# The EXCITE International (Excellence in Clinical Innovation and Technology Evaluation) Summit: Findings and Discussion

**Drs. Les Levin and Richard Kuntz and**
**Panel Chairs**
**Drs. Sean Tunis, Joseph Ross and Bryan Luce**

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## *Executive Summary:*

EXCITE International (Excellence in Clinical Innovation and Technology Evaluation) convened high-level health care leaders at an inaugural multijurisdictional Summit on June 2-3 at the MaRS Discovery District, Toronto's science, technology and innovation hub. The Summit is the first comprehensive attempt to answer one of health technology's most pressing challenges**: How do we accelerate the development and adoption of promising, disruptive new technologies so they reach the patient faster and more quickly impact the effectiveness and value of health care delivery?**

Across the world, the introduction of new innovative health technologies is a complex process with many potential obstacles. Payers are often concerned with the possible overuse and rapid uptake of low value technologies and developers can be challenged by the long delays of getting a product to market. The journey of a new technology from initial concept to market comprises many steps and involves traditionally siloed stakeholders such as government, regulators, payers and health care systems. Further, new technologies are evaluated mostly when they come to market, so early opportunities for refinement are lost. Most importantly, the opportunity to positively and significantly affect patient outcomes can be stifled or delayed.

EXCITE International (EI) is attracting international interest to a new approach. Bringing together key scientists, practitioners and patient representatives as well as health system leaders, industry, payers and regulators from Canada, the UK, USA, New Zealand and the Netherlands, the Summit examined how new health technologies could be evaluated through multinational studies using a single protocol into which the needs of each stakeholder party are included upfront in the pre-market space. "We know that this approach of early collaboration and buy-in works," said EI founder and Chief Scientific Officer Les Levin. Conceived in 2011 at MaRS Discovery District, Levin and his team have successfully piloted the new model in Ontario. "EXCITE International is an attempt through a recently formed independent non profit corporation to drive global innovation and expedite adoption and early access by patients to disruptive impactful new health technologies. It will achieve this through multiple international partners representing existing strengths, programs and realities in each jurisdiction. These partners attended the Summit and represented regulators, payers, patients, health systems, industry, scientists and expert end users."

In its design, EI's evaluation approach allows for customization to service the needs of a host country's health care, payer and regulatory system. It also allows for efficient adoption of new innovative technologies in the global market. The Summit discussed the needs of the separate parties in bringing a technology to market, explored the uses and attributes of pragmatic versus explanatory trials and discussed leveraging new sources of data and statistical methodologies.

Addressing the needs of multiple stakeholders, maximizing expert knowledge and employing groundbreaking methodologies, EI is poised to speed the emergence of innovative new technologies to market, benefiting patients and adding value and effectiveness to our health care systems.

**Key messages:**

- ✓ The Excite International Summit convened key leaders to answer one of health technology's most pressing challenges: How do we accelerate the development and adoption of promising, innovative new technologies so they reach the patient faster and more quickly impact the effectiveness of health care delivery?
- ✓ EXCITE International (EI) is attracting international interest to a new approach - using a single protocol into which the needs of industry, practitioners, patients, regulators, health care systems and payers are included upfront in the pre-market space.

## *Background:*

Summit attendees convened to answer the following question: How do we accelerate the development and adoption of promising, disruptive new technologies so they reach the patient faster and more quickly impact the effectiveness of health care delivery? Richard Kuntz, EI board chair and Les Levin, EI founder, CEO and CSO began the Summit by describing the current health care environment and introducing the EI model.

Throughout the world, health care as we know it is currently undergoing significant and important shifts. In response to rising health care costs and in an effort to control them, health care business models are in flux. The United States, for example, has seen the emergence of alternative health care payment systems, with approximately 30% of traditional Medicare payments now proceeding through bundled payment models or accountable care organizations.[1] Patients in every jurisdiction are taking an increasingly active role, demanding not only a focus on maintaining high standards of care and access to the latest treatments but more involvement in decisions about their care. Over the last decade the availability and generation of data has grown exponentially, as has our ability to analyze and understand it. What is now commonly referred to as "Big Data" influences models of treatment delivery and drives productivity and efficiency in health care as in other industries. In addition, data science has introduced new large players into the field such as IBM™ and Google™. It has also facilitated relationships between a new generation of technologies, vendors and partners, such as IHS, a material management IT system which is revolutionizing outcomes for cardiac catheterization clinics in Europe.

The changing face of health care presents challenges and opportunities to the introduction and adoption of new innovative medical technologies. While the driving question to innovation continues to be how to overcome the barriers of bringing new technologies to patients at an appropriate speed, shifts in the health care environment are demanding change and insisting that we evolve with them.

