

ARE PRAGMATIC STUDIES PRAGMATIC?

**Proceedings from a Symposium at the Third Annual
Canadian Therapeutics Congress**

May 2006, Toronto

ARE PRAGMATIC STUDIES PRAGMATIC?

PROCEEDINGS FROM A SYMPOSIUM AT THE
THIRD ANNUAL CANADIAN THERAPEUTICS
CONGRESS, TORONTO, MAY 2006

ABSTRACT

A multi-stakeholder symposium at the third annual Canadian Therapeutics Congress (May 2006) discussed the nature of pragmatic studies, and helped to further define their role in the drug regulatory system, formulary access decisions and in clinical practice. The symposium panel appeared to have agreed that pragmatic studies were beneficial, but revealed differences in how, when and where they should be done.

SUMMARY OF PRESENTATIONS

Introduction

In what can now be considered the early days of the modern pharmaceutical era, no one questioned the value of many medicines brought to the practice of healthcare. Drugs such as antibiotics reduced mortality. If that was the benefit, there was little need to worry about the cost, which was relatively modest in any event, certainly compared to that of other interventions. Over the years that view has changed. There are more and more medicines to both treat and prevent more diseases and conditions. The value equation has changed to make the results less obvious. As a result, more and more influential stakeholders in the healthcare system are discussing the importance of “naturalistic” or “pragmatic” studies to help guide their decision-making throughout the lifecycle of medicines.

The goal of this symposium was to ask whether these pragmatic studies are, themselves, pragmatic in helping guide these decisions, given their methodological complexity and their expense. The speakers represented a variety of perspectives: research methodology, clinical practice, pharmaceutical industry and drug policy. The speakers all agreed that pragmatic studies are, indeed, helpful, but revealed differences in how, when and where they should be done. These differences are, quite naturally, driven from the participant’s vantage point in the system. But, by

taking their observations together we can learn something about the essential nature of these studies and the value they bring to our healthcare system.

What they offer may be the best method of evaluating very complex questions, which has not been faced before in medicine. Our scientific advances have resulted in us having many more medical and clinical resources available than could reasonably be used or afforded in many circumstances. While this is a problem, it is also, in fact, an incredible luxury in a realm of human endeavour where, for most of its history, the physician has been an informed but often relatively helpless bystander to natural events. Now that we understand and can control many more medical events than ever possible before, we are, for the first time, faced with questions of prioritizing their effectiveness and value. This is the challenge of the pragmatic study – moving beyond measuring the medical and clinical value of a medication, to evaluating its social and economic value in the context of the complex and controversial structure, which is any national healthcare system. It is no wonder that different players have different perspectives, as reflected in their presentations to this symposium.

The session was sponsored by an educational grant from Pfizer Canada Inc. and was chaired Drs Stuart MacLeod and Jacques LeLorier.

Jean-Paul Collet, MD
McGill University, Montreal

The symposium opened with a presentation by Dr Jean-Paul Collet of McGill University about the methodological issues and solutions faced in pragmatic studies and how these differ from those in clinical trials. The vital differentiator, Dr. Collet said, is that clinical trials are clearly for decision-making – to determine the safety and/or efficacy of a medicine. Pragmatic trials, however, seek answers to different questions: Does the drug work in real life? How is its cost-effectiveness in comparison with other alternatives?

As opposed to clinical studies which involve questions of science and commerce, pragmatic studies involve questions of treatment, economics, politics, social equity and population health. This wide spectrum of questions results in a more

complex structure. Pragmatic studies must account for a wide variety of possible confounding factors in the results and must account for selection and observation bias as well.

In looking at the characteristics of “explanatory” (or clinical) trials versus pragmatic trials, Dr Collet noted that the key feature the trials usually have in common is randomization, but that randomization does not need to be blinded for pragmatic studies because there is no need to remove the placebo effect – in fact, we want to have it and measure it along with the other effects on the total outcome. Every other element of the pragmatic study differs from that of explanatory trials: the objective (effectiveness and efficiency vs. efficacy), settings (community vs. hospital), participants (representative vs. selected), outcomes (clinically relevant vs. mechanism of action or surrogate endpoints), sample size (often large vs. as small as possible), duration (as long as necessary vs. as short as possible), quality control (minimal vs. strict) and ethics (minimal vs. detailed informed consent).

Dr Collet indicated that there is a definite need for pragmatic trials to improve disease management and population health management. However, a lack of data creates confusion in the ultimate decisions, which was illustrated with survey information showing that those who make drug listing decisions felt that, except for hard cost information, the availability of information about drugs fell below the importance they assigned to it, particularly on factors such as comparative efficacy, comparative safety, cost-effectiveness and effect on overall healthcare costs. As a result of this gap in information, listing decisions have been contradictory in different provinces and, as he said, “We know what we spend (on drugs), but we don’t know what we get!”

He concluded by noting that developing pragmatic trials requires a public health vision and political support. There are a large number of parties involved in decisions and execution of pragmatic studies, including pharmaceutical companies who are “a very important partner.”

Jeffrey A Johnson, PhD
University of Alberta

Jeffrey Johnson, of the Institute of Health Economics at the School of Public Health at the University of Alberta, looked at pragmatic trials from the perspective of how they can be used to measure, or even improve, healthcare interventions by primary care providers. Hospital and doctor costs, after all, are the largest component of healthcare expenditures, so there is a need to be as concerned about the value of these expenditures as there is about individual drugs.

However, Dr Johnson outlined some issues related to quality improvement for pragmatic trials, including the fact that interventions worthy of study must be those that are easily implemented by busy healthcare providers. He added that pragmatic studies should be looking at improving current treatment gaps, because there is rampant evidence of poor quality care, particularly in such areas as diabetes. But treating such conditions effectively involves multifaceted and behavioural interventions, which can be difficult to blind.

He also emphasized that pragmatic studies must take into effect the background overall improvement trend in healthcare, what he called the “secular improvement” of care. This refers to the fact that even without conscious intervention, healthcare practice and delivery tend to get better with time. He used, as an example, a study that might show that a certain treatment or process produced a 20-percent improvement over time. However, a control group with no use of the treatment or process could show a 5-percent improvement over the same period, mitigating the impact of the apparent 20-percent improvement from the study population. The challenge in pragmatic studies, he said, is how to separate the true impact of the treatment from the background improvement.

Dr Johnson presented, as an example, the DOVE Intervention recently conducted in northern Alberta. The purpose of the Diabetes Outreach Van Enhancement (DOVE) program was to evaluate an intervention to overcome barriers to best practice for rural physicians treating patients with type 2 diabetes. The primary outcome was a composite of 10-percent improvement in any of blood pressure, total cholesterol or glycemic control. Secondary

outcomes were medication starts and patient-reported outcomes, including quality of life and satisfaction.

The DOVE study involved multi-faceted interventions, including academic detailing, preceptor-based consults, in-services delivered by physicians, nurses, and dieticians to rural-based health professionals and public forums. With this pragmatic design, study subjects could not be randomized. Instead “randomization” was created by designating one study region to receive the services after the other, as determined by a coin toss, thus creating a “control” group.

This was crucial to interpreting the study results, Dr Johnson reported, because in the intervention region they found a 44-percent improvement in the cardiovascular and glycemic measures. “Had we not had our control regions,” Dr Johnson said, “this result would have seemed amazing.” However, the control region showed a 37-percent improvement, resulting in a 7-percent absolute improvement in the study region, and a 19-percent relative improvement ($p = 0.19$). In individual factors, the study at six months found a significant improvement only in blood pressure but not in total cholesterol or glycemic control. It is possible this was due to blood pressure being more easily changeable after just six months. In terms of quality of life, however, DOVE intervention participants reported an important and significant positive difference, indicating patients were more satisfied with the interventions, even if clinical measures were not hugely impacted. The overall results show a positive trend across multiple indicators, in spite of using a pragmatic, rather than a conventional randomized control trial.

Dr Johnson concluded by drawing attention to the TREND statement, a 22-item checklist for the Transparent Reporting of Evaluations of Non-randomized Designs (www.trend-statement.org). Developed by behavioural scientists studying illicit drug use and HIV/AIDS prevention in the U.S., it is a way of assessing the quality of the evidence for pragmatic non-randomized designs. Dr Johnson noted that it is important that trial results be translated into practical changes to achieve improvements, “otherwise we will have ‘orphan’ interventions – nice publications on our CVs, but doing nothing to improve patient care.”

**Jack McMillan, PhD, Vice-President
Worldwide Outcomes Research, Pfizer Inc.**

Jack McMillan, global head of Outcomes Research for Pfizer Inc, presented the industry perspective on pragmatic studies. He began by emphasizing that he was presenting “*one* industry perspective, not *the* industry perspective.” While the work of his group involves investigating what effect the product could have on health outcomes, he added that he believes the role also involves “bringing the face of the payer and patient into the organization.”

He then looked at the nature of recent pharmaceutical advances. In an earlier era, starting in the 1950s, major advances were made to treat or prevent acute illnesses with treatments such as anti-infectives, anesthetics, anti-convulsants, insulin, trauma care and vaccines. There was, he said, “great demand and clear value for these products.” Recent new products, however, “are more problematic from a conceptual view.” Presented against a background of alternatives, they are focused on improvements in tolerability, convenience to the patient, managing decline from illness and management of long-term risk, which implies a need to compare them against long-term cost. These new products beg the question – what are we getting for our money?

At the same time, the population is aging and demand for these new products is rising in an environment of payers facing more and more pressures and asking to be shown value for their money. As a result, while the former driving forces for drug development were efficacy and regulatory issues to achieve registration, development must now address the needs of what he termed “emerging information stakeholders” – payers, administrators, clinicians, patients, caregivers and advocacy groups who, while still interested in efficacy, are also focused on cost effectiveness.

In the past, naturalistic or pragmatic studies were conducted primarily in the post-marketing phase. Now, however, more is being demanded as part of the development process. Along with asking if a new drug works and is better than alternatives, the question now asked is, “Is it sufficiently better?” This requires a different mindset among those designing clinical studies.

However, while pragmatic studies are useful earlier in the development process, they are, in fact, only practical to conduct later, when the medicine is on the market and being used by “real” patients. This can lead to a catch-22 situation in which broad use cannot be achieved without reimbursement, yet reimbursement often cannot be achieved without broad use.

Adding pragmatic studies to the development process also has several potential costs, not just the obvious drain on human and financial resources. Internally within industry, they cause portfolio tradeoffs that can result in important projects being delayed or dropped, while externally the need for these study results can result in access delays because they are a hurdle to coverage. Ownership of responsibility for pragmatic studies is also an issue because different stakeholders have different views of the “worth” of answering the questions. This matter of “worth” can be an issue of perspective, depending if one is a payer or not. It must be asked if studies are worth the cost, both in financial terms and in the costs of delaying access to patients. One must also be aware of how one will react to the conclusions reached. “If you find x, what happens then?” he asked.

Dr McMillan concluded by recommending an ongoing dialogue among all stakeholders to avoid unnecessarily complex and formal barriers to open discussion, to ensure research questions are reasonable, that the method matches the questions, and that a target health objective is determined to ensure good decision-making. “Industry needs to sit at the table instead of just making submissions in a courtroom-type defence-prosecution setting,” he said. “We need a better relationship.”

