Report Back From CADTH Symposium April 14-16, 2019

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The theme of this year's Symposium was " Supporting Health System Transformation ". It was a well organized and comprehensive view of the landscape and certainly contained up to date information about how the present health systems are changing. Transformation is a bit over reaching in terms of where we are headed and there are some real danger signs for patients with life threatening and serious medical conditions in what I heard.

Disclaimer : This is not a scientific or a comprehensive Report Back as the reporters did not attend all sessions. It is also entirely my personal perspective and does not necessarily represent the views of any organization with which I am associated.

Plenary Session Day 1 : Disruptive Innovation: the Hope and Hype of Transformation

This session did not live up to the promise in the title regarding disruptive innovation. As for the reference to "hype" I trust that was just intended to peak people's interest in attending as there should really be no hype in research and science related to health care . I heard little about real disruptive innovation. In fact, the discussion was fairly tactical. One comment I noted was that equation of value based health care and value based pricing. In principle this sounds fine, however, much depends on how one is **defining value based health care. Value to whom and from whose perspective?** The Porter/ Teisberg definition in "Redefining Health Care " is that of **patient values based on patient reported outcomes.** This is not the definition being used by these stakeholders. Patients need to be very cautious about buying into the "value" [proposition without a clear definition of the term (much like the issue in the present national pharmacare debate).

Recommendation 1 : Reimbursers should be relying on a definition of value that is patient defined in terms of outcomes. See Redefining Health Care by Porter/ Teisberg for a model.

Concurrent Session A5- Toward a pan-Canadian Understanding of the Economic Impacts of Cancer care on Patients, their families and Society: Implications for Decision-Making

This session was interesting but had no patient representative on the panel so the discussion was sterile and clinical. The point that emerged for me was the growing reliance on the "uncertainties" in trials rather than the relative benefits and harms as an explanation for making a negative reimbursement decision. As one panellist put it : We don't have all the data

we need and what we have isn't harmonized. That may well be but the person needing the treatment should not bear the brunt of these inadequacies in the system.

There have always been uncertainties in clinical trials, i.e., questions that the trial cannot answer. Novel treatments mean greater the uncertainties since there are not comparable treatments already approved against which to compare the treatment. Trials may not tell us efficacy and safety in certain underrepresented or unrepresented populations in the trial. It certainly cannot tell us how it will perform after the trial nor for people in the real world with issues of comorbidities, compliance, mental health issues and social determinants of health barriers to name some.

For people with other alternatives in treatment and /or whose condition is not life threatening or does not greater reduce quality of life it is perhaps understandable that a reimburser seeks more certainty to agree to reimburse a treatment.

For people with life threatening and serious conditions, particularly where no other effective and safe treatment exists, the balance of benefits or harms is quite different. The benefit is staying alive or having a greatly improved quality of life. The harm is that the drug does not work for you, leaving you in the same position you were and perhaps having had to endure adverse events or side effects as a result of the treatment. As a person who had a life threatening illness for which there was no treatment for many years, I can tell you that the people in the HIV community including myself were more than willing to take the drugs even though we knew there were adverse effects and side effects. We also knew there were many uncertainties including whether the drug would work in the long term, whether side effects would worsen over time, whether it would work on women (very few were in these trials), whether it would work in HepC co-infected people. Notwithstanding these uncertainties, when the one certainty is that without these drugs you will die, you take the drugs. Fortunately, we convinced the federal government to implement Notice of Compliance with Conditions (NOC/C)

(usually the condition being the collection of more data). People could then access these treatments.

This is the case with many cancers as well. I appreciate that these drugs come with a high price tag. This must be managed. Surely, the way to do so is not to refuse to accept Phase II trial data or to say that there is too much uncertainty in the trial data (unless there really is in which case Health Canada should have dealt with this during its review stage).

Recommendation 2: For needed cancer drugs, pCPA should negotiate pay for performance, managed entry and risk sharing agreements including a requirement for companies to collect, share and analyze real world evidence of those on trial and those taking the treatment

subsequently. Treatments are made available without unnecessary delays and the risks posed by uncertainties are shared or entirely borne by the manufacturer as appropriate, keeping in mind that some things cannot be foreseen in the course of a trial, however rigorously developed and implemented.