For example:

- Methodological changes are enabling unprecedented developments in the quality of research. *Example:* The UK's IDEAL collaboration recommends evidence-based study designs for each of the five stages of surgical innovation (Idea, Development, Exploration, Assessment, Long-term Follow-up), and is driving improvement in the quality of research in surgery.
- Medical technology assessment, traditionally undertaken in the post-market stages of development, is being increasingly conducted throughout the life cycle of a technology innovation, allowing for much greater fluidity and speed in the refinement and improvement of technologies. *Example:* The FDA/CMS and NICE are moving to a total life cycle approach in medical technology assessment.
- With the availability of data there is an increasing focus on data transparency and a far greater appetite to share data. *Example:* In February 2016 leading health scientists around the world pledged to share all data on Zika in an attempt to combat the international public health emergency and speed the development of potential treatments and vaccines.
- Technology is evolving at an increasingly rapid rate, making it no longer feasible to operate in a world where an effective innovation takes 5+ years to reach a patient. *Example:* Apps and wearable devices are creating real-time data which can be shared with physicians and used to tailor a health care plan, as well as uploaded and compiled with other users' data.

The current approach to accommodating these changes globally is outdated, fragmented, unpredictable, costly and carries a high risk to innovators and investors. If allowed to continue, the approach will stifle innovation; what is needed is a collaborative approach to pulling new impactful technologies into the health system to benefit patients rather than pushing technologies in as market merchandise.

The EI collaborative is ideally positioned to change the manner in which innovative new health technologies are introduced and adopted. EI's approach is to establish a collaboration between industry, regulators, payers, patients, health systems and expert end users upstream in the evaluation phase, prior to regulatory approval for pre-selected technologies that are disruptive and impactful on patient outcomes and health system efficiencies. Piloted successfully in Ontario, the model is ready for deployment across national boundaries.

*"EXCITE International is a logical solution to the changing health care environment - its model addresses many of the shifts which are currently occurring [in healthcare] and embraces them."* - Richard Kuntz, Chair of EXCITE International and Snr VP and Chief Scientific, Clinical and Regulatory Officer - Medtronic

[1] Obama B. United States Health Care Reform: Progress to Date and Next Steps. JAMA. Published online July 11, 2016. doi:10.1001/jama.2016.9797.

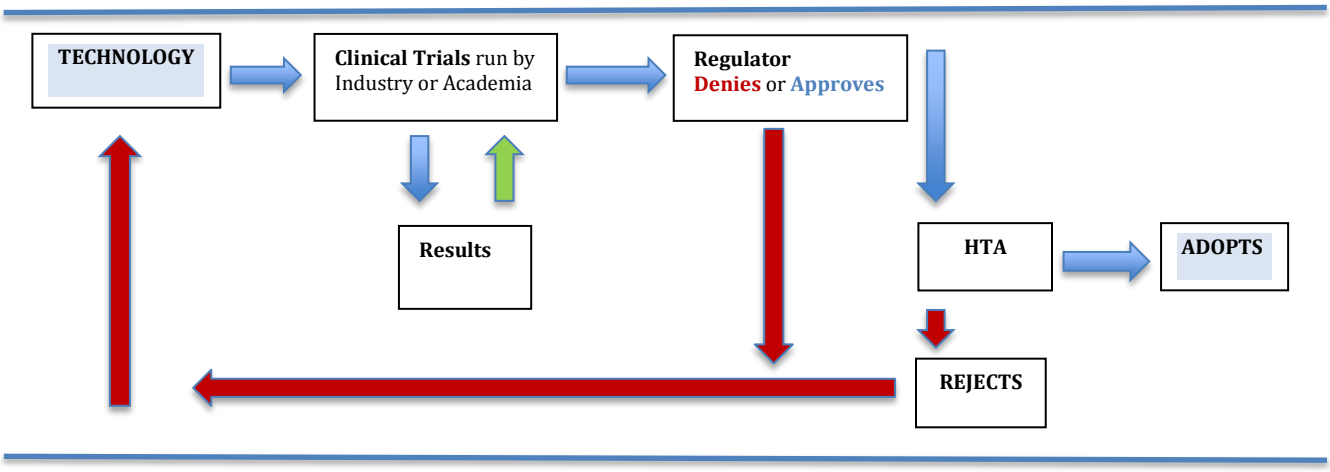
**Key messages:**

- ✓ Health care is currently undergoing significant shifts: business models are changing in response to rising costs; patients are taking an increasingly active role in their care and the development of data science is creating new opportunities and challenges.
- ✓ New innovative technologies are also responding to these shifts: research is benefiting from new methodologies; there is more interest in sharing data and technology is rapidly evolving, making it no longer feasible to operate in a world where an effective innovation takes 5+ years to reach a patient.
- ✓ Assessment of medical technology is shifting to a life cycle approach, allowing for much greater fluidity and speed in the refinement and improvement of technologies.

## *What is the EXCITE International model?*

In bringing their product to market, health technology innovators invest resources into testing their technology. Often, results are enough to obtain licensing and regulatory approval, but not enough to show the value of the technology and convince the health system to invest and adopt it. Currently, approval and adoption rests on evidence-based assessment which mostly occurs once the technology enters the market. This system delays the generation of evidence needed by regulators, payers and health systems; fails to address the needs and expectations of payers, patients and health systems during the initial evaluation phase which is mainly directed at satisfying regulatory requirements (and in so doing, increases the risk of rejection post regulatory approval); and also delays the feedback which is vital for innovators, investors, industry and patients.