Claire Bombardier, MD, FRCPC
University of Toronto

The perspective of the clinician was brought to the symposium by rheumatologist Dr Claire Bombardier, University of Toronto. With the recent controversies involving the COX-2 inhibitors, Dr Bombardier noted the special view rheumatologists have towards the challenges of the current environment. “We’ve been whipsawed,” she said.

She outlined the events in the COX-2 inhibitor controversy and the fact that clinical

signals of issues were given early on but were not serious enough to be acted upon. Less time could have been taken to act with more observational studies, she said, asking if this represented a “system failure.” The observational studies that were available sent mixed messages. Reviews of administrative databases, for example, have a variety of confounders which, she said, “make it very hard as a clinician to understand the validity of these studies.”

What has been found with the coxibs, she noted, is that as more studies were done, it was indeed shown that all coxibs increase the risk of vascular events. However, this finding also led to the discovery that traditional NSAIDs (other than naproxen) have a similar excess of vascular events. Though these drugs have been used for 30 years, these risks had not emerged previously because trials had not been performed. This raises an issue of how much study is enough for new medications, she asked, noting that NSAIDs had been approved on the basis of trials with about 300 patients, coxibs were approved on studies of about 1,000 patients and new cardiovascular products are involving trials on 30,000 patients. “Where do we stop?” she asked.

The coxib experience, however, has shown that there is a need for earlier and better observational studies linked to primary clinical data collection, and that it is necessary to work with clinicians to collect this data. The experience also showed the need for earlier and better meta-analyses of data to detect trends, as well as the need, she said, to invent a new type of study to allow industry, researchers and clinicians to “move along together” to determine a new drug’s role. She expressed concern that perhaps the coxib lessons have not been fully learned, wondering if a repeat of the coxib experience could occur in other new classes, such as the biologics.

In the treatment of rheumatoid arthritis, the new biologic medicines have revolutionized treatment, but involve a very high cost. This increases the need for pragmatic studies in this area. In fact, she said, “We need to transform our clinical practice into research” by capturing more data, and this is possible with electronic health records. This would provide real data on real patient experience, compared to the data that comes from current study designs which, as she put it, look at groups of patients “who belong to

the 'happy, healthy few' with optimal adherence and compliance, but do not reflect the individual patient you usually encounter in common clinical practice." New types of studies would make broad use of electronic data from clinicians but, in return, would promptly give back to the clinicians, real information that can be applied in their clinical practice. Patient empowerment also has a key role to play in ensuring the transformation of data into useful practice changes, she said. Patient groups and associations have a large role to play in this process, including the collection of data from patients about their real-life experiences.

The current system, she said, has some serious limits. The increased costs of development lead to increased needs for large sales and aggressive marketing, but even large development programs involving 3,000 patients cannot reliably detect adverse events with an incidence of less than 1 per 1,000, even if they are severe. As a result, half of drugs have label changes after approval due to major safety issues - one in five get new black box warnings after marketing and 4 percent are ultimately withdrawn for safety reasons. These events then result in over-reaction by regulators, resulting in increased pre-marketing requirements and delays and the cycle escalates, resulting in a huge disincentive for innovation which is detrimental to all.

Paul Oh, MD, FRCPC, FACP
University of Toronto

The final speaker at the symposium was Dr Paul Oh, also of the University of Toronto, but who addressed the group about his experiences and observations from his former role as a member of the Ontario Drug Quality and Therapeutics Committee, responsible for advising the Ontario Drug Benefit program on drug listing decisions.

He started, however, by giving a dictionary definition of "pragmatic": "relating to matters of fact or practical affairs often to the exclusion of intellectual or artistic matter." He noted that calling naturalistic studies "pragmatic" might not fit this definition because the pursuit of scientific answers they embody should be considered an intellectual pursuit.

He then moved on to explaining the context for drug decision-making in Ontario (before the passage in June 2006 of Bill 102 which has

changed the drug approval system substantially). Spending on drugs has been rising substantially in recent years, both in absolute terms and as a share of total health spending. This should not be surprising, however, given the greater number of drugs available to address more conditions and the overall aging of the population. The challenge for operators of drug plans which strive to provide coverage for all "necessary and reasonable" medicines is looking at new products and deciding what evidence is needed to judge their value against possible alternatives.

For the Ontario public drug plan prior to Bill 102, evidence was evaluated by the Drug Quality and Therapeutics Committee (DQTC), an expert advisory board of 11 members and a chair. (Bill 102 has created a new "Committee to Evaluate Drugs" which will include patient members, which Dr Oh termed "fabulous.") The DQTC could recommend drugs be included on the formulary as a general listing, limited use or a facilitated access listing or could recommend they not be included, either with different types of exceptional reimbursement permitted (Section 8) or no reimbursement at all.

Dr Oh outlined a number of issues faced by the DQTC in evaluating the clinical data. There often were no studies with relevant comparators, using placebo only or offering only indirect comparisons on efficacy. As well, target populations often are not evaluated, either not representative of the typical level of disease severity, age and/or presence of co-morbidities. Other issues include the likely dose being unclear, an absence of published studies, limited long-term data, submitted studies not being all inclusive, lack of adverse event information, lack of evidence to support outcomes (such as evaluation scales that are not relevant), endpoints not being clinically relevant, clinical definitions not being clearly presented and there being no information about possible off-label use. With these drawbacks in the data, it becomes very difficult to determine a new drug's true value, particularly if it is more effective but more costly.

Dr Oh defined traditional explanatory trials as determining efficacy ("Can it work?") and whether the new treatment is superior to control. Pragmatic trials are to determine effectiveness ("Does it work?") and to find the best treatment and to optimize the use of health resources. But

the true value of pragmatic trials is achieved only if they are done in time to inform the formulary decision-making process. "By the time we do these it's way too late," he said. "Either we've missed the safety boat or no one cares any more." At the time of the symposium, Ontario's reform to its drug plan, Bill 102, had just recently been introduced. Dr Oh noted that the changes proposed a greater emphasis on ensuring faster listings but perhaps with more conditional listings "while awaiting further evidence." This could provide a new opportunity for the role of pragmatic studies in the ultimate decision. The challenge, he noted, is that someone would still have to make decisions on whether to grant conditional listings.

Dr Oh issued an appeal to decision-makers to insist on high quality evidence in making decisions, which means they must be prepared to say no if the quality isn't there. If this happens, he

said, researchers will be motivated to provide the data required, payers and purchasers will be able to make clear to manufacturers that favourable decisions will be expedited and manufacturers will be motivated to perform head-to-head comparative trials if they are required.

In looking at how things should develop, Dr Oh said an important question is whether formulary decision-making could best be helped by having more, and more timely, pragmatic studies, or by improving explanatory phase 3 studies. He tends towards the latter, having them involve wider patient populations and with real comparators, not placebo.

But pragmatic studies that are done must be timely if they are to assist formulary decision-makers in making the best choices for patients. "Major health gains are possible," he said, but warned: "Major harm is also possible if we don't do the right thing."

Pragmatic Trials: Methodological Issues and Solutions

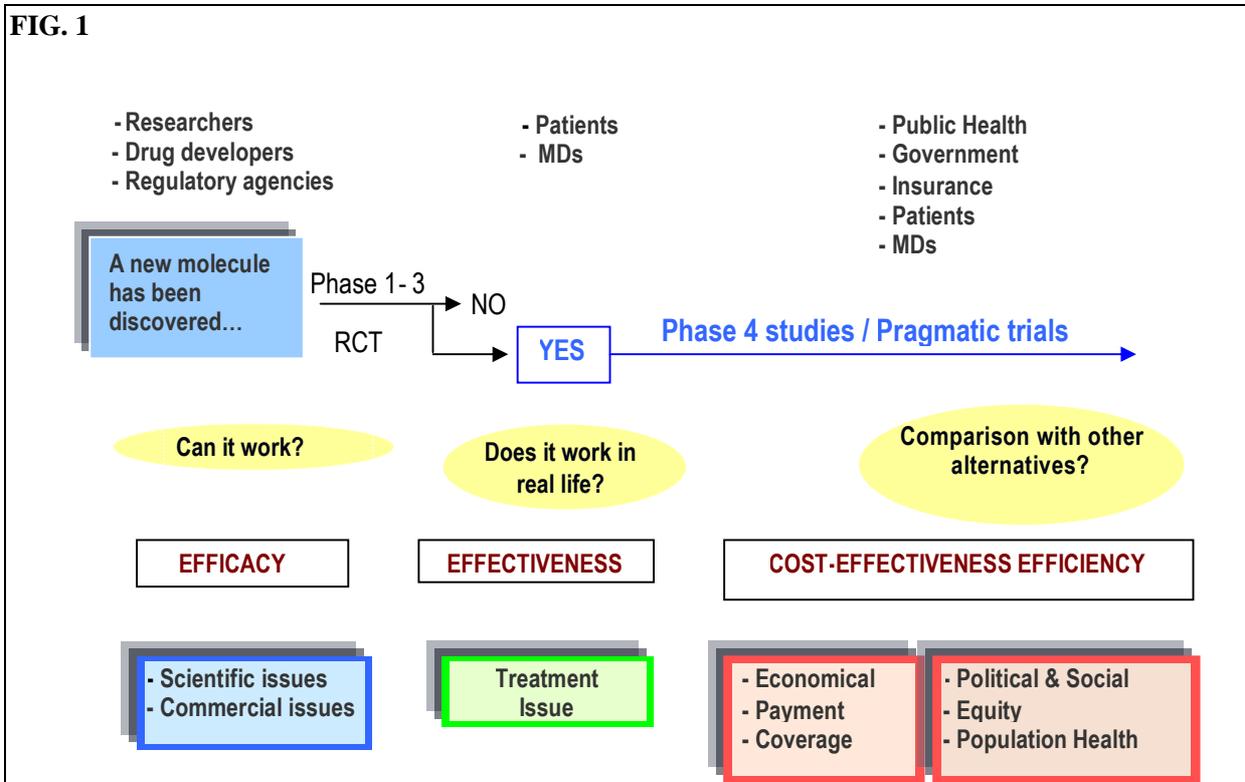
Jean-Paul Collet, MD
 Child & Family Research Institute
 Children's Hospital of British Columbia

Introduction

Dr Collet's presentation focused on the place for pragmatic trials within an overall approach to strategies for evaluation. His goal was to show why the development of pragmatic trial methodology is critically important.

In considering clinical trials, definitions are important. The trial itself is a manipulation of the real situation – there is an intervention – and this leads to different definitions. The MRC Clinical Trial Unit states that “*Clinical trials are research studies involving patients which compare a new or different type of treatment with the best treatment currently available (if there is one). Some clinical trials also look at possible ways to prevent illnesses.*” On the other hand, the International Committee on Harmonization defines trials as “*Any investigation in human subjects intended to discover...drug safety and/or efficacy.*”

The latter is more specific to drugs and the MRC definition includes any type of intervention. Whatever the definition, a trial is certainly not an observational exercise; rather, it must be seen as a prospectively planned attempt to answer questions about what is best for individual patients or for a population.