Recommendation 3: Phase II trial data should be reviewed since Health Canada accepts these data. Funding contracts with manufacturers can reflect the greater level of potential harms and uncertainties.

Concurrent Session B3- Pharmaceutical Policy

This panel covered a few topics. First was a discussion of conditional approvals (See NOC/C above) to reimbursement decisions (health technology assessment/HTA recommendations to the federal /provincial and territorial governments). As noted above, there is a misalignment between these two policy decision makers. The purpose of the implementation of NOC/C was to expedite access to treatments for life threatening and serious illness. The trade off was the requirement for more data gathering by the manufacturer.

The lack of acceptance of these conditional review decisions by reimbursers defeats the purpose of NOC/C. They can surely develop agreements with manufacturers that ensure that the manufacturers bear the appropriate amount of risk for these treatments.

We moved from there to a discussion of biosimilars (similar to biologics). In oncology there are a number of biosimilar products coming to market. They have the potential to save money on the drug budget so they are obviously attractive to reimbursers, public and private. Health Canada reviews them as new biologics and explicitly states that they are not interchangeable with the originator biologic.

The issue of biologics is generally complicated. Unlike generic drugs that use the same active ingredient as the brand name drug, biologics are apparently actually different batch to batch so even the same biologic is not the same with new prescriptions. This is not well understood by clinicians or patients.

It is also complicated because we have little collated and analyzed data about real world experience with biosimilars although some have been on the market in Europe for many years and there have been no reports of serious collective adverse events.

The issue of switching from one to another either during a course of treatment or as a new treatment after an originator biologic was used earlier in treatment adds further complexity to the situation.

The Patented Medicine Prices Review Board (PMPRB), the federal agency that determines if a price chosen by a manufacturer as the entry level price for sale in Canada is excessive, presented. PMPRB made a strong pitch for the savings that would be gained by implementing biosimilars. (See more below under Panel D-1)

The third presentation was about values in pharmacare. The presenter certainly pointed out the most stark options for national pharmacare i.e. a federal first payer plan versus a "fill the gaps" in provincial coverage plan. It was disconcerting that repeated several times that there was consensus that we need something different than we have. I have yet to read of any consensus except perhaps amongst academics (and even then) on this point.

Concurrent session C2- Chasing Leprachauns : The Curious Future of Cancer Drug Reimbursement, Clinical Trials, HTA and Real World Evidence

This panel continued with the theme of uncertainties in trials leaving reimbursers unwilling to pay for trials, the need for real world evidence to resolve some of these uncertainties and the need for trial design that will better pinpoint those populations that will benefit from the treatment e.g. those having a particular genetic mutation.

While I agree with all of these points, the result cannot be that people in need of treatments for life threatening and serious illnesses do not get these treatments while we wait years for a robust integrated real world evidence data collection and analysis system. The system must develop tactics to deal with the need for novel precision and personalized medicine options in a timely and effective manner.

I also take strong exception to the argument that, in deciding to pay for an innovative treatment that is safe and effective for people living with a lifethreatening or seriously debilitating illness, we need to take into account the impact of lost opportunity costs *i.e.* if we pay for one treatment we do not have money for another. Once again, the system is forcing people who need treatments to bear the brunt of government decisions about drug budgets. This is not to say that everyone should get everything they want all the time but the concept that populations needing treatments for life threatening and serious illnesses should be vying with each other is simply unethical. Among other things this leads to some people ending up in emergency rooms in a hospital when this could easily have been avoided had they had access to needed medications.

Another way a panellist phrased it was "you should care about people you don't know as much as people you do know " in terms of balancing who should get drug coverage.The fact that a health economist thinks he needs to remind us of this shows a lack of any real ongoing interaction with patient groups and what they do, at best.

Recommendation 4: Health budgets should not be siloed but should reflect the actual usage in populations in each area of the budget, with the money on the budget following the patient rather than patients endeavouring to find one silo in the budget which will treatment them, even if not optimally.

