Journal of Population Therapeutics and Clinical Pharmacology
INCORPORATING FETAL ALCOHOL RESEARCH
Journal de la thérapeutique des populations et de la pharmacologie clinique
Available Online @ www.jptcp.com www.cjcp.ca/

PROCEEDINGS OF A SYMPOSIUM AT THE CANADIAN ASSOCIATION OF POPULATION THERAPEUTICS 2010 ANNUAL MEETING

ASSESSING THE VALUE OF NEW THERAPIES: WHERE DO WE GO FROM HERE?

Disclaimer:
All opinions are those of the authors and not of the institutions with which they are affiliated. Authors are responsible for the content of their individual sections only.

Funding Source:
Supported by an unrestricted educational grant from Pfizer Canada Inc.

Corresponding Author:
Angela Rocchi
angela@axiaresearch.com

INTRODUCTION

Scott Gavura
Cancer Care Ontario

Few issues in health system administration are more controversial than resource allocation. Health technology assessment (HTA) is the systematic review of the clinical, economic, legal and ethical aspects of a healthcare technology. HTA has its roots in the evaluation of technologies such as imaging, and evolved to include the evaluation of drugs where it is now scrutinized for its role in resource allocation decision-making. Using HTA for drug evaluation has been driven mainly by public payers who recognize the benefits of an objective, apolitical process to make very difficult funding decisions.

About 10 per cent of our overall economic spending in Canada is currently allocated to health care. For the past several years, spending has grown at approximately double the rate of the economy, and has commanded a growing proportion of provincial government spending. The upcoming 'patent cliff' with loss of exclusivity may moderate the growth in drug spending over the next few years, but given the high acquisition costs of new therapies, the systematic evaluation of new drugs remains a high priority. Since many new drugs seem to offer incremental benefits at incremental cost, the result is continuous upward pressure on expenditures, and challenging funding decisions, balanced by the opportunity for improvements in health outcomes.

How can a formal evaluation of clinical and economic benefit help us determine the optimal way to allocate resources? A panel was formed to represent five different perspectives on the issues and challenges of drug HTA as it is currently practiced in Canada, and to share potential improvements and new approaches. The panel addressed the Canadian Association for Population Therapeutics at the 2010 Annual Conference. Each of the five panelists authored a section of the following proceedings from their perspective.

Payer Perspective

Mona Sabharwal
(Formerly, Ontario Public Drug Programs)

Ontario's total-provincial health care budget was almost $100 billion in the fiscal year of 2009/10, of which $4.2 billion of the health care budget is invested in drug programs. These programs cover almost 3 million individuals, predominantly senior citizens. Over 4,000 different drug products are funded through various programs.

Ontario has a two-part drug evaluation process. The Committee to Evaluate Drugs (CED) is an advisory board to help the Ministry understand the clinical evidence and therapeutic role of a new drug and its cost-effectiveness. They also provide some commentary on social values, and their accountability is to the Executive Officer (EO). The EO actually makes the funding decision, and is accountable to the Minister for managing drug program spending. The EO takes into consideration advice from the CED and other advisory bodies, as well as additional considerations (ethics, political priorities, legal obligations, and societal values).

The CED addresses the question, "Will the drug provide good clinical value and good use of scarce health care resources if it is funded?". They review the clinical and scientific evidence, in a comparative analysis versus other funded alternatives (which could be drug or non-drug alternatives). What are the overall risks versus benefits? Are there are particular safety issues in the patient population served by the public drug plans that need to be taken into consideration? The CED examines evidence of value for scarce resources, using formal pharmaco-economic evaluation and budget impact analysis (what would

the new technology actually cost us if we were to implement?). The CED also considers patient impact. Two patient members were added to CED in late 2007. In April 2010, Ontario launched an initiative inviting patient advocacy groups to provide patient-specific evidence.

How does the EO decision-maker use health technology assessments? One of the myths around HTA is that it *is* the decision. It is not. Instead, it is a *tool* to help make decisions. It's not the sole determinant of how drug funding decisions get made, but it is one of many important inputs.