The trial is part of a decision-making cascade, which means, in short, that different stakeholders have different questions, and each question may require a different design. When a new molecule is discovered, the questions asked by researchers, drug developers and regulators will have to do with efficacy and safety, and phase 1, 2 and 3 efficacy trials are conducted to answer these questions.

If the results are positive, there are other questions asked by patients and physicians: “Does it work in real life? Does it work for me?” and, on another level, “How does it compare with plausible drug and non-drug alternatives?” This is an important question that is also asked by all those who are payers - public health decision-makers, governments and insurance companies. It is at this level that effectiveness and efficiency trials must be developed, and it is within this spectrum that pragmatic trials find their place.

At the first level, considerations are certainly scientific and commercial and, at the second, the focus is treatment. The third level is also treatment-related, but from an economical and political standpoint. At a societal level it is necessary to consider the Canadian Charter of Rights that stipulates access to all for medical needs.

A consideration of evaluation principles makes it clear why pragmatic trials find a special niche. When conducting a study, be it observational or experimental, the desire is to find a causal association between real exposure and true effect. In practice, however, it is usually proxies for exposure and outcomes that are being assessed. Examples would be the amount of drug purchased at the pharmacy (exposure) and a clinical event (outcome). In this situation it is a statistical association that is being measured, not the true causal association, and the statistical association may be fraught with biases and confounders. Dr Collet went on to say that the goal and art of pharmacoepidemiology is really to eliminate or minimize biases and confounders to increase the internal validity. This is the reason that clinical trial methods have been developed.

Box 1

The goal and art of pharmacoepidemiology is to eliminate or minimize biases and confounders to increase the internal validity.

Randomized clinical trials established their strength and became the reference for evidence-based medicine because they could, by appropriate design selection, eliminate bias resulting from inadequate power and other confounding factors. Double blind clinical trials have particular strength in this regard. But clinical trials have their own limitations – such as working with a very selected population, being short in duration and having a small sample size. There is also the Hawthorne effect, wherein patient or caregiver observation modifies the trial situation. In psychiatric trials this bias is particularly problematic, because simply taking part in a trial is a treatment, making it impossible to discern the real effect. These limitations raise the question whether, to gain external validity, it would be better to do observational studies in spite of their equally severe limitations. This is a catch-22 situation, where it is not possible to find a desirable compromise.

Dr Collet went on to describe ways of pursuing maximum internal validity while at the same time achieving good external validity to promote generalizability. First of all, there are interesting observational studies working with administrative databases that can provide very useful information. Models can be developed on which sensitivity analysis can be performed to find the effect according to some maximal or extreme situations. There is also a rapidly developing Bayesian approach, which takes into account the prior knowledge about a situation and integrates further new knowledge to make an estimate of the probability of the observed effect.

TABLE 1 Efficacy vs. Pragmatic Trials

Key Features	Explanatory Trials	Pragmatic Trials
perspective	drug development	user (physicians, patients); payer (government, insurance)
objectives	efficacy	Effectiveness; efficacy
concern	internal validity	internal and external validity
design	'classic' standard	innovative 'mixed' models; administrative database
setting	hospitals	community
participants	selected	'representative'
population	highly selected	usually treated
outcomes	mechanism of action surrogate endpoints	clinically relevant
intervention	'controlled'; strict protocol	'usual practice'; often complex; new policy
randomization	yes	yes
blinding	yes	not usually
randomization unit	subject	subject; group; cluster
sample size	as small as possible	often large
duration	as short as possible	as necessary
statistical analysis interpretation	per protocol; intent to treat	intent to treat; bayesian
quality control	strict	minimal
ethics	detailed informed consent	minimal information

Pragmatic Trials

A pragmatic study is a form of trial, which means it is a situation where treatments will be controlled. It is not an observational study. Pragmatic approaches are aimed at improving external validity to allow generalization but, because randomization has occurred, at the same time they have strong internal validity. Dr Collet drew attention to some of the especially important points of differentiation between explanatory and pragmatic trials (Table 1).

The pragmatic trial is concerned with both internal and external validity and the design is often complicated and requires innovation. An example would be a mixed model, in which there is a randomized part that is followed by a naturalistic follow-up, thus integrating epidemiology and clinical trial within the same design.

Trial setting tends to be at the community rather than the hospital level, and this is an important issue because most drugs are evaluated in hospitals but used in physician offices. It may be that there is something different about treatment in the office compared to the hospital. This should be kept in mind because the goal, above all, is to be able to generalize the results obtained. Physicians participating in a pragmatic trial should be representative of the community, rather than highly selected.

The population under study should be the one usually treated and the outcomes should be clinically relevant, whatever the definition. The intervention should be usual practice: it could be a new policy that is being evaluated, or a new health care organization or health care access. Randomization is another key feature, and this is the only characteristic identical between explanatory and pragmatic trial designs: both are randomized. The randomization unit can be the individual, but it is very often a group of people. Such cluster randomization permits a natural design, because cluster randomization has less effect on patient participation, i.e., there is less Hawthorne effect. Blinding is often not possible, but this is not a problem because in real life people like the placebo effect, so that, in pragmatic trials there is no need to remove it.

Sample size is often very large and duration as long as needed to generate relevant answers. By using administrative databases linked to pragmatic trials it is possible to do long-term follow-up without too much difficulty. Statistical analysis would be on an intent-to-treat basis for both pragmatic and explanatory trials. However, pragmatic trials may also benefit from a Bayesian approach. Finally, Dr Collet said that quality control should be minimal because, again, having too stringent quality controls can modify the behavior of the caregivers and patients and create some artifactual effect.

Do We Need Pragmatic Trials?

Dr Collet answered his own question with a resounding 'yes'. They are needed to improve disease management, to optimize population health management, including health promotion, disease prevention and decisions about health administration policies. The issue is really to find a way to develop them and to reach consensus on appropriate research methods.

Lack of data can create confusion. A study his group conducted in Canada showed that, in fact, at the time of decision-making, the people making decisions to accept new drugs for provincial formularies often lack critical information needed. (West, *et al.* Can J Public Health 2002;93:421-5). Important information, such as comparative efficacy against alternative therapies and cost of alternatives, was unavailable for most of the decisions studied. The same was so for information about cost-effectiveness, comparative safety and the effect on overall health care costs.

Again at the level of decision-making, when different provinces were compared in this study, the rejection rate of submissions for formulary listing over a one-year period ranged from 121 to 9 submissions across the provinces. Committees are examining exactly the same data, but without the proper information, the decision as to whether to approve or reject an application is a matter of subjective assessment. The trend in health care expenses over the last 15 years shows that hospital spending is declining while drug expenditure is rising. Unfortunately the trend alone does not reveal the consequences of these formulary decisions.

Best Research for Best Health

Box 2	
Pragmatic Trials in Practice	
decision & execution	<u>all parties should be involved:</u> - patients, physicians, researchers, population health managers - disease networks - hospitals - insurance companies - government
funding	- public - private (e.g., HMO, insurance)
infrastructure	- disease oriented networks - web based electronic platform - administrative databases - highest standards of communication (e.g., HL7, CDISC-ODM (XML))

The “Best Research for Best Health” strategy of the National Health Service (NHS) in the UK takes the lead worldwide in developing clinical research networks. Six large networks have been established in conjunction with industry. The NHS is also developing a health technology assessment (HTA) program to provide high-quality research information on the costs, effectiveness and broader impact of health technologies for those who use, manage and provide care within the NHS. As part of the HTA program major new funds will be available for pragmatic clinical trials. Overall, a commitment has been made to provide 2.5 % of GDP for this development by the year 2014.

Developing pragmatic trials requires public health vision and political support. Involvement by all parties is essential, especially users and payers. Funding could be public or private. However, one question remains unanswered and that concerns the place of the pharmaceutical industry. Manufacturers do not consider pragmatic trials their first priority, but they are definitely very important partners in the undertaking.

Finally, Dr Collet said, there are considerations about the practical organization of such trials. He believes that they should be based on disease-oriented networks, use Internet-based electronic platforms for continuous data collection and capitalize on administrative databases. Overall, he said, the work should be facilitated by using the most up-to-date standards of communication.

Further Reading

1. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutic trials. *J Chron Dis* 1967;20:637-648.
2. Hotopf M. The pragmatic randomized controlled trial. *Adv Psych Treatment* 2002;8:326-333.
3. Wilson S, Delaney BC, Roalfe A, et al. Randomised controlled trials in primary care: case study. *BMJ* 2000;321:24-27.
4. Roland M, Torgerson DJ. Understanding controlled trials: What outcomes should be measured? *BMJ* 1998;317:1075-1080.
5. Thompson SG, Barber JA. How should cost data in pragmatic randomized trials be analysed? *BMJ* 2000;320:1197-1200.
6. Tunis SR, Stryer DB, Clancy CM. Increasing the Value of Clinical Research for Decision Making in Clinical and Health Policy. *JAMA*.2003;290:1624-1632.
7. <http://www.hta.nhsweb.nhs.uk/news/newsitem06031501.htm>;
<http://www.hta.nhsweb.nhs.uk/news/newsitem06050901.htm>;
http://www.acao.org/docs/pdf_2006_best_research_best_health.pdf

Pragmatic Clinical Trials: Evaluating Quality Improvement Interventions

Jeffrey Johnson
 Institute of Health Economics
 School of Public Health, University of Alberta

Introduction

Dr Johnson addressed the topic of pragmatic trials from the perspective of quality improvement interventions. Such studies seek to change health care service processes and the outcomes of the health care they provide. The goal is to attempt to change some aspect of the process in such a way as to effect improvements further down the line that ultimately achieve positive outcomes.

These interventions are also concerned with the efficiency of care delivery and the optimization of use of health care resources, i.e., the economic political perspectives, as Dr Collet has mentioned. The delivery of health services, including hospital and community care and all of the personnel involved, is the largest component of health care expenditure. With such massive funding, there should be as much concern about the evidence supporting the effectiveness of health care services as there is about the efficacy and safety of individual drugs.

Box 1
Issues with Pragmatic Trials for Quality Improvement
<ul style="list-style-type: none"> • interventions must be feasible for busy practitioners • concern about treatment gaps e.g., quality of chronic care • interventions are often complex, multifaceted • interventions often target provider behaviour and are difficult to blind • measurement of effect is complicated by positive secular trends

On the one hand there is the need for good evidence, and of course the conventional randomized control trial provides the best evidence. On the other hand, there are situations where it is not always appropriate to apply these principles. It must be stated to begin with that the quality improvement process should result in interventions that are feasible in practice, otherwise it will be impossible to get acceptance by very busy providers. Favorable reception by dynamic health care systems is also a must. With these requirements, it is necessary to be practical and to conduct pragmatic studies that will allow intervention within a dynamic health care system. Another issue is improvement of treatment gaps, for example, there is copious evidence of poor quality care for chronic conditions.

For quality improvement interventions to be successful they should be multifaceted, but, in spite of this aspect of complexity in some features, the aim is still to deliver a relatively simple and feasible intervention. The goal of many interventions is to change behaviours, typically of health care providers, but trial design is complicated by the difficulty of conducting blinded studies.