Concurrent Session D1- Enhancing Access to the oncology biosimilars in Canada – Challenges and Opportunities

Returning to the knotty topic of biosimilars, and focussing on oncology, this session described the work and consultations undertaken by Cancer Care Ontario (CCO), the Ontario public cancer agency and the pan-Canadian Pharmaceutical Alliance (pCPA) that negotiates drug prices for federal/provincial and territorial public drug reimbursement plans. After a broad stakeholder consultation these groups have come up with an action plan of tactics required to enhance access to biosimilars in the oncology area. It is a five point plan which focuses on (1) acting now, given the tidal wave of oncology biosimilars on the horizon (2) moving together, given the many stakeholders and health systems that are impacted and impacting this topic (3) recognizing that there are multiple pan-Canadian markets (welcome to our Federation) (4) education, of both patients and clinicians and (5) saving money in the drug budget that is redirected back into the oncology budget to permit more access to innovative treatments.

It is commendable that these organizations are working on this urgent issue and that they have invited patients and patient groups as well as other relevant stakeholders to develop the tactics. It is particularly heartening to know that there is an understanding that the savings achieved should go back to the oncology treatment budget.

Education is a huge component of patient decision making. Patients rely on their clinicians for advice as well as research they do themselves from other available sources. This education must be done urgently and must be undertaken by trusted parties that are considered objective and knowledgeable. The Health Canada representative on the panel stated that this was not a role for Health Canada. On the contrary education is a key component of Health Canada's mandate.

Recommendation 5: Health Canada, in partnership with CADTH and pCPA and patient groups in oncology should develop and deliver an education programme directed at clinicians and patients about the science and policy of biologics and biosimilars to inform decision making.

These tactics are well supported by patient group surveys of their members. One such survey was conducted by the Canadian Breast Cancer Network. This group was represented on the panel and reported back on recommendations for improvement in breast cancer care and treatment based on members' lived experience. The five key recommendations are (1) improved educational resources (2) increased access to treatments (3) increased access to

information (4) integrated systemic support (5) increased understanding and awareness of metastatic breast cancer.

Concurrent Session E7- Oncology

This session repeated the information on breast cancer and biosimilars reported above.

There was also a study of the impact of timeliness of diagnosis on outcomes that found that provinces that had systemic programmes focussing on early diagnosis did lead to enhance patient experience but did not positively impact outcomes. The reason for this is that these systems do not actually speed up diagnosis by more than a few weeks at best.

Recommendation 6: Since it is well understood that early diagnosis greatly enhances the potential for a positive outcome, there should be a pan-Canadian approach to dealing with the systemic issues creating barriers to early diagnosis, potentially facilitated by The Canadian Partnership Against Cancer as part of its refreshed federal Cancer Control Strategy.

Cancer Care Ontario rounded out the panel by doing a study of impact of cancer “rarity “on CADTH reviews from 2012 to 2017. The results did not point to a strong correlation between rarity defined either as < 5/10,000 or < 1 / 100, 000. The main concern I have with this study is that in fact there are other ways to define rarity, *e.g.,* genetic biomarker correlation, mechanisms of action, that may be more relevant and produce a different conclusion.

Recommendation 7: CORD has been leading the work to develop a Rare Disease Framework for some time. Other groups including Cystic Fibrosis have also been grappling with the issue of rare disease management and definition. It is important that any definition of rare disease adopted in Canada recognize and include oncology as part of the definition. There are many cancers, and stages of cancer, and genetically related cancers that may well be classified within the definition of what is a rare disease.

Concurrent Session F1- Building the RWE Blueprint : A coordinated Approach to RWE Use in Pharmaceutical Policy and Reimbursement Decisions in Canada

Health Canada has always monitored the impact of the drugs in the real world in a limited way through its Branch dealing with post-approval activities. The problem has been until recently that only manufacturers were required to report post trial and then only serious adverse events. The amount of information gathered in that way was very limited; not collated and disseminated in a timely fashion. It was rare that people were able to interpret them in order to make decisions and recommendations. With the passage of **Vanessa’s Law,** Health Canada had stronger powers to remove products based on RWE and a broader reach of stakeholders required to report.

