manufacturers' Association

RRR
relative risk reduction

SACC
South African Cochrane Center

SAINT
South African Intrapartum Nevirapine Trial

SANAC
South African National AIDS Council

STD
sexually transmitted disease

TRIPS
Trade-Related Intellectual Property Rights

UNAIDS
Joint United Nations Programme on HIV/AIDS

WHO
World Health Organization

WTO
World Trade Organization

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Australian Update

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United States

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Kendra Rothert is Program Evaluation Consultant at Kaiser Permanente's CMI, a position she assumed in 1999. Her work focuses on outcomes measurement in diabetes, elder care, and cardiovascular disease, as well as project management and evaluation of the national Health Risk Appraisal (HRA) pilot study. Rothert earned her doctorate from the Johns Hopkins University School of Hygiene and Public Health in the Department of Population Dynamics. She also holds master's degrees in biostatistics and population dynamics from Johns Hopkins and a bachelor's degree in international relations from Stanford University.

Robert M. Crane is Senior Vice President and Director, Kaiser Permanente Institute for Health Policy for Kaiser Foundation Health Plan, Inc., and Kaiser Foundation Hospitals. He also has executive responsibility for the Kaiser Foundation Research Institute. In his 18 years with KP, Crane has held several executive positions. Prior to that, he served as the New York State Department of Health's Deputy Commissioner for Program and Policy Development and as Director of its Office of Health Systems Management. He holds a master's degree in business and public administration from Cornell University and a bachelor's degree from the College of Wooster in Ohio.

William Caplan has been Director of Clinical Development at Kaiser Permanente's CMI since 2000, overseeing the development of Chronic Conditions Management Programs, Clinical Practice Guidelines, and content for the Clinical Information System. He joined the Permanente Medical Group in 1979; in 1992 he was named Director of Operations Development for the Permanente Medical Group of Northern California. In that role he led many practice redesign efforts, chaired the Diabetes Steering Committee, and codirected the Innovation Program. He received his B.S. from the University of Wisconsin and his medical degree from Washington University in Saint Louis.

Helen Pettay is Communications Director at Kaiser Permanente's CMI, joining in 1997 after serving as Program Director at Mosby Consumer Health. From 1991 to 1996 she worked in KP's communications and public affairs department; prior to that, she was Communications Manager in the corporate offices of Catholic Healthcare West. Pettay has worked on newspapers and magazines in the West, Midwest, and New England and was editor of *Business Digest* in the Boston area. She has a bachelor's degree in journalism from Indiana University's Ernie Pyle School of Journalism and studied sociology and philosophy at Edinburgh University, Scotland.

Norway

Mari Trommald works as a researcher in the Department of Population Health Sciences at Norway's National Institute of Public Health. Her recent research has focused on prioritization in health care, the use of effectiveness data in policymaking, and the collaboration between policymakers and researchers. She holds a medical degree as well as a doctorate in neuroscience, having focused on the subject of learning and memory.

Arild Bjørndal is Professor of Public Health at the University of Oslo and head of the Department of Population Health Sciences at the National Institute of Public Health. His main goal is to reform Norwegian health care: better use of reliable evidence and more explicit inclusion of patient (and societal) preferences will lead to better decisions about health in clinical medicine (and public health).

Einar Skancke is Deputy Director General in the Budget Department of the Norwegian Ministry of Finance. From 1999 until October 2000 he was Deputy Director General in the Department of Health of the Ministry of Health and Social Affairs. Skancke is currently responsible for the coordination of the yearly budget proposal for four governmental departments. He has been a member of several governmental committees that have assessed health priority issues.

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Andy Oxman is Director of the Health Services Research Unit at the National Institute of Public Health, Oslo, Norway. He completed his medical training at Michigan State University in 1979. From 1984 to 1994 he was at McMaster University in Canada in the Departments of Family Medicine and Clinical Epidemiology and Biostatistics. He has worked extensively in the Cochrane Collaboration since 1993. He has worked with policymakers as a researcher but does not have any experience as a policymaker.

United Kingdom

Andrew Dillon is the first Chief Executive of the National Institute for Clinical Excellence (NICE), a position he assumed in July 1999. Before moving to his current post he was Chief Executive of St. George's Healthcare, an undergraduate teaching hospital in London. He has held various operational management posts in the National Health Service (NHS), including positions at the Royal London and Royal Free Hospitals. Dillon graduated in 1975 from Manchester University, UK, with a B.S. in geography.

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Trevor Sheldon is Professor of Health Studies and head of that department at the University of York, UK, where he established the NHS Centre for Reviews and Dissemination. Trained in medicine, economics, and medical statistics, he was part of the team that developed the new formula for allocating resources to England's health authorities and has been active in promoting the use of research evidence in health care decision making, including editing the *Effective Health Care*bulletin and producing national guidance on the commissioning of cancer services. He is Vice Chair of the Commissioning Board of the Service Delivery and Organisation R&D Programme.

South Africa

Patrice Matchaba is Director of Novartis South Africa, a pharmaceutical company. In 1998 he joined the South African Cochrane Centre (SACC) at the Medical Research Council (MRC) of South Africa, preparing systematic reviews of the effects of health care interventions. From 1992 to 1998 he lived in Durban, where he qualified as an obstetrician and gynecologist and witnessed the beginnings of the epidemic that has since ravaged the province of KwaZulu-Natal. Prior to that he spent three years in Botswana as a mine doctor managing AIDS cases. He earned his medical degree in Zimbabwe in 1986.

Merrick Zwarenstein, a physician epidemiologist, is Director of the Health Systems Research Unit at the MRC. His work includes qualitative studies that lead to the development of complex health care interventions, such as the design of outreach programs for clinicians on the care of children with asthma, and quantitative studies, which are often randomized trials of these same interventions. His policy experience includes participation in the advisory committee to the first post-apartheid health minister, Nkosazana Zuma, on the financing and structure of the health care system, and in committees on health management at local and provincial levels.

Jimmy Volmink is, since May 2001, Director of Research and Analysis at the Global Health Council in Washington, D.C. Before that, as Director of the SACC, he promoted the preparation and dissemination of systematic reviews of the effects of health care interventions, the primary focus being on high-priority health problems in Africa, such as tuberculosis and HIV/AIDS. He was a member of the Clinical Trials Committee of the Medicine Control Council and served on President Mbeki's AIDS Advisory Panel; he has also been an adviser to the World Health Organization on tuberculosis. He is a physician with a master's degree in public health and a Ph.D. in epidemiology.

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