The final issue of concern is one of the most important for quality improvement studies, and that is the problem of secular trends. On the whole, quality does improve gradually with time: evidence emerges, practices improve and health care delivery gets better. However, unfortunately, most of the quality improvement studies use a before-after study design. This simple, non-experimental, observational design, as Dr. Collet mentioned, has many threats to validity: inclusion of different patients, treatment by different physicians during the 'before' and 'after' time periods, regression to the mean, the Hawthorne effect, possibly biased outcome ascertainment and lack of blinding. All of these can be problems, but perhaps the most important threat is the presence of secular trends.

An example would be the demonstration in a before-after trial that a certain intervention was associated with a 20% improvement over a 2-year period. Given the study design, the question is whether or not this is a real improvement. When it is not possible to use a conventional randomized control trial design, an alternative to the simple before-after might be a before-after trial that uses concurrent controls. This design is useful for pragmatic quality improvement interventions in a dynamic health care system where it might not be possible to randomize at the individual level. Of course, without randomization there are still problems with validity.

The Example of the DOVE Study

With that general introduction, Dr Johnson proceeded to discuss the Dove (Diabetes Outreach Van Enhancement) study that was recently conducted in northern Alberta. The purpose of this study was to evaluate an intervention to overcome barriers to best practice for rural physicians treating patients with Type 2 diabetes. Specifically, the objective was to increase attention to and quality of management of cardiovascular risk in patients with Type 2 diabetes, arguably the worst aspect of care for people with this disease. The primary outcome measure was any improvement in the composite of blood pressure, cholesterol and glycemic control, but these were also examined individually. In addition, because the intervention was aimed at disease management, other secondary outcomes of interest were medication starts and patient-reported outcomes, including quality of life and satisfaction.

The intervention was multifaceted. A team from a tertiary care hospital in Edmonton comprising of a physician, pharmacist, nurse and dietitian visited rural regions in northern Alberta once a month for six months to discuss important aspects of treatment with local health care professionals. Some of the information was provided through academic detailing: specialists in diabetes management interacted with groups of rural family physicians, and pharmacists conducted academic detailing sessions with individual physicians. There were preceptor consultations wherein specialists discussed particular patients and management problems. The team also provided in-services to other health providers in the region, for example, the dietitians, and held public forums in collaboration with the Canadian Diabetes Association.

The study design was pragmatic: the intervention was offered in one region immediately and the other later, but both regions eventually received it. Order was determined by coin toss. This design was chosen because randomizing the intervention only to certain rural areas while others served as controls was not considered to be a reasonable option. Team members discussed the study directly with medical officers and directors of the regions, admitting that it might cost some money and that participation might not be worth the cost.

Persistence of the effect of the intervention was tested by continuing to collect data from the first region for a follow-up period of 6 months. The results of the first six months in the first intervention region showed a 44% improvement in the composite measure (blood pressure, cholesterol or A1c improvement). However, the control region before the intervention improved by 37% over the same period of time.

Box 2
The "DOVE" Intervention
<ul style="list-style-type: none"> • <u>Academic Detailing</u> <ul style="list-style-type: none"> - specialist physician to groups of rural physicians - trained pharmacist to individual rural physicians • <u>Preceptor-based Consults</u> <ul style="list-style-type: none"> - limited number, with rural physician participation - focused on one management problem • <u>In-services</u> delivered by study physicians, nurses, dietitians to rural health professionals • <u>Public forums</u> in conjunction with Canadian Diabetes Association-related activities

Without the control group, the improvement would have appeared to be far greater than it actually was. It is interesting to note that most quality improvement interventions, at least in the diabetes care literature, report amazingly successful interventions when there is no control group or recognition of secular trends. Statistical analysis showed a non-significant but positive trend for the primary outcome. As for secondary outcomes, looking at hypertension, cholesterol and glycemic control individually, there was a significant improvement in hypertension and no change in cholesterol or A1c. Medication starts measured the increased use of agents known to be associated with better outcomes for the primary outcome variables.

In all cases there was increased prescribing, for control of blood pressure, cholesterol and glycemia. A possible physiologic explanation for achieving a significant effect only for blood pressure may be that this parameter can be changed relatively quickly, whereas 6 months may be too short to see changes in cholesterol. However, the data did suggest a positive trend.

Box 3
Pragmatic vs. Randomized Control Trials
<ul style="list-style-type: none"> • <u>Strengths</u> <ul style="list-style-type: none"> - Valid designs - Simple, multifaceted interventions - Broadly applicable - Multiple outcomes, clinical- and patient-reported • <u>Limitations</u> <ul style="list-style-type: none"> - Non-randomized designs - Cannot examine separate effects of components of the intervention - Surrogate outcomes used

In addition to these clinical outcomes, humanistic, or patient-reported outcomes were also measured. It is important to remember that the intervention was aimed at health providers. Despite this, patient satisfaction showed an important and statistically significant improvement. Patients were more satisfied with their care compared to patients who received standard care in the control region at the same time. The overall results show a positive trend across multiple indicators, in spite of using a pragmatic, rather than a conventional, randomized control trial.

Pragmatic studies with valid trial design are possible, be they randomized and pragmatic in their inclusion criteria and follow-up plan, or non-randomized, as is the case for many quality improvement interventions. Both have aspects that allow assessment of internal validity. They may be simple but at the same time allow for multifaceted interventions. A key requirement is that they be feasible and the results therefore broadly applicable, otherwise these studies would not be pragmatic.

Limitations, aside from the non-randomized design, which cannot be avoided and will always be a concern, include the fact components of the intervention cannot be examined separately. Conclusions can pertain only to the multifaceted intervention taken as a whole. Another limitation is that more often than not, surrogate outcomes are measured, e.g., treatment rates rather than clinical events.

The TREND Statement

The TREND statement, like the CONSORT statement, is concerned with the reporting of trial results. Whereas the latter is concerned with parallel group randomized trials, the TREND is a 22-item checklist for the Transparent Reporting of Evaluations of Non-randomized Designs (www.trend-statement.org). It is a way of assessing the quality of the evidence for pragmatic non-randomized designs. Given that evidence for making public health decisions will require using data from studies with non-randomized designs, the intention is to improve the quality of reporting by emphasizing the need to describe intervention conditions and research design, as well as ways of dealing with possible biases. It was developed by behavioural scientists studying illicit drug use and HIV/AIDS prevention studies by the Center for Disease Control and other groups in the United States.

One of the first questions asked about this statement is: “Is it theory-based?” Such a basis may alarm many trialists, who debate its usefulness mainly because there are no items concerning efficiency and cost-effectiveness. But, said Dr Johnson, the statement is a beginning for non-randomized study designs.

The other important issue for quality improvement interventions is sustainability. These pragmatic studies are done to improve quality of care within a dynamic health care system. The interventions must be proven to be effective in order that the health care system and the providers make changes, so it is incumbent on the investigators to take an active role in translational activities following the trial.

The DOVE study investigators have done just this in Alberta, taken an active role, working with the government and health regions to translate the findings to practitioners and patients. The evidence is generalizable, and the intervention can be implemented in other regions. The danger of not putting an effort into translational activities is the creation of orphan interventions and the opportunity to achieve improved quality of care will be lost.

Dr Johnson ended with a quote from an anonymous “Reviewer B”, commenting about the DOVE publication: “... *study fits into the category of translational research...contains methodologic flaws if rating it against efficacy criteria..., but as an effectiveness trial, it has the strengths of generalizability and assessment of multiple indicators.*”

Acknowledgement

Dr. Johnson holds a Canada Research Chair in Diabetes Health Outcomes and is a Health Scholar with the Alberta Heritage Foundation for Medical Research.

Further Reading

1. Des Jarlais DC, Lyles C, Crepaz N. Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: The TREND statement. *American Journal of Public Health* 2004;94:361-366.
2. Johnson JA, Eurich DT, Toth EL, Lewanczuk RZ, Lee TK, Majumdar SR. Generalizability and persistence of a multifaceted intervention for improving quality of care for rural patients with type 2 diabetes. *Diabetes Care* 2005;28:783-788.
3. Maddigan SL, Majumdar SR, Guirguis LM, et al. Improvements in Patient-Reported Outcomes with an Intervention to Enhance Quality of Care for Rural Patients with Type 2 Diabetes: Results of a Controlled Trial. *Diabetes Care* 2004;27:1306-1312.
4. Majumdar SR, Guirguis LM, Toth EL, Lewanczuk RZ, Lee TK, Johnson JA. Controlled trial of a multifaceted intervention for improving quality of care for rural patients with type 2 diabetes. *Diabetes Care* 2003;26:3061-3066.

Pragmatic Studies: An Industry Perspective

Jack McMillan, PhD
 Vice President, Global Outcomes Research, Pfizer Inc.

Introduction

An industry perspective of pragmatic studies was described by Dr Jack McMillan of Pfizer Canada. He began by pointing out that there is no single industry perspective; that views depend very much on the particular circumstances. The Outcomes Research group at Pfizer supports products both under active marketing and earlier in the development process, with about half the effort being spent in each area. Dr McMillan's comments pertained to health outcomes issues relevant to products at both of these stages. He stated at the outset that a key focus of all of the work done by the group is to bring the faces of the payer and patient into the development process.

In addition to this, there are a number of issues that are of constant concern, and for which there are no simple answers. A key question to begin with is who should determine the research questions for pragmatic studies. The danger in determining effectiveness is that the question may be so broad that the research will never be completed. It is also important to understand who the stakeholders are and who should be expected to pay the costs of the different phases of these studies. When it comes to translating clinical studies into clinical practice it is well recognized that the results of randomized control trials are not totally generalizable. Dr McMillan said that concerns about how the "average" patient will react are front and centre throughout the development process. Industry researchers are always trying to isolate reasons for variability in subgroups and the emphasis on this becomes greater as the process proceeds.

The Changing Environment for Pharmaceutical Innovation

Box 1	
Character of Pharmaceutical Advances	
Mid-1950s	Today
• therapies for acute disease	• against a backdrop of alternatives
• perceptible benefit	• management of long-term risk
• high perceived value	• improvements in tolerability
• immediacy of benefit and risk	• management of patient convenience
• no/few alternatives	• management of 'decline'
• 'the right thing to do' vs. efficiency	

Dr McMillan went on to talk about changes that have occurred in the nature of pharmaceutical advances over the last five decades. Starting in about the mid-1950s, new therapies were for acute conditions for which often single doses or short-term courses of treatment had perceptible value. The benefit and risk of such therapies as vaccines and insulin were readily understood and drug efficiency was not an important issue.

The situation with more recent pharmaceutical advances is problematic from the standpoint of perceived value, and this has resulted in requests for efficiency and effectiveness studies. There are alternative therapies to these drugs, some of which are cheaper, others cheaper and less effective and still others with better tolerability. Another difference from the earlier situation is that the focus is increasingly on chronic disease, with the need to manage long-term risk, long-term cost and, possibly the most problematic, declining health.

The system has moved into an era of increased demand: more conditions, many of them chronic in nature, can be treated for longer periods of time at an increasing cost. The question of what is being gained for money spent is being asked more and more often and in stronger language. The financial issue is important and must be dealt with.