Patients and patient groups have relied on anecdotal or RWE all along through peer group meetings, newsletter information and other means of communication.

Definition : It must be remembered that RWE includes following people who were in trials post-trial as well as people who are taking the treatment for the first time after the trial, either on or off label.

Other government agencies did not fully understand the importance of, or rely on, RWE until recently in its analytical work and decision making.

CADTH's patient group and clinician submissions are limited recognition of the value of RWE as is the introduction of patient (pERC) /public (CDR) members on its review committees.

Provincial payers have primarily taken into account RWE in individual cases, often by public shaming in media or direct pleas from family, patients and patient groups.

In the session Health Canada, CADTH and its Quebec counterpart INESSS as well as the Canadian Centre for applied Research in Cancer Control (ARCC) presented their activities in RWE.

Health Canada announced its partnership with CADTH and INESSS to accept from manufacturers "high quality RWE" both pre and post market to inform decision making, with particular emphasis on (populations often excluded from clinical trials *e.g.,* children, seniors and pregnant women, drugs and diseases where clinical trials are unfeasible *e.g.,* rare diseases and situations where clinical trials are unethical. The link to this notice is : https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/optimizing-real-world-evidence-regulatory-decisions.html

This is laudable as a first step. There are some notable gaps.

1. People excluded from trials are much broader than the example list suggested. Many people disadvantaged by lack of access to social determinants of health do not get the opportunity to enter trials, not due to explicit exclusion criteria but rather by practical realities of their life circumstances.

Recommendation 8: Health Canada, CADTH and INESSS should create a working group of organizations that represent people adversely impacted by social determinants of health to help them develop a roadmap for reaching these populations not only for RWE but also for clinical trials.

2. While it is excellent to see the recognition of rare diseases in this list there are other situations where trials may not be completed for ethical or other reasons. That was the purpose of the NOC/C policy at Health Canada. Other agencies CADTH and INESSS included have not followed suit to accept Phase II data or other trial designs that do not meet the gold standard of Randomized, Double Blinded Controlled trials (RDCCT). With the number of innovative treatments coming in cancer and other disease areas that will be reaching smaller populations and are otherwise not going to fit this RDCCT model, these agencies must find a way to move the conditional approval passed Health Canada's jurisdiction for sale approval to conditional reimbursement with conditions. Patients cannot wait years for RWE when they need the treatments now. RWE will help the next generation of patients but is not a substitute for helping this generation. Arguing that trial evidence is too "uncertain" is rarely a good explanation to deny drugs to people with life threatening or serious quality of life destroying conditions.

Recommendation 9: Health Canada, CADTH, INESSS and pCPA must urgently collaborate to develop a conditional reimbursement process for successful PHASE II trials and other trials that clearly meet immediate safety and efficacy criteria for some or all populations in the trial, even if the trial design is not RDBCT. To refuse people with life threatening and serious conditions drugs that have shown safety and efficacy is unethical.

The ARCC representative on the panel reported that a group has set up called CAT of which it is a member that formed out of a Health Canada, CADTH, Institute for Health Economics and Canadian Association for Population Therapeutics workshop looking at RWE in the context of pharmaceutical regulatory and reimbursement decision making and looking at RWE. Unfortunately I did not see in the list of contributors patients or patients group representatives.Thus, it appears that we were not included in the design of the program. ARCC did say that working groups will include patients.

Recommendation 10: An ethical and practical first principle of any group working on RWE is adequate, meaningful and appropriate patient representative at decision-making tables.

Closing Plenary

The closing plenary had a panel of stakeholder representatives that answered five questions of importance to CADTH. Patients were excellently represented by Maureen Smith who sits on many government advisory boards, is a member of CORD and is a person living with a rare disease. The audience was then invited to vote on the questions.