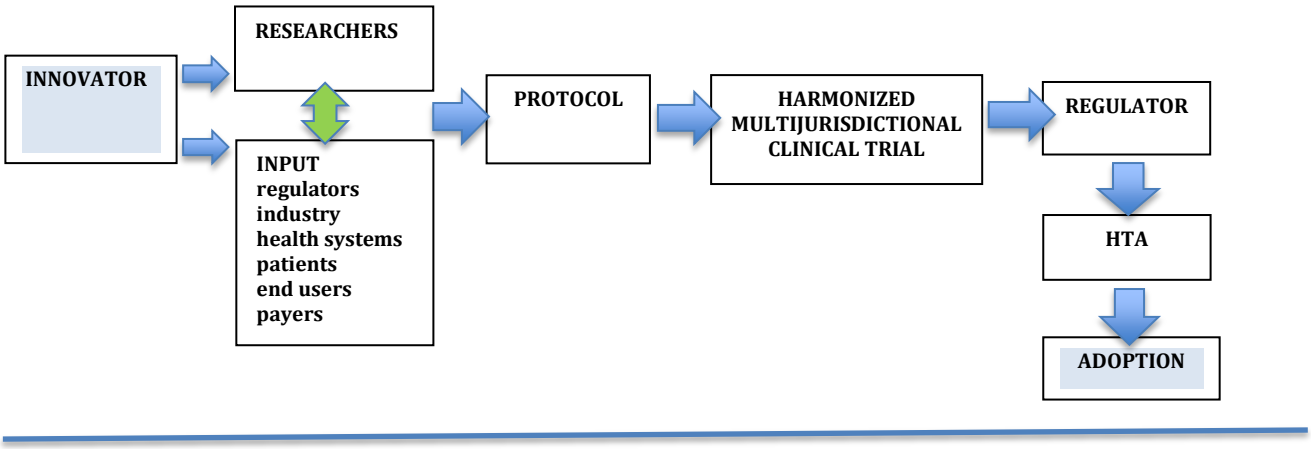
The Current Paradigm




If, after all these stages, the technology is approved by a regulator but subsequently rejected by payers, industry must begin the process anew, expending further capital and time. Industry risks loss of funding and time and patients miss out on effective new treatments. The cycle is burdensome and iterative and results in outcomes focused on regulation and pricing instead of value.

*"Unfortunately, the current paradigm uses evidence to police adoption instead of drive it, which ends up stifling innovation. We all need to think in a new way – innovators and industry are A PART of the health corporation, not APART from it."* - Les Levin

The Excite International Paradigm




EXCITE International shifts medical technology assessment from a postmarket cycle to a harmonized pre-market model, using evidence to drive innovation. Trial results not only satisfy licensing and regulatory requirements but showcase the value of the technology to health systems and payers and more readily lead to successful adoption. Operationalization of EI is currently underway.

*"Narrowing the time lag between regulatory and reimbursement decisions is critical for patient access and innovation. MDMA looks forward to working with EXCITE and other stakeholders to improve patient care and reduce overall costs*." Mark Leahey, President and CEO of the Medical Device Manufacturers Association, US

EXCITE International has built on the MaRS EXCITE evidentiary package which can be used by all its partner jurisdictions for both **regulatory or licensing approval** *and* **reimbursement and purchasing reviews.** Participants leave with experience connecting with the health system and relevant feedback concerning conditions needed for successful adoption of their technology. In similar ways, EI has profiled and incorporated the important work of other efforts established by international leaders, including: the National Institute for Clinical Excellence (NICE); the IDEAL network, which enhances the quality of surgical care, including device placement; the UK National Office of Clinical Research Infrastructure (NOCRI) and Office for Life Sciences (OLS); first in human studies at the Mayo Clinic; MedValue at Radbound University Medical Center, Netherlands (a transparent, methodologically validated process for screening potentially impactful technologies and accessing patient perspectives); human factors analysis at the ECRI Institute; and Healthcare Human Factors, University Health Network, Toronto, amongst many others. EI is also working with important forward-thinking payers such as Blue Cross Blue Shield Association and health systems in the UK, Ontario and the USA, to more strongly emphasize their perspectives in the pre-market evaluation of new technologies, and with industry leaders including AdvaMed and the Medical Device Manufacturers Association in the USA and MEDEC in Canada.

EI's collaborative approach:

- Better meets the needs of regulators, payers and health systems
- Accelerates the availability of potentially new and effective treatments to patients
- More quickly impacts the effectiveness of health care delivery
- Allows patients, end-users and health systems to achieve outcomes which are more responsive to their needs
- Mitigates rejection and repeat studies
- De-risks adoption through workshops, thought leadership, and global capacity building
- Drives innovation

*"It's important to reflect on innovation as a continuous process from invention through to adoption. We are eager to work with our global partners to foster health care innovation around the world."* - Les Levin

A response from the Ministry to the Ontario MaRS EXCITE model:
"We know that the challenge [for innovators] in every jurisdiction is to overcome the barriers to adoption and rapid diffusion