The Changing Demand for Information

The changes in types of therapies have led to changes in the driving force in drug development for the industry. Regulatory agencies may have more to say about efficiency, but their bottom line is still efficacy, as demonstrated by the randomized control trial. This will not change. However, the newer stakeholders – the payers, clinicians, patients, caregivers and advocacy groups – are asking about efficiency and cost effectiveness. Answering these questions can be significant barriers for the drug development process.

Box 2
Questions the manufacturer asks about all compounds at all phases of development
<ul style="list-style-type: none"> • In what populations? • At what doses? • Against what comparators? • Is a treatment <ul style="list-style-type: none"> -Cost saving? -Cost effective? • Improved patient reported outcomes?

Box 3
Pragmatic Studies
<ul style="list-style-type: none"> • Compatible with sample size requirements • Compatible with broad populations of interest • Naturalistic set of forces <ul style="list-style-type: none"> - comparators - variations in practice patterns - variations in patient behaviours • Dynamic reimbursement environment

Dr McMillan talked about a series of questions that industry researchers ask about every compound selected for development starting at phase 2. An illustrative sample is shown in Box 2. The questions concern every aspect of the research process, from target populations to cost to patient reported outcomes, and are repeatedly asked of every possible target subgroup. In this way candidate drug profiles can be compared and at the same time the researchers can be ready to supply information requested by the various stakeholders.

Whereas phases 2 and 3 studies have long been defined by the randomized control trial (RCT) that determines whether or not a drug is effective, pragmatic studies have been conducted almost exclusively after marketing. This timing is not likely to change, since it is under conditions of free usage in a large enough, relatively unselected, population in which, answers to many questions will be found. In essence, under these conditions the forces that determine patient response are the most naturalistic. Basically, although pragmatic studies are carefully designed, there is very little control and the effect has been likened to chasing a moving train because the health care system is changing at the same time. With studies that last, say, six years, the system is not the same at the end as at the start of the study. Reimbursement, market and practice patterns are all dynamic and can change considerably during this time.

More is being demanded of the drug development world and, while this is to be expected, it does cause problems in clinical trial design, Dr McMillan said. On the one hand, the clinical trial purist who designs phase 2 and 3 studies wants to isolate a systematic effect by mandating conditions that minimize sources of variation. The outcomes research person, on the other hand, is focused on patient and payer issues and wants to know if the therapy will work in common practice and, if better than alternatives, whether the difference is important.

Box 4
Managing Secondary Sources of Variation
<ul style="list-style-type: none"> • <u>eliminate</u> <ul style="list-style-type: none"> - exclusion criteria - include only evaluable patients - disallow concomitant medication
<ul style="list-style-type: none"> • <u>control</u> <ul style="list-style-type: none"> - blocked designs - covariates - block randomization of concomitant medication
<ul style="list-style-type: none"> • <u>allow</u> <ul style="list-style-type: none"> - randomize - allow concomitant medications, assume even distribution

Although a clinical trial purist may add pragmatic extensions to a study, these are still within the context of an RCT. In pragmatic studies, the influence of variation is preserved: second-degree sources of variation, the so-called nuisance variables, are left to have their own effect on therapy. Box 4 lists strategies for dealing with the secondary sources of variation mentioned by Dr McMillan. They can be eliminated, as happens in the RCT. They can be controlled using different methods, including blocked study design; or they can be allowed, with the reasoning that randomization will result in an even distribution of the variables among patients in the study groups. All of these management techniques influence the balance between internal and external validity.

Turning a therapy loose in a population and watching to see what happens requires some types of control, and the more control, the less generalizable the findings, and the more the balance between internal and external validity will be affected. The conventional approaches to control will always have such effects. Also, it will never be possible to do most pragmatic studies in the early stages of drug development because too little is known about the drug and it is not permissible at this point to study large enough populations. However, extending drug investigation into the world of pragmatic studies should always be kept in mind, even in the early stages of development.

Secondary sources of variation require careful management in the pragmatic setting. This is difficult, given that it is a constant challenge to even envision what these unwanted sources of variation might be, let alone decide how to manage or control them five or ten years before a drug is introduced into the system. To make reasonable predictions, both the system and how the drug would be used would have to be well understood. However, the more challenging situation is probably when these sources of variation are incorrectly forecasted and factored into trial design early in the development process. To complicate matters even more, it goes without saying that causal relationships obviously will always be difficult to identify.

Pragmatic Studies: Issues for Development

Dr McMillan next talked about problems related to the fact that the nature of a drug profile changes as information accumulates. There is a progressive balance between clinical understanding and exposure. Building the profile starts with phase 2 studies and continues into phase 3, at which time phase 2 studies are still underway. Phase 2b involves studies of other indications, i.e., in different populations. The constantly changing profile must be kept in mind during early development phases when trying to make decisions about the eventual pragmatic population-based trials. It is risky to make firm decisions that will determine the pathway of development, before being comfortable with the state of understanding of the many possible mediators of effectiveness of a product under study.

The question is quite clear: At what point is there sufficient understanding of the many possible mediators of effectiveness to design the very large pragmatic studies and to commit the significant resources required? The objective is to understand how new drugs will be used in common practice before they are common in practice. This leads to a catch-22 situation: it is generally not possible to achieve broad use without reimbursement, and reimbursement is not available until efficacy in these populations has been demonstrated. The conclusion is that valid pragmatic studies are not really possible without some degree of commercialization.

Box 5
Pragmatic Studies: Issues for Development
<ul style="list-style-type: none"> • generally cannot achieve broad use without reimbursement • often cannot achieve reimbursement without broad use

Sometimes the results of a pragmatic study suggest that the drug is not as efficacious as shown in the RCTs. Dr McMillan suggested that, in this situation it might be useful to consider what has been measured: there is always the possibility that it is the deficiency of the system to get the most out of the therapy, rather than deficiency of the therapy that is being measured. It should be kept in mind that a therapy is a static entity - it is what it is. It is possible that in the future the question will be how to use a given therapy in a population or in a health care system to get the most out of it, to use it most efficiently. Such questions require a quite different mindset from that current in drug development.

Costs of Pragmatic Studies

Clearly there are issues with the fact that the time required to conduct pragmatic trials may become a barrier to access. Some of these trials are very large and of prolonged duration; and access to patients is denied until some difficult efficiency measures have been demonstrated. Patients have to wait, and this does not meet the needs of those populations that will respond only to a particular therapy.

In determining the overall effect of going this route the opportunity cost must also be considered, both in human and financial resources. These studies can be very expensive. Even large organizations with extensive research endeavors have budget constraints, and these must be considered when committing substantial resources to long-term studies. To add to the burden, industry is often asked to answer more and more questions that require larger and larger studies. It is important that the stakeholders understand what it takes to answer these questions. The magnitude and feasibility of effort required to answer some questions can bear on which compounds are chosen to move forward in a portfolio.

Who Owns the Question?

As far as efficacy is concerned, it is the industrial developer who decides what questions will be addressed by research. However, as the state of knowledge progresses and effectiveness becomes more important, decisions are no longer entirely under the control of the originator. If this is to be the way of the future, a different, better relationship between the industry and the requester is needed to ensure clear understanding of what is being asked and why. There should be some kind of partnership with respect to decisions about these research questions.

There is the matter of whether it is worth answering a question. Worth depends on perspective: any question can be asked if someone else pays to find the answer. In some cases, the decision can very quickly be made that it is just not the right business decision to agree to conduct more studies. Pragmatic studies have become fashionable, but it is important to carefully consider exactly what is being asked and whether answering the question is worth the cost – both the cost of delaying access to drugs and the financial cost. There have been some excellent studies done in the past that took a lot of time and, when study findings were finally evaluated, the results were no longer of interest because the market had

changed. We are rapidly reaching a stage where there has to be a partnership to manage the magnitude of the effort required to answer some pragmatic questions. There has to be a clear understanding or agreement of what the consequences will be if a certain finding is reported. The partnership does not have to be contractual, but there should be at least a meeting of the minds about the research question being asked.

Recommendations

The current, unnecessarily complex, methodological and formal barriers between the stakeholders and industry prevent open discussion. The process can be likened to a dossier being thrown over a wall, which is followed by a reply coming back over the wall, and so forth. In many cases, just as intense effort can be put into the review process by sitting together at the table and asking the questions:

Box 6
Dialogue Among Stakeholders is Essential
<ul style="list-style-type: none"> • avoid complex formal barriers to open discussion • research questions must be reasonable • research methodology should match the question • a target health objective is essential

“What is of value, can this drug profile deliver it, and under what conditions and in what populations?” It could be a straightforward relationship, as opposed to a courtroom-type defense-prosecution situation. It is essential that ongoing dialogue between stakeholders be encouraged. Research questions must be reasonable. The best way is to discuss them face to face to understand what is being asked and why. Furthermore, the methodology should match the question: it is not practical to do a pragmatic study out of idle curiosity. There has to be a real need to know the answer to a question.

Finally, and most important, there must be a target health objective. Often the manufacturer is asked to analyze a new drug against a large number of competing therapies to determine which is most efficient. The response to such a request should always be “to achieve what end?”, because, unless there is a specific target, any therapy might be efficient at delivering some benefit of unacceptable magnitude.

Are Pragmatic Trials Pragmatic?

Claire Bombardier
Director, Division of Rheumatology
University of Toronto

Introduction

Dr Bombardier talked about pragmatic trials from the perspectives of both clinician and epidemiologist, as a rheumatologist and founding director of clinical epidemiology at the University of Toronto. She pointed out that she has contacts with many pharmacoepidemiologists and can understand their perspective as well. Her practical experience includes conducting observational studies and randomized control trials, both investigator- and industry-driven, over the last 28 years. The presentation began with a quote from the Nobel laureate Arthur Kornberg: "The future is not predicted, it is invented." Dr Bombardier said that the process of conducting trials is an attempt to see what is in the future. However, it is not really possible to predict the future because the knowledge used in the process comes from the past, and since it cannot be predicted from the past, it must be invented. This means that serendipity is involved: an attempt is made to find out what will happen with a certain therapy and the challenge is to learn from this experience to create something new.