Question 1 dealt with whether drugs should be made available before we have complete evidence we need to know about the drug. This question is odd to me since we will never likely really know everything we need to know and who is "we" in any case. As one may predict the health economist and payers on the panel had a different view than the patient representative. Industry recognized that for earlier access it must be willing to bear a larger burden of the increased risk associated with earlier access. 55 % of the audience voted to make drugs accessible before "complete" evidence is available.

Recommendation 11: See my recommendations 1,2,3,7, 8 and 9 above.

Question 2 related to transparency at CADTH. It was in two parts, one relating to the fact that industry insists on redacted information in some cases for public information distributed by CADTH and the other about whether CADTH review meetings should be public. The answer to both questions was mixed – industry being concerned about intellectual property protection for some information and patients and other panel members being concerned about a frank and open dialogue if the entire review committee meeting including voting was open.

Question 3 was about the impact of clinicians and patient groups receiving funding from industry on their advice. There was a general recognition that everyone has a potential for conflict of interest but it can be managed. Everyone also has a bias which they may or may not realize themselves.

Recommendation 12: Governments should set up a funding mechanism in some objective manner , potentially public/private that will alleviate this perennial allegation of conflict of interest. All bodies receiving funding from any source should have to declare it to government bodies to whom the submit any forms of intervention since potential conflicts of interest are by no means limited to clinicians and patients.

Question 4 asked people to choose between six competing priorities. The top priority chosen by the audience was health data infrastructure. This makes complete sense since we cannot make any informed decisions or move the yardstick toward value-based health care without data. My concerns, shared by many, include whether we are collecting data from every source, whether we are collecting the data we need to make informed relevant patient outcomes-driven decisions and whether we are sharing and collating the data. Real world evidence came up as high as did tying payment for drugs to "value" (undefined).

Recommendation 13: A multi-stakeholder approach that is coordinated must be developed and implemented to understand the scope of what is being collected and where; to determine what is actually relevant to patients in terms of outcomes and the data needed to analyze this; to determine how to harmonize data sets and to develop a privacy policy for patient data that is

consistent, ethical and patient driven. Linking existing data sets alone is not enough to obtain optimum results.

The last question was about pharmacare. As is generally the case, the question related to whether it should be a single payer first dollar coverage plan or whether it should be a fill-the-gaps plan. I have generally been in favour of a starting point of filling the gaps as I prefer we get some enhanced access than either less access based on a defined list of drugs for coverage or no national pharmacare at all because the provinces won't agree to the federal plan. I am now in a quandary because the health economist on the panel pointed out that a "fill-the-gaps" federal approach will lead to provinces/territories providing little or no coverage for drugs, leaving the lion's share of the cost for drugs to the federal government. While I can certainly understand a fiscal instinct to do this, I can only hope that the potential for political backlash will temper that instinct. It does raise a serious question though that will need addressing if a fill the gaps approach is adopted.

Conclusion

There has definitely been progress made in government collaborations on clinical trial data sharing and analysis and in RWE gathering. CADTH has also expanded its field to include not just assessment but management of drugs along the life cycle including reassessments where appropriate. This definitely has the potential to provide better results for patients.

A balance must be maintained that gives people the often innovative drugs they need **now** while RWE is gathered based on available evidence including access after PHASE II trials where appropriate and /or whenever it is ethical to do so; ensuring that the risks in terms of safety and efficacy are understood and accepted by the patients in conjunction with their clinicians; ensuring that negotiations with manufacturers include risk sharing, pay for performance and managed entry agreements so that they bear an appropriate share of the risk for early entry into the market and a robust coordinated RWE system across all jurisdictions, **that is an adjunct not a replacement for ethical access** at the appropriate point in trial implementation, and that can lead to a reassessment of the treatment at reasonable time frames along its life cycle.

Ultimately we need Value Based Health Care as outlined in Porter/Teisberg's book "Redefining Health Care" that determines patient outcomes based on patient reported outcomes by population, taking into account the impact of social determinants of health on that population or parts thereof ; allocates funding as appropriate from the health budget, removing the siloes between parts of the budget; that includes social prescribing as an integral part of the system *e.g*. prescribing outside the usual drug/ devices areas into activities that will positively impact health and monitor, evaluate and improve the system at regular intervals.