What HTA can provide is a very helpful summary of what is known in terms of the clinical data, in a systematic and unbiased manner. Having said that, clinical experts, clinicians, and patients are needed to provide context and interpretation of that data. HTA also shines a light on what is *not* known, even if there is not always have consensus around how to reduce or manage that uncertainty. HTA can also help evaluate harms that may not be captured early on in drug development. HTA opens a window on dialogue regarding opportunity cost: what do we get from a new technology versus what do we give up.

The public drug plan faces many pressures. There is increased public pressure for rapid reviews of drugs. Decisions are very complex, and getting more complicated every day. How does one balance speed with thoroughness and obtaining input? Decisions are expensive. There are economic and clinical prices that are paid in making a wrong decision – both decisions to fund and decisions not to fund have consequences. What about different drugs for different diseases? If all diseases are unique, should there be different evaluation standards depending on the disease? For example, in Ontario, there is a specific oncology subcommittee to the CED. What are the values, implicit or explicit, that are brought to decisions? Should an expensive drug be funded that provides a small benefit? Should a drug be funded that has weak evidence but potentially large benefit? At what point does a drug become too expensive to fund? Whose perspective should dominate, and when?

Do these pressures and challenges mean that we should stop using HTA? The simple answer is no, but the full answer is to look at ways to be more refined in the use of HTA – to look beyond HTA as *the* answer and consider innovative approaches to answer some of those tough questions. Moving forward, payers will continue to use HTA but they *do* see that there *are* challenges that require new initiatives.

Ontario now has a rapid review process. New drugs are evaluated prior to their approval by Health Canada when the drug is either clinically or economically compelling.

Ontario has developed and made publicly available a compassionate review policy, to help make more consistent and fair funding decisions while still trying to balance patient needs with consideration of potential policy implications.

Ontario has developed a new framework to evaluate drugs for rare diseases. The framework acknowledges that there are inherent difficulties for these types of drugs to generate scientific evidence, including evidence on meaningful clinical outcomes and value for money. The focus is on the construction of predictive models that are based on an in-depth review of what is known about the natural history of the disease and its impact on patients, and overlaying the potential treatment benefit on that natural history.

Ontario has created a new citizens' council to add societal values to the drug review and funding process. This is targeted at citizens, not patients. Their first question was structured around drugs for rare diseases, and there is a public website for this group. Increasingly, Ontario engages in listing agreements to improve the province's ability to provide patient access. The agreements can have clinical components, aiming to target prescribing for certain criteria. The agreements can have financial components, such as reduced prices, price volume discounts, cost offsets and risk sharing. There is accountability both on the manufacturer and on the Ministry to encourage appropriate marketing and utilization. This enables the Ministry to reduce the reliance on some administrative hurdles that have been used in the past to contain utilization. Some agreements have a monitoring and surveillance component, where there is an obligation to do additional research to answer some areas of uncertainty.

In the future, Ontario is considering developing principles from a provincial perspective on managing the information gap: the "adequate versus feasible divide in evidence generation". This may involve coverage with evidence. In the meantime, the Ministry remains open to suggestions and to dialogue.

Legal Perspective

Amir Attaran
University of Ottawa

According to the popular media, patients have major issues with the health care system that are unaddressed by governments. Headlines in *The Globe and Mail* state that patients feel 'bankrupted', 'at war with government', and that the government is the 'monster' in healthcare – a telling barometer of attitudes. One reason for discontent is the fractured payer system in Canada. Since each province decides on drug coverage, in effect, there is a postal code lottery with variation from province to province, and patients who lose that lottery feel aggrieved compared to other Canadians. The Common Drug Review (CDR) was intended to mitigate this, but the problem remains.

In our current environment of health technology assessment, we have forgotten that there are legal requirements which must be adhered to, but which are routinely violated by the provinces. Patients could address their issues by legal suits. Patient litigation for access to medicines happens in other countries, and patients are routinely successful. It is only a matter of time before it occurs in Canada.

Very roughly, there are three routes for patients to sue: (i) a lack of procedural fairness; (ii) a failure to abide by the *Canada Health Act* and provincial laws concerning medicines administered in hospital, and; (iii) a right to not be discriminated against.