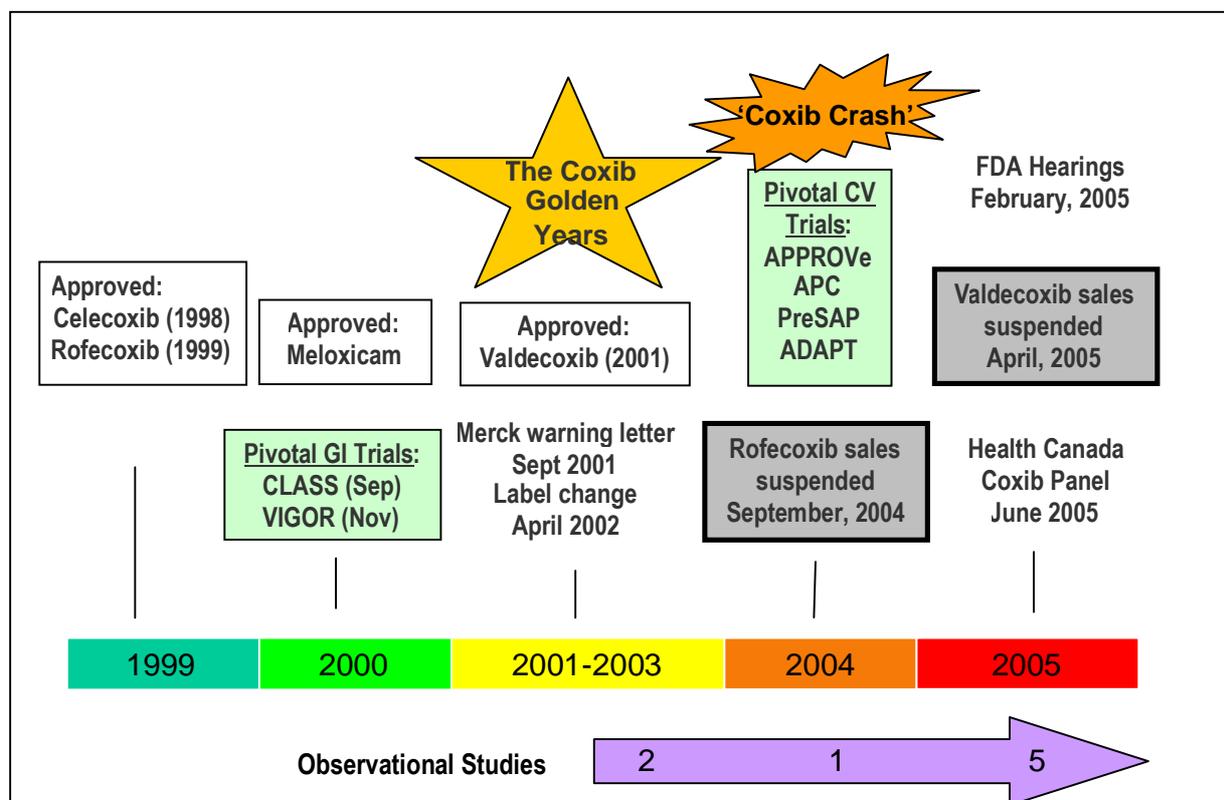
Challenges

The presentation focused on three challenges: changing therapeutic strategies, increased use of pragmatic studies and patient empowerment, all as seen from the perspective of a rheumatologist. Researchers involved in therapeutics in the field of rheumatology over the past few years have been whipsawed: new drugs have been introduced to the market, and then removed, and this has been followed by the introduction of still more new drugs, including biologicals. It has been a rich learning experience and it is this experience that Dr Bombardier drew from in her presentation. Scientists now feel very strongly that it is of paramount importance that drug regulation moves beyond the randomized trial. Impressive strides have been made internationally, although not as yet in North America. In fact, the United States is further behind in this regard than Canada. On the other hand the Europeans, through the European Medicines Agency (EMA), moved forward this past April in announcing that they will now allow conditional approval. This has generated an explosion of innovation in deciding how this should be accomplished. A new era of innovative trial design is on the doorstep.

Finally, about patient empowerment: this is going to be a very large part of what researchers will be dealing with. It is no longer enough to interact with governments and industry: interaction with patients will be more and more the focus. At the same time, it is important to consider colleagues and other clinicians, because the coming changes will not be successful unless they are acceptable to the prescribers.

The COX-2 Experience

The story of the COX-2 inhibitors unfolded over a period of six years, from 1999 to 2005. It could have taken less time if conditional approval had been in place, because observational studies would have been planned from the beginning. Three COX-2 drugs were approved in 1999-2001: valdecoxib, celecoxib and rofecoxib, and major outcome studies were done in 2000. Between 2000 and 2004 there were some signals concerning safety that came in various forms. This led to a warning letter from the FDA to the makers of rofecoxib, which was followed by a label change based on the results of the VIGOR study that showed differences in myocardial infarction between standard NSAIDs and the COX-2s.

FIG. 1 COX-2 Inhibitor Event Timeline

During this period large trials were done by the industry in an effort to find out if there were other indications for COX-2s, such as polyps, cancers and Alzheimer's. It was through these trials, in particular the APPROVe study (N Engl J Med 2005;352:1092-1102), that the difference in cardiovascular events became clear. The question is whether something could have been learned before 2003.

The "coxib crash" occurred in 2004 with the withdrawal of rofecoxib and the consequences for industry and patients. Also affected was public and media trust of the industry, clinicians and the FDA. The FDA is still being battered on the front page of newspapers. The next COX-2 to be withdrawn was valdecoxib and this was followed by FDA committee hearings, a very traumatic experience for those involved. Observational studies of the coxibs did not start until 2001 and 2003, in spite of the fact that administrative database information on use of these drugs had been available from the beginning. In fact, only two such studies were done early on, and then another in 2004. There were another five in 2005, but by then, it was too late: the answers were known from randomized trials.

Dr Bombardier went on to give more details of the three observational studies conducted before 2005 in which the risk of myocardial infarction in rofecoxib users was compared to non-users. The study by Ray in 2002 (Lancet 2002;359:118-23) found an increase at the higher of two doses, but there were only 12 events. The Mamdani study (Arch Intern Med 2003;163:481-6) using the Ontario database showed no difference, and the Solomon study showed a difference, but the odds ratio was only 1.14, and the number of events was again very small. This was not strong evidence.

However, when all of the observational studies available were taken together, the media and the public got the impression that there was a strong signal. But, said Dr Bombardier, although it can be argued that

there were signals, all observational studies are not equal: study design and quality have to be taken into account. The bottom line is that four studies were positive and three were negative, which does not suggest any particular conclusions.

There is no doubt that administrative databases are very useful. But the problem for clinicians is that it is difficult to believe in the validity of the studies without diagnosis ascertainment and information about compliance. The latter is especially problematic when comparing a drug that is taken three times a day to one taken only once a day. Also, the fact that a drug was purchased does not mean it was ingested by the patient. Another issue is that over-the-counter medications do not appear in billing databases, and in this case, it is important to know about co-use of aspirin and NSAIDs. Finally, there is little information about comorbidities. Dr Bombardier summarized by saying that it is very difficult to see clearly with this lack of information.

Furthermore, from a methodological point of view, observational studies require a very high effect size to be able to say that perhaps the potential for bias has been overcome. To quote Shapiro: *“If an association is of relatively low magnitude (RR<2), it may not be possible to judge whether or not it can be entirely accounted for by bias.”* (American Journal of Epidemiology 2000;151:939-45) Taken in isolation, results from studies using administrative databases are problematic. Novel ways of using these databases are needed.

Moving on to meta-analysis of randomized trials, Dr Bombardier said that there should have been good meta-analyses of randomized trials done earlier. She presented the findings of a paper by Colin Baigent that had just been accepted for publication in the British Medical Journal (BMJ 2006;332:1302-8). This is probably the most comprehensive and best meta-analysis that has been done. Baigent requested from industry all of the data on the 138 COX-2 trials – 144,000 patients in all. There was a range of indications and different comparators, although the latter were mainly traditional NSAIDs.

Box 1
Conclusions Baigent Meta-analysis
<ul style="list-style-type: none"> • coxibs increase the risk of vascular events by about 1.4-fold overall • traditional NSAIDs other than naproxen have similar risk • risk has not emerged previously because trials were not performed

Dr Bombardier focused on the findings from trials that included a placebo group. There was a 41% increase in cardiovascular events across all the trials. If the data is examined for individual COX-2s, the estimate is the same; however, the confidence interval for some is very large. The interesting outcome is that, except for naproxen, there is no statistically significant difference when COX-2s are compared to NSAIDs. Naproxen shows a reduction in vascular events compared to the COX-2s. Baigent concluded that all coxibs increase the risk of a vascular event by about 40% and, for the first time, there are studies large enough to show that the drugs that have been used for 30 years, the traditional NSAIDs, have a similar risk.

Dr Bombardier said that this way of testing drugs should be considered a “failure system”. The NSAIDs were just becoming available when she started to practice and at that time randomized trials including 300 patients were sufficient for FDA approval. When the COX-2s first came on the market about 1,000 patients had been treated. Then the number required increased to 3,000. More recently, the large cardiovascular outcome studies that the FDA has required of the industry have 30,000 patients. The question is- where does it stop? What are the implications of this reaction to events that are not rare, but are not the kind of events that can be detected in a randomized trial of a few thousand patients? Dr Bombardier suggested that new and innovative observational studies need to be designed and these studies must be linked to primary data collection. Billing and administrative databases have their uses, but they are missing key data. It will be necessary to start working with the clinical community and the pharmacoepidemiologists to collect the appropriate diagnoses, comorbidities and data on drug use, and then use billing databases to collect rare adverse events passively. This will be possible even for those events that occur after a long time lag, such as cancer or lymphomas.

There is also a case for earlier and better meta-analysis. The Baigent meta-analysis should not have been done five years after the fact. There is a need to invent new study designs: the form they will take will be worked out as researchers explore the possibilities and find out what works and what doesn't work.

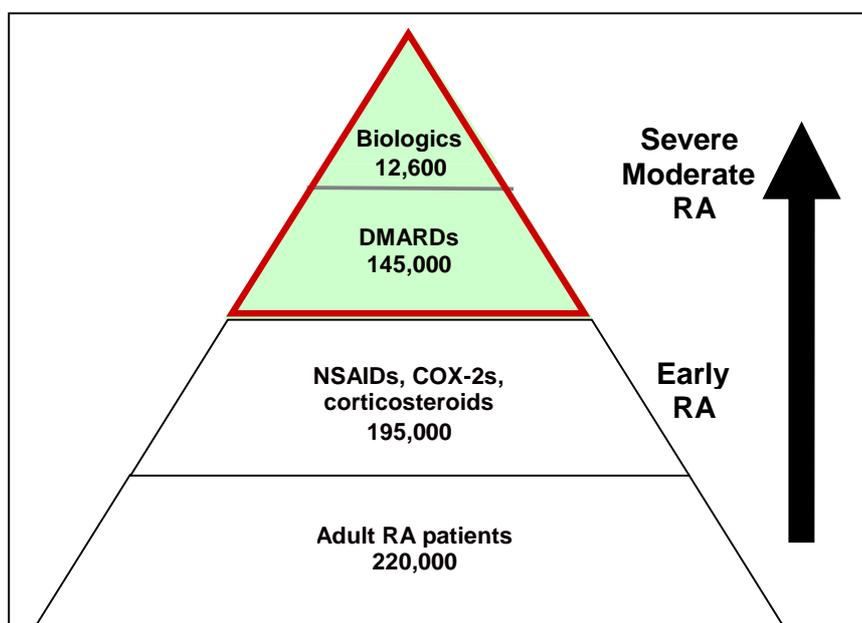
Speaking from her experience as a rheumatologist treating patients, Dr Bombardier said that patients were first told they could not take rofecoxib any longer. Then Bextra was off the list of therapies and, finally, the traditional NSAIDs joined the COX-2s. Now, several years later, new drugs are available and the goal is to avoid repeating the COX-2 failure. Communication of findings and the ability to transfer the knowledge quickly as it evolves will be the challenge.

Box 2
Lessons Learned from the COX-2 'Failure'
<ul style="list-style-type: none"> • earlier and better observational studies (linked to primary clinical data collection) • earlier and better meta-analyses • invent a new type of study

The New Drugs for Inflammatory Conditions

The new drugs are biologics that are administered subcutaneously or by infusion. They are very expensive, costing about \$20,000 per year per patient. They are effective in such conditions as rheumatoid arthritis. This very debilitating disease features swelling of the joints leading to deformities throughout the body that markedly limit activities of daily life. Figure 2 shows a pyramid illustrating numbers of rheumatoid arthritis patients in Canada by disease severity, about 200,000 in total.

All but 2-3% of these patients are treated with standard NSAIDs and COX-2s. These anti-inflammatory drugs are prescribed regardless of cardiovascular risk because there are no alternatives and patients must have some treatment. Since the 1930s, the traditional disease modifying drugs have been used for patients with the next level of disease severity, about 145,000 patients in Canada. They are quite toxic. The most severely affected patients are now receiving the new biologics; the numbers are increasing and have now reached about 12,000. There was a period of about 25 years when there was nothing new in the armamentarium for rheumatoid arthritis. Then, in just the last five years, a whole host of new medications has appeared. All are biologics – leflunomide, etanercept, infliximab, anakinra, adalimumab, abatacept and rituximab. The last two of these have been approved for use in the US but not in Canada. As well, there are about ten new drugs currently being tested in phase 2 and 3 trials.

FIG. 2 Current Treatment Options and Estimated Number of Patients in Canada

Dr Bombardier noted that the total annual dollars spent on these drugs in Ontario rose from about \$15 million in 2002 to almost \$100 million in 2005. This change should be compared to that for all prescription drugs in Canada, which is increasing at a rate of 11% per year, with a total of \$20.6 billion spent in 2005.

Increased Use of Pragmatic Studies

The new disease modifying drugs are either approved or will soon be approved for use in Canada. That approval is based on efficacy studies of only a few hundred patients, which raises the spectre of reliving the COX-2 experience. The solution may lie in a requirement for pragmatic studies. Dr Bombardier also suggested that physicians could transform their clinical practices into research practices and with the development of electronic medical record systems such a possibility is now feasible.

In the traditional drug development system large numbers of patients are treated with a new drug only after it is approved by regulatory agencies, i.e., in phase 4 studies. Unfortunately, these studies are often not conducted and, if they are, the quality can be unacceptable. None of the regulatory agencies have the legal mandate to demand that such studies be done. Dr Bombardier reviewed the path of drug development from the perspective of the industry. The process takes about 15 years, starting with the synthesis of 5,000 to 10,000 molecules that could possibly have a certain activity. Of these thousands, 10 to 20 proceed to animal testing, and perhaps 5 will be given to healthy humans in phase 1 clinical studies. At phase 3 only 1 or 2 candidates remain. It is quite common to have 2 at this stage: one that appears to be the best candidate and a spare in case something goes wrong with the chosen compound. The 15-year process costs close to a billion dollars. It is not surprising that the industry is reluctant to be solely responsible for what happens when the drug is first used in large populations.

The high development costs put pressure on the industry to mount aggressive marketing campaigns. In the case of the COX-2s this has included extensive direct-to-consumer advertising in the US, which certainly played a role in the very widespread use of these drugs. The problem is that, with the discovery in the last few years of serious adverse events with drugs used by many millions of people, the bar is being set higher and higher. Now a few thousand patients will no longer be enough for drug approval. With 3,000 patients, reliable detection of an adverse event that occurs with an incidence of less than one per thousand is not possible. The number required will be 20,000 patients or more. Dr Bombardier finds this situation alarming because, even if done, such large scale efficacy trials will not necessarily help the practitioner. Patients in these trials are relatively healthy: those who are not adherent, have co-morbidities or adverse events have been excluded so that trial results do not translate to patients seen in the clinic. Real-world trials are what is needed.

Adverse events will surface after drug approval. In the current system 51% of drugs have label changes due to major safety issues that are discovered after marketing and 20% of these eventually require a serious black box warning in the package insert. Four percent are withdrawn, always accompanied by scandal with fingers pointed at the industry - the congressional hearings, lawsuits and strident whistle-blowers are definitely a disincentive to pursue drug innovation. It should be kept in mind that by far, most of the therapeutic advances in the past 30 years have come from industry. It has been suggested that the risk could be managed by making it mandatory that all clinical trials are registered so as to avoid losing any information. This would add marginally to our knowledge as they deal with what has already happened, and not the future. It is the future that is of concern.

Box 3
From Passive to Active Surveillance
<ul style="list-style-type: none"> • large, simple trials in post approval stage <ul style="list-style-type: none"> - insufficient for very rare events - can determine balance between benefit and risk in actual practice • prospective registries • claims or medical record studies • population based case control studies

Another alternative is to institute conditional approval. This is easier said than done because it means legislative change, and laws do not change quickly in most countries. However, in April of this year the EMEA decided to move ahead with conditional approval, and the possibility of instituting conditional approval is under discussion in both Health Canada and the FDA in the US. But it will be necessary to do more than talk about it, because this may be the only way to answer some of the key safety questions. Dr Bombardier said that, in her opinion, the responsibility at this stage should rest with the industry, that conditional approval should be an integral part of the process. After approval it would be time for others to share the responsibility.

We are now moving from a world of passive surveillance with spontaneous reporting – with all the attendant problems – to a world of large, simple trials that may or may not be randomized. They may or may not have sufficient power to detect rare adverse events, but they certainly will be able to shed light on the balance between benefit and risk in real practice. The pharmacoepidemiologic studies will still be necessary, including those using claims or medical records data as well as population-based case control studies, to detect rare events.

There are three important investigator-initiated trials in rheumatoid arthritis that have been done or are underway in Europe right now: TICORA in the UK, the BeSt study in the Netherlands and the Swefot study in Sweden. There are no investigator-initiated trials in North America in this field. The reason for this may be that the European agencies are funding these trials and that the European health care systems have the infrastructure to support such trials. In the UK, TICORA is being supervised by nurses in rheumatic disease units who are paid by the National Health Service. Without such infrastructure it would be difficult for clinicians to do such trials in our system. As Dr Collet has pointed out, there is a need to create the infrastructure.

The TICORA study is an example of what is possible. This was a naturalistic study comparing the effect of careful monitoring of RA patients to usual care. Drug therapy did not include the newer biologics. The result was an important, clinically significant improvement in the better monitoring group. To do this in our system would mean transforming medical practices into research practices and providing funds to the clinician specifically for the purpose. Another key requirement will be obtaining acceptance of colleagues who will have to be convinced that they have to play a role. It will take time to change the silo mentality – of colleagues, of industry, of formulary administrators and of regulators, Dr Bombardier predicted.

Patient Empowerment

In Ontario, the rheumatologists are working with the government, the formulary administrators and all the other major stakeholders in rheumatology, including the Canadian Arthritis Network, the Canadian Rheumatology Association, the Arthritis Society and the Canadian Alliance of Patients with Arthritis, to bring them on board with the concept of the pragmatic study. Patients have developed powerful organizations and can play an important role since many of the study outcomes are patient-based, such as pain, ability to function and ability to work. Dr Bombardier described a study that she and her colleagues are planning to conduct using a clinical cohort of patients who have started treatment with biologics. They will be recruited in the physician's office and will have a major role in data collection. With patient permission, this information will be linked with the ICES databases, including vital statistics, hospital discharges, physician billing, mortality and cancer registry data, to detect rare adverse events passively and at a low cost. Privacy and ethical issues have yet to be worked out and these may be the major stumbling block.

However, the investigators are very optimistic that this study will be done. One reason for optimism is that the patients want to do it. Also, the clinical care system is changing and electronic data entry, essential for this kind of study, is more and more common. Electronic data entry software developed for patients with chronic disease is available in some clinics. It allows the patient to report on his or her condition – physical functioning, painful joints, global score, etc – and the printout of the report is useful to both clinicians and patients. The report can also be done at home, allowing patients to inform their family physicians and physiotherapists and to follow changes over time. The point is, if pragmatic trials are to be done, data should not disappear into the researcher's database where it may never help clinicians and patients. It is important to be innovative, and give something back to the clinicians and patients.

Earlier and better observational studies should be part of any drug approval. It should be mandated rather than conducted in a rush after a signal is detected. There should be earlier and better meta-analyses of cumulative trials. Finally, the community of researchers, need to invent new types of studies that are adaptable to clinical practice.

Acknowledgement

Dr Bombardier holds a Canada Research Chair.

Further Reading

1. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomized trials. *BMJ* 2006;332:1302-8.
2. Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 2004;364:263-9.
3. CONSORT statement. <http://www.consort-statement.org> (accessed October 23, 2006)
4. Biologics, radiopharmaceuticals and genetic therapies. Health Canada. http://www.hc-sc.gc.ca/dhp-mps/brgtherap/index_e.html (accessed October 23, 2006)

Pragmatic Studies: View from a Clinician / Formulary Committee in Ontario

Paul Oh
Cardiac Rehabilitation, Toronto Rehab
Division of Clinical Pharmacology, University of Toronto

Introduction

Dr Oh, as a former formulary committee member as well as a physician, is well placed to address the consumer as well as the clinician point of view on pragmatic trials. Consumers are the recipients of therapies that are approved by formulary committees based on evidence generated by pragmatic and other trials. In this presentation he talked about, in particular, some lessons learned from his experience on the Ontario Drug Quality and Therapeutics Committee (DQTC).

Pragmatic Studies from a Formulary Perspective

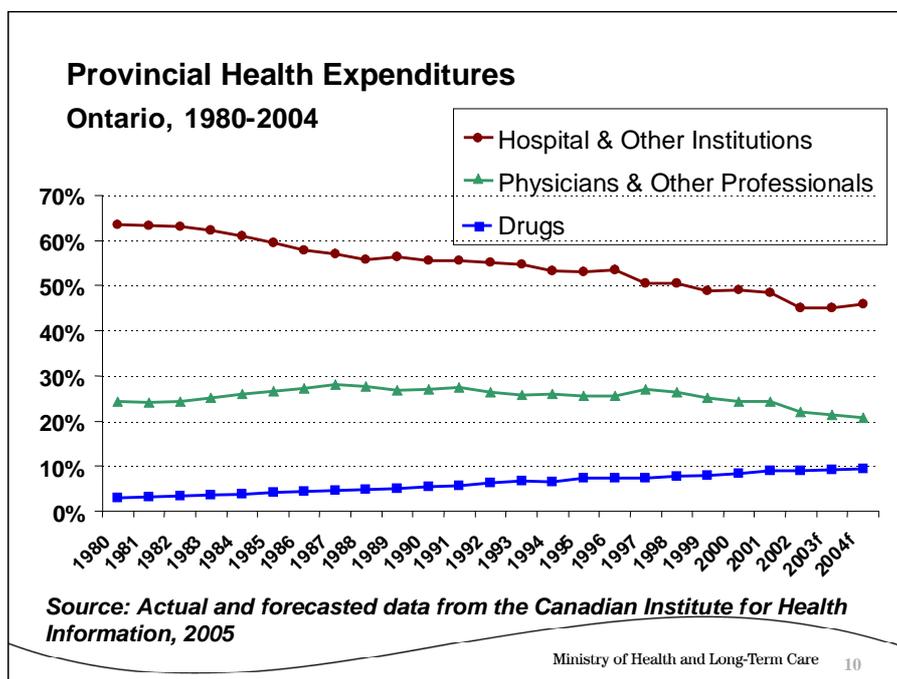
He first described the context for drug decision-making in Ontario, since it is important to understand the framework into which pragmatic studies would be introduced and why the requirement for such studies is being contemplated. There are issues that come up during the drug review process that suggest the need to change research requirements so as to focus more on economic, in addition to, clinical considerations. The question is, where do pragmatic studies fit, and, addressing the topic of the symposium, are pragmatic studies in fact pragmatic?