The first route, and the most far-reaching, is procedural fairness – also called 'due process' or 'fundamental justice'. This is an unwritten common law principle several centuries old, which applies to all government decisions. It has several aspects. The first aspect is that a government decision cannot be arbitrary, but should possess a certain rationale. When it comes to drugs, often there is a lack of clarity specifically with drugs that fall in the grey zone of special access medicines, and the criteria that government applies to grant or deny these medicines are not especially clear. The second aspect is that a person affected by a government decision should normally be given reasons. Again, this is often not the case for special access drugs, and when persons are denied a medicine often government provides no reason at all. The third aspect is that there always must be a place for a person affected by a government decision to be heard, to challenge the rationality of the decision. Here, there is a total vacuum, and governments ironically go further out of their way in providing the means to challenge minor infractions (e.g. a parking ticket, which can be reviewed in traffic court) than to provide the means to challenge the denial of what might be a life-saving drug (no review mechanism at all). The lack of fundamental justice for drug formulary decisions, and especially those decisions taken in the special access programs, is flagrantly illegal, though not all cases could be challenged successfully and a lawyer should be consulted for advice.

The second route is the *Canada Health Act*, which defines certain services which must be insured publicly. An insured person is entitled to in-patient services without charge. Some of those in-patient services are listed in the *Act*: "drugs, biologicals and related preparations … prescribed by an attending physician … in accordance with accepted practice and administered in a hospital …". Clearly, if a drug is prescribed by a physician and administered in the hospital according to the hospital's practice, then it must be paid for. And yet, in many provinces including Ontario, there are a number of expensive medicines, such as the infused cancer chemotherapeutics, that are administered in hospital and for which patients are made to pay. This too appears flagrantly illegal and subject to court challenge (but again, consult a lawyer).

The third route is the prohibition on discrimination found under provincial laws such as the *Ontario Human Rights Code*, which includes the right not be discriminated against on the basis of disability. Yet, discrimination is commonplace, particularly for the "orphan" or rare disease medicines. For example, a province may pay for an enzyme replacement therapy for Gaucher's disease—surely a disability—but not for Hunter's syndrome or Pompe's disease. All these genetic diseases are caused by point mutations in single individual genes and all are treatable by enzyme replacement. And yet, for *some* genetic mutations, some genetic disabilities, a province will pay; for other genetic disabilities, it won't pay. This is clear

discrimination. Since no rationale is ever provided in explanation of that reality, it is also arbitrary, and a violation of procedural fairness.

In summary, the tools of formulary decision-making such as health technology assessment are only part of the story, because there are also legal requirements. In a democracy, the law encodes social values—for example, the value that government action not be arbitrary government action, or the value that persons not be discriminated against—and governments that violate these covenants surely should expect to be sued. There are two audiences for whom this message matters. First, Ministries of Health should start paying attention to the legal requirements and incorporate them into decision-making processes, or they are risking court challenges that can greatly upset their programs. Second, if Ministries fail to be pre-emptive, then patients who are affected adversely by government decisions to deny them treatment should see a lawyer and seriously consider action through litigation. While litigation is never a first option, it is better than losing one's health, or tolerating routine illegalities in the health system, of which governments are fully aware and have failed to address. If the experience of other countries is any guide, these legal issues will eventually be dealt with in Canada – whether proactively or reactively.

Industry Perspective

Jens Grueger
Pfizer Inc.

Over the last 10 years, the yield of the pharmaceutical industry has not really improved: it still takes about 10,000 molecules to get 250 molecules into clinical trials, and to get *one* new drug onto the market. As a consequence, the costs for bringing a new molecule to market are now above a billion dollars per successful medicine. That is the reason why certain prerequisites are needed for the pharmaceutical industry to be successful. The starting point is patent protection of intellectual property. This gives us a time-limited exclusivity, and it leads to a number of critical questions – which HTA, in some form or another, tries to answer.

How do we provide broad access for patients to innovative medicines? How do we create a predictable environment for long-term drug development investment? How do we provide clear incentives for innovation? How do we ensure sustained health care financing around the globe?

Access decisions always have to be made in the face of uncertainty. As a result, the decisions can be wrong. We are often concerned about false positive decisions – decisions to reimburse a technology and finding out the therapy ultimately is less valuable than we thought at launch. This is a bad decision because it wastes money. However, we see our mistake and can take appropriate action as we get more experience with therapy. There are also false negative decisions – not to develop a drug, and not to reimburse a drug that has been approved. This is probably a more challenging mistake, because it is very difficult to observe whether we made the right decision or the wrong decision. If we kill a drug during development or at the time of market access, we will never know whether patients would have had benefits. We saved money on this specific drug, but we may have wasted lives if the drug had been successful.

Waiting for final outcomes is not an option. The problem with waiting several years to complete final outcomes trials is that the results become available at a point in time where the original research question has become irrelevant. Medicine has moved on in the meantime, and we're answering a question that is no longer interesting.

HTA is more than just a systematic review of clinical evidence and of economic evaluation – HTA *includes* social, legal, ethical aspects of these technologies. HTA is the basis for what people would call "value-based decision-making." We don't have an efficient market for health care, so we cannot leave access and reimbursement decisions up to market forces. We need to inform these value assessments and purchasing decisions. Value-based decisions are a balance between level of price and breadth of coverage. We cannot make a decision about a cost of a medicine independent of the intended use of this medicine.

HTA evaluation will vary depending on the specific patient group, the treatment context, and value preferences. As a result, HTA guidance will differ across countries, and it will differ across patient populations.

For the past five years, industry has committed to principles of what we consider good practice in HTA. The European Federation of Pharmaceutical Industry Associations has formulated twelve principles that should be adhered to in the conduct of HTA:

- Use a clear sophisticated view of what constitutes value – broader than just cost.
- Be transparent and balanced.
- Engage in early and conclusive dialogue – including dialogue with patients.
- Allow new data to be considered.
- Provide flexibility in handling uncertainty.
- Have a comprehensive understanding of the benefit of a drug in disease management.
- Commit to rewarding added value by payers.
- Implement decisions.
- Apply to all health care interventions, not just drugs.
- Occur at the national level.
- Remain separate from the regulatory review.
- Include indirect benefits.

These principles are very similar to those proposed by the International Working Group for HTA Advancement. This Group reviewed 14 HTA organizations – including Canadian organizations – regarding adherence to their principles. Some were being followed very well: being explicit about HTA goals and scope, being unbiased and transparent, and considering a wide range of evidence and outcomes. Other principles had little support or consensus, such as: being transparent on the link between HTA findings and the decision-making process, addressing issues of generalizability and transferability, monitoring the implementation of HTA guidance, and considering a full societal perspective.

These are the areas that I believe we should explore in the future:

- Clarity about evidence expectations and requirements at the earliest opportunity
- Management of uncertainty
- Coverage with evidence development for appropriately selected therapies
- Conditional reimbursement – depending on the provision of additional data or of certain criteria
- Agreement on the validity and use of biomarkers and surrogate endpoints
- Trade-offs between price and level of reimbursement
- Performance-based agreements and risk-sharing agreements to insure appropriate use of medicines
- Implementation of HTA guidance
- A clear legal context for implementation of guidance at all levels.

We support rigorous assessment of the value of our medicines. Quality, efficacy, and safety are assessed during the regulatory process. Relative effectiveness, cost-effectiveness, as well as, legal/societal/ethical issues should be assessed through systematic HTA. This is a different assessment from the regulatory review.

We support competent, transparent HTA that considers various sources of evidence, includes all sources of value, recognizes the local country context, and insures broad stakeholder engagement (including patients). HTA should not be misused for cost-containment purposes.

Patient Perspective

Durhane Wong-Rieger
Consumer Advocate Network

Does HTA-based allocation embrace patient values? First, how do you define HTA? It includes effectiveness, cost-effectiveness, impact both on patient health and the health care system and costs/savings both to the patient and the health care system. Many definitions also consider social and ethical perspectives.

Second, how do you define what the patient values: psychological and social impact, lifestyle, ability to work, tolerance, impact to family and care-givers, offering hope? Are these values systematically included, and is this inclusion sufficient?

First, let's examine: what *do* patients value in therapies? To correct a misconception, not *all* patients value switching to the newest therapies, having the highest levels of evidence or drug therapy intended to 'cure at all cost'. There may be a preference for therapies that address quality of life or ease of use over curative intent. Furthermore, some patients are very willing to tolerate risks or side effects for therapies that will have certain advantages.

What is common is that all patients value having access to what they would consider to be the most appropriate therapy for their individualized case. They want to have the right to make an informed choice. This means two things: that they have the information around *all* the therapeutic options, and that they have *input* into that decision. Their choice might revolve around the impact in terms *of* their life, their lifestyle, quality of life, family life, as well as, the impact in terms of disease symptoms and potential curative ability.

Patients value personalized treatment protocols. Can we take guidelines and insure that it they can be adapted to individuals? Standards of care may be based on the average patient, but as we know, most people are not average patients. Patients would like to see facilitative guidelines that allow a physician to do the optimum prescribing. The physician can achieve an individualized treatment plan in a way that an HTA committee's restrictive guidelines cannot.

Patients value timely access based on sufficient data. Patients would rather have quicker access with *just enough* data to reasonably demonstrate safety and efficacy, rather than wait for ideal, long-term evidence. We can't wait for the long-term evidence sometimes.

Patients do consider resources, whether it's a private insurer or a public payer or whether it comes out of their own pocket. There will be a willingness to pay for therapies that are proven effective or have manageable tolerability or offer convenience, even if that involves their own resources as well as public or private plans.

Currently we may not have a language to describe credibly some values that affect patient perceptions of the benefit/risk equation. What the system labels 'convenience' may be a significant management issue for a patient. A good example is the new oral, once-a-day chelation therapy which replaces an 8-hour drug infusion. In this case, patients might accept an unknown long-term efficacy or risk, to yield important improvements in current quality of life. A therapy that will leave you unable to work for a period of time due to administration or toxicity, versus something that will allow you to get back to work is *not* just convenience, it's *not just* something that improves tolerability.

We need to understand that patients may value funding therapies (often expensive therapies) that offer a large benefit to only a few people – and yet, the current system is often biased in favour of making smaller benefits available to larger populations. The challenge of the ICER is that it really cannot take into consideration innovative therapies that appear to have smaller incremental values from a dollar point-of-view but have tremendous value from a patient point-of-view. The ICER is intended to transform benefits into a cost-effectiveness ratio, but does the ICER capture anything of value to patients?

Patients need a systematic framework that goes beyond the ICER. Raising the ICER threshold for end-of-life treatments, as was done recently in the UK – is a start but does not really answer the question

of how to value the end of life. We may require a separate process and separate funding for these drugs, as well as drugs for rare diseases – something that is being developed in many jurisdictions.

We need to consider a lifecycle funding process alongside the lifecycle approach to the regulatory process, so that drugs with shorter trials and shorter review times can be recommended by HTA reviewers. We need to consider the role of post-market surveillance and patient registries that can incorporate appropriate funding. We need to consider coverage-with-evidence to address timeliness of access.

At the end of the day, we don't treat populations, we treat individuals. While we need standards of care that may be guided by population measures, we need to apply them individually to achieve the principle of patient-centered care. This principle will yield the best outcomes for the system. Can we re-design a cost-effectiveness based HTA process to so that it insures getting the right therapy to the right patient at the right time? Patient values in terms of timely access, suitable options, information, and quality of life impact need to drive HTA decisions and not just be *additional* comments considered after the fact.

Embedding Ethics in HTA and Allocation of Healthcare Resource Decisions

Margaret Somerville
McGill University

First of all, what is ethics? Very simply, it can be summed up as, "trying not to do the wrong thing, and trying to do the right thing," in that order. There is a stronger moral imperative not to do *harm* – "first do no harm" – than there is to do good. Difficulties arise when trying to work out what that requires in any given circumstances. When values conflict, we have to choose which will be honoured and which will not. That can mean choosing between the harms we will avoid and the harms we will allow or inflict – it's what we call "a world of competing sorrows," because there is no "no harm" option.

Assessing the value of new therapies involves the complex ethics of decision-making about the allocation of health care resources and access to them. Doing ethics in this context requires that ethics be embedded in all aspects of the decision-making from its inception and not be treated as just an "add on" after the decisions have been made.

How do we decide what is ethical and what is not?

There are five steps to what we call "doing ethics." First, we have to identify all the ethically relevant facts – good facts are essential for good ethics. For instance, what are the facts regarding benefits and risks? What counts as a benefit? What counts as a risk? What weight should be given to each? Whose assessment do we use? One ethical answer is that the patient's assessment should be taken into account, but not everybody would agree even with that. And if there is uncertainty, as is so often the case, how do we deal with it ethically? Part of the answer is not to convert it to false certainty. Many ethical mistakes have their genesis in doing that.

The second step is to identify all the values that are relevant to the facts that should be taken into account, such as: respect for life; respect for individuals' autonomy and self-determination; relief of suffering; saving lives; advancing science; saving costs to the health care system; justice; and so on.

If we can take a decision that will honour all the values brought into play, then there is no ethical problem. When that is not possible, that is breaching some values is unavoidable, we have to proceed to the next two steps: identify the conflicts of values, and prioritize the conflicting values. In prioritizing, we decide which values should be honoured and which ones should be breached. When we've decided which values we're going to breach – for example, by deciding not to fund a drug, we're not going to try to extend the life of somebody – then, the fifth step, and the heart of "doing ethics" is that we must be able

to ethically justify breaching those values. That requires us to look, also, at the wider impact of such decisions, for instance, their impact on shared societal values, in general.

Setting up an ethical decision-making process involves deciding 1) who decides, and 2) using which criteria.

Because the decision-making we are talking about involves a great deal of discretionary judgment, first, we must examine who should exercise the discretion. The more people who are involved and the more the decision-making responsibility is diffused, the less responsible any one decision-maker feels for that decision. In fact, research shows that a committee will make decisions that not one single member of that committee would make if they were acting alone. So we have to ask, "Are these ethically appropriate persons or bodies to make these decisions? Are they subject to the same limitations, for instance in access to healthcare, that they impose on others? Is every voice that should be heard at the table?" We also have to avoid decision-makers who are in a conflict of interest.

The second component of an ethical decision-making process asks the question, "On the basis of which criteria should we make these decisions?" The cost-effectiveness ratio is a necessary criterion in decision-making about access to healthcare or funding it, but it is far from a sufficient one. Other matters must also be considered for the process through which such decisions are made to be ethical.

There's often a bias that objectivity is better than subjectivity in decision-making. The reality is that we need both. We cannot make good ethical decisions in carrying out HTA, if the basis of our decision-making is limited to cognitive reasoned mentation, important as that is. It needs to be informed by a full range of human ways of knowing that include "examined emotions", commonsense, human memory (history), moral intuition, and even imagination and creativity. Many of these "other ways of knowing" have traditionally been regarded as subjective, and dismissed by some on that basis. Ethical decision-making must also take into account cultural, social, and legal factors. In short, it is important for us to understand that HTA cannot make the decision, the person who employs it is making the decision, using a broad range of considerations and many ways of knowing, which, research shows, help to render the decision more ethical than it would otherwise be.

The features of the decision-making process can also alter our perceptions of how ethical it is. The more we can identify the decision and the decision-maker, the more we know who the victim will be, then the less likely it is that a decision that results in harm will be seen as ethical. When we have a named victim (for instance, a specific person who will suffer from lack of access to a drug), then a non-allocation decision is less likely to be seen to be ethical, than if the person were unidentified at the time the decision is taken.

There are four basic presumptions that we can use when making decisions and which we use can make a difference to the decision outcome: "*no*" – the drug will not be made available; "*no unless*" – no, it won't be made available unless those who want it are in a certain category of people; "yes but" – yes, everyone can have it but we're going to exclude them if they're in a certain group; or "yes", the drug will be made available. The difference between "No unless" and "yes but" is in allocating the burden of proof. If we use "no unless", the person trying to get the drug has the burden of proof. If we use "yes but", the person withholding the drug has the burden of proof. That means, when we are equally uncertain whether or not the drug should be supplied, in exactly the same circumstances, under a "no unless" approach the person will be denied the drug, under a "yes but" one they will be given the drug. For rare and very expensive drugs, NICE is using "no unless". This is easier to justify ethically than "no", because it gives the right of appeal if this is something that affects life and death.

Another consideration is that ethics can vary at different levels of the health care system. A process or decision can be ethical at the level of the institution or society, for instance, taking efficiency and the needs of other patients into account is ethical at these levels, but taking those same factors into account at the individual doctor-patient decision-making level is likely to be unethical. We have to make sure that we know the level at which we are operating.

As well, we need to consider justice. If we are only using reason-based, hard-evidence facts, without considering other factors, very often we can arrive at an unjust decision. Important examples in this regard are to be found in decisions about allocating resources to people with rare diseases and disabled people.

Assessing the "value" of new drugs involves major ethical challenges, because the decisions we must take involve complexity, uncertainty, and potentiality. Currently, having realized the complexity of this decision-making and how much we don't know, we are in a stage of confusion. It's ethically important, however, to know that we don't have all the answers, as that understanding precedes the stage where we can make better decisions for known reasons. A number one principle in being a responsible professional is to learn to live comfortably with unavoidable uncertainty. So many ethical mistakes are made by trying to reduce such uncertainty to certainty, and then acting on what is in effect a false certainty. That is the stage from which we are moving away.

In conclusion, it's a reality to be celebrated that those involved in HTA, healthcare funding decisions, and the pharmaceutical industry are taking steps expressly to include ethics in their decision-making. To do so will be an on-going process not just a one-time event and so far, we have just scratched the surface of the in-depth consideration that will be needed to ensure we embed ethics in this decision-making.

SUMMARY

Angela Rocchi, Axia Research Inc.
Scott Gavura, Cancer Care Ontario

HTA was recognized by all panelists as a useful tool to summarize clinical, economic, legal and ethical data in a systematic and unbiased manner. While HTA is a necessary place to start when making funding decisions, it is not the decision in itself. HTA is the first step in ethical, legal, value-based decision-making. Resource allocation decisions must include other considerations and go beyond objective cognition to include many kinds of subjective knowledge. Importantly, considerations beyond HTA should not be considered as 'add-on' elements. They should be as fundamental to the decision process as the consideration of HTA.

The opportunity cost of decisions not to fund were recognized by all panelists. Payers recognize that decisions not to fund have consequences that can be harmful. From an ethical perspective, there is no 'no harm' option – there is only the choice between which harms will be avoided and which will be allowed, and how to justify that choice. From a patient perspective, decisions that are population-based could ignore the benefits that accrue to individual patients, as well as a patient's opportunity to provide informed input to their own healthcare options. From an industry perspective, the false negative decision – not developing or reimbursing a drug – can generate harms that are not measurable (since potential benefits are prevented from occurring) but broadly affect drug development. From a legal perspective, there is simply no defense for the lack of an appeal process or discrimination on the basis of one's health condition that are the consequences of a decision not to fund.

Moving forward, many ideas were generated for future improvements. The most important is an attitude shift, such that non-evidentiary issues are considered in a process that is as routine and systematic as the process for evidence consideration via HTA.

Timeliness is an essential criterion for all parties – the payer, the patient, the clinician and the industry. Not making a decision *is a decision* not to fund, and delaying difficult decisions needs to be well justified. Payers are introducing rapid reviews to speed access and reduce the period of ambiguity, during which the reimbursement status is effectively negative.

The patient voice is now understood to belong at the table. Payers have included patient considerations in a variety of means: the inclusion of public members on advisory boards, the opportunity for patient input to the reviewers, and even the establishment of citizens' councils to shape policy and priorities. More practice is needed to integrate these contributions fully and robustly into decision-making. Ethics demands that we consider, perhaps from a fresh perspective, who should be making decisions, and using which criteria.

Some drug decisions are more difficult than others. In particular, drugs for rare diseases pose unusual challenges with respect to evidence generation and the balance between compassion and cost-effectiveness. Payers are considering or implementing frameworks for the evaluation of these drugs. It is important to recognize for ethical and legal reasons that a 'no, unless' decision may need to be offered, to provide a recourse for appeal, and to recognize that population-level funding decisions may not be the sole condition for deciding upon individual patient eligibility.

The individualization of drug therapy can be difficult to achieve in a population-based system. However, without fair opportunities to customize care, patients feel short-changed and in fact could legally pursue access via the court, rather than within the drug funding bureaucracy. Patients expect involvement in their own health care choices, rather than imposition without appeal. Our current evaluatory framework may not address this systematically.

One aspect of HTA that remains troublesome is the evidence gap. HTA defines the evidence that can be used for decision-making, and it can also define areas where evidence is absent or inadequate. In order to be timely, HTA has to be conducted close to the launch of a new technology, when the evidence is restricted to efficacy as observed in clinical trials – not the optimal data to make decisions about real world use. This calls for new approaches, like 'coverage with evidence development' or 'conditional reimbursement' which can provide access and funding for a technology alongside the collection of additional evidence, in order to review the decision at a defined future point in time. Legally, ethically and practically, it behooves us all to define an adequate amount of evidence, and a feasible means to enhance the evidence. This will make HTA evaluations all the more valuable in the decision-making process.

In Canada, we also have a funding gap, since drug funding decisions are a local (provincial) responsibility. While the Canada Health Act includes hospital-based drugs, it does not include outpatient drugs, and here 'discrimination' – defined as inequities in access – clearly exists. It was hoped that this would be mitigated with the adoption of central review agencies, and their use of HTA to provide consistent recommendations. Nevertheless, local implementation of national recommendations, and different criteria to qualify for public benefits, continue to result in troublesome inconsistencies between provinces. In fact, the recent development of confidential purchasing agreements, with preferential pricing in some provinces, has the potential to expand these inconsistencies, and raises concerns about fairness of treatment for all Canadians.

From a national and international perspective, there are a number of measures being implemented to integrate rigorous HTA into other processes that will more actively seek to bridge coverage and funding gaps.Within Canada, a new plan was announced by Ministers of Health in late 2010 to collaborate more in the negotiation of drug funding and pricing decisions. While details are unclear, public pronouncements suggest that public payers are seeking alternatives to current processes that place provinces as "price takers" that determine funding based solely on evaluation of a drug's value-for-money based on the manufacturer's listed price.

There is also new interest in moving reimbursement towards a "coverage with evidence development" model that would work similarly and complementary to a proposed Health Canada "life cycle" licensing framework. Such a model could link reimbursement to an evaluation of a drug's actually effectiveness based on real-world utilization. Alternatively, it could provide funding on a provisional basis, while supporting data collection to refine estimates of clinical- and cost-effectiveness under real-world conditions. Both strategies could help to address the common situation of insufficient information leading to negative funding decisions.

Internationally, the new government in the United Kingdom has announced significant changes to the way it will evaluate and fund drug products. In 2010, the government published a White Paper: *Equity and Excellence: Liberating the NHS* that will mean significant changes to the role of the National Institute for Health and Clinical Excellence (NICE). In the new system, NICE will no longer be able to reject drugs for NHS funding. Instead, physician groups will have the responsibility to decide on funding, based on national value-based pricing (VBP) plans that are expected to be implemented by 2014. VBP is envisioned to lead to a process that iteratively determines how much the NHS should pay for a particular therapy. Consequently, the role of HTA may remain central to the evaluation process, if it continues to guide the evaluation of the value, and consequent price, of new therapies. Until the new scheme is in place, the NHS has committed to making specific funding available for cancer therapies which were popularly believed to be excessively restricted from access. Decision-making will be pushed into the hands of regional bodies, where more patient-focused decision making is believed possible.

Significant changes also appear on the horizon in Germany. As of 2011, price negotiations will take place between manufacturers and insurers. If agreement cannot be reached, the Ministry of Health is expected to establish a price maximum, and an HTA by the Institute for Quality and Efficiency in Health Care (IQWiG) will be conducted. If value-for-money is not demonstrated, the product's price may be subject to reference pricing.

In summary, HTA has been adopted by Canadians and Canadian decision-makers as an important first step in ethical, legal, value-based decision-making. In Canada and internationally, there are continuing improvements in the decision-making process beyond HTA; creativity and cooperation will help to address this challenging task.