Dr Oh drew attention to a dictionary definition of pragmatic: “relating to matters of fact of practical affairs often to the exclusion of intellectual or artistic matters” and remarked that the pragmatic studies debate might not entirely fit this definition because the emphasis on science can be considered an intellectual pursuit.

Context for Drug Decision-making in Ontario

The escalation in drug expenditures, at the same time that spending on all other aspects of health care is declining, is obviously an issue. As Dr Collet suggested, it is not clear that the extra dollars have purchased better health. The challenge here is to produce a health report card showing that, in fact, health has improved as a result of increased expenditure. If newspapers are to be considered a source of valid information, the national health priorities are waiting times and overcrowding of emergency departments. Dr Oh suggested that these problems should not be surprising in view of the cutback in resources spent on hospitals.

Nor should the increased cost of drugs be unexpected, since the population is aging and uses more drugs. Drug spending in Ontario now stands at about \$3.5 billion per year and it will continue to increase. In his opinion there needs to be some basic planning. A recently released CIHI report shows that, except for the US, drug spending increases in Canada are similar to the three other OECD countries that have the highest GDP. Spending in the US is significantly greater.

FIG. 1 Cost of Health Services in Ontario

Dr Oh then talked about pricing trends, using examples from cancer care. Year over year cost per treated case has been steadily increasing. There are a number of reasons for this, including more drug use. There is also the possibility that the disease has become more difficult and that different kinds of therapies have become available. But there is another phenomenon taking place. Over the last 5 – 10 years the cost of drugs has increased in parallel with the approval of major breakthrough cancer therapies. In fact, the rate of increase in expenditures has been exponential. This is a difficult environment for drug evaluation, although, in spite of what many think, cost concerns are not the mandate of DQTC.

The DQTC does not have budget per se. The mandate is to make “necessary and reasonable” drugs and therapies available to patients, and this is the framework into which new products are introduced. Recommendations for all products are based on the evidence, including high impact products and those for which there are already a number of alternatives available for management of a particular condition.

The Ontario Drug Quality and Therapeutics Committee

The makeup of the DQTC is the same as for other formulary committees in Ontario. There are 12 members, including a chair, who have a range of expertise from pharmacy, pharmacology and epidemiology to health economics and pharmacokinetics. Most are clinicians who look after patients, write prescriptions, and struggle with prior authorization and individual clinical reviews in the same way as all physicians. The DQTC process is well coordinated with the Canadian Expert Drug Advisory Committee (CEDAC).

Dr Oh explained that, with the implementation of Bill 102, the DQTC may be renamed the Committee to Evaluate Drugs, or it could also be done away with altogether. However, there will still be some form of committee to evaluate drugs. One difference will be the inclusion of patients as committee members. As Dr Bombardier mentioned, the legislative process required to bring about this change was difficult.

Box 1
DQTC Recommendations
<ul style="list-style-type: none"> • include in formulary <ul style="list-style-type: none"> - general listing - limited use - facilitated access listing • exclude from formulary <ul style="list-style-type: none"> - expedited section 8 process - section 8 with individual clinical review - no reimbursement

The DQTC can recommend that a therapy be listed generally or for limited use, which means that certain specific criteria must be met. As well, some products are given facilitated access status. Within the excluded category is the section 8 process, which has evolved into another way of listing a product, but with more stringent requirements for prior authorization. The last category is no reimbursement and, not surprisingly, this is the recommendation most distressing to the manufacturer. It is made when a therapy does not appear to offer an advance, either clinically, or from a safety or economic point of view.

Issues Encountered in Assessing Clinical Data

A review of the problems encountered with information the DQTC receives as part of submissions is necessary to understand the place of pragmatic studies. Often studies with relevant active comparators are missing. This means that decisions must be based on indirect comparisons, e.g., “A is better than B, B is better than C, therefore A is better than C”. Other problems are lack of information relevant to the population that will receive the drug, e.g., severe cases are studied when the drug will be used for mild cases, or the data is pertinent to relatively young patients when the elderly will receive the drug in practice. Exclusion of patients with co-morbidities is another common data deficiency.

Fundamental information such as therapeutic dose is often not well defined. There is usually very limited long-term information and rarely are there publications in the literature about a new drug at time of launch. A troublesome deficiency is failure to report all available information. Also, as Dr Bombardier pointed out, there is limited information about adverse events. Oddly, there is sometimes a lack of evidence that supports the outcome claims, or it may be that a measurement scale used was developed particularly for the drug in question and never validated. End points may not be clinically relevant: there may be a specific clinical disease definition, but it does not translate into what the practitioner is facing when prescribing. Other deficiencies are vague clinical definitions and inclusion of information relevant to off-label use. The litany of problems is no different today than 10 years ago, and the same problems are seen again and again.

There is the question of ‘value’, the economic argument about the worth of a new drug. Dr Oh showed the 2 x 2 table from the 1992 publication by Laupacis and colleagues (CMAJ 1992;146:473-80), in which drugs that are clearly more effective and less costly are more likely to be accepted than those that are less effective and more costly. Many new products are in the “more effective, more costly” quadrant, but the cost per QALY is about \$100,000, albeit with a wide confidence interval. For such products the evidence for adoption and appropriate utilization is considered to be weak.

In his presentation, Dr Collet presented some definitions for explanatory and pragmatic trials. Explanatory trials are supposed to answer the questions “Can the new treatment work?” and “Is it superior to control?” There are dozens of

Box 2
Issues in Assessing Clinical Data
<ul style="list-style-type: none"> • absence of studies with comparators • target population not studied • likely dose unclear • absence of published studies • limited long term studies • submitted studies not all inclusive • adverse effect information lacking • evidence supporting outcomes lacking • endpoints not clinically relevant • clinical definitions not clear • information relevant to off-label use

ways in which data from explanatory studies, that are intended to answer these questions, can be inadequate. Yet, now the suggestion is to require pragmatic trials, studies that will be larger and longer-term with the intention to find the best way of using the drug and at the same time optimizing the use of health resources. Pragmatic studies will be an ideal way to inform decisions if indeed these issues are addressed. The methodology will yield excellent information; however, by the time the results are available, it could be that acceptable safety has not been demonstrated, or else the market is no longer interested in the product. There is no doubt that better information is needed and that there are rigorous methods available to produce this information. The question is whether the information should be available before or after putting a drug on the market. As Dr Bombardier pointed out, label changes are required for 51% of drugs after marketing, 20% of these will lead to a black box warning, and 3-4% will be withdrawn from the market. This is the expected outcome using the current review processes.

Health Canada has just announced that it will be moving to a progressive licensing system. Also very recently in Ontario, there is new legislation that may mean an opportunity for more pragmatic studies – Bill 102. The *Transparent Drug System for Patients Act* is expected to pass final reading in June 2006. High on the list of objectives is the government's plan "to improve access to new drugs by enabling listing drugs under certain conditions while awaiting further evidence." This can be translated to mean conditional approval, i.e., allowing a new drug on the market in advance of any final Health Canada decision. The ultimate goal is to allow faster decisions. There is also a statement about increasing transparency by giving patients a role in drug listing decisions, as Dr Oh mentioned previously.

This may be an opportunity for pragmatic studies. But, Dr Oh cautioned, if there were many problems with the old paradigm of registration trials, is it certain that the situation will be any different with pragmatic trials. There is no reason to assume that it will be easy to decide which drugs should be released on conditional approval. He quoted from Laupacis, Anderson and O'Brien, suggesting that no one would dispute this statement: "To the extent possible, drug policy should be based upon good quality evidence. This must extend beyond the traditional focus on efficacy and safety in carefully selected patients to evidence about real-world effectiveness, cost-effectiveness and safety of drugs." (Healthcare Papers 2002;3:12-30) This has been stated in different ways by others, for example by Tunis and colleagues at the Agency for Healthcare Research and Quality: Practical Clinical Trials? (JAMA 2003;290:1624-32): "The production of high quality clinical trials will increase significantly when health care decision makers decide to consistently base their decisions on high-quality evidence."

Dr Oh said that this is all very well, as long as decision makers will say 'no' if the evidence is of low quality. To simply allow the use of a drug under conditional approval may not be a disincentive to continue with the current framework of inadequate studies. If, on the other hand, high quality is demanded, sponsors of research will be motivated to provide the type of clinical research required. Payers and purchasers will have to clearly indicate what kinds of information they want so that manufacturers will be motivated to perform, for example, head-to-head comparative studies.

Are Pragmatic Studies Pragmatic?

Dr Oh went on to discuss the question of whether pragmatic studies are pragmatic for formulary decision-making. To begin with, it may be a good idea to develop the infrastructure that will allow the study of whether conducting such studies helps or harms in the real world. Towards this end, the National Pharmaceutical Strategy may be moving in the direction of working out such an infrastructure. The more difficult question is whether pragmatic studies will compensate for poor explanatory studies. There is no doubt that the studies now available are problematic, but there is the danger that creation of a whole different phase 4 system, to get the information not in phase 3, will not solve the problems. A better solution may be to have superior explanatory studies.

Box 3	
Is a Pragmatic Study Pragmatic for Making Formulary Decisions?	
• Should an infrastructure be developed to study whether products help or harm in the real world?	√
• Should pragmatic studies compensate for deficiencies in explanatory trials?	?
• Or...can explanatory studies be improved?	!

Such a change in the drug review process would mean embracing the principles of pragmatic studies: more varied populations, fewer exclusion criteria, examination of relevant end-points and comparison to another drug instead of placebo. These requirements are not unique to pragmatic studies – they describe good studies of any kind. Dr Oh stressed the point that, to make a pragmatic study practical it is necessary to have the information today, and not later. Otherwise the framework for decision-making is not different from the old system, where guesswork is necessary and some bad outcomes are to be expected.

Dr Oh summarized by saying that a lot of money is spent on a lot of people in the very important area of therapeutics. Major health gains are possible, but so is major harm if the right decisions are not made. There are clinical and economic challenges with the new drug review process and pragmatic studies might help in terms of the methodology, but there also needs to be some fundamental change in the kinds of studies that come to the table in the first place.

Further Reading

1. The Ontario Ministry of Health and Long Term Care. The Transparent Drug System for Patients Act, 2006. http://www.health.gov.on.ca/english/public/legislation/drugs/hu_drugsact.html (accessed 31 October 2006).
2. Laupacis A, Anderson G, O'Brien B. Drug policy: making drugs available without bankrupting the healthcare system. *Healthcare Papers* 2002; 3:12-30.
3. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: Increasing the value of clinical research for decision making in clinical and health policy. *JAMA* 2003;290:1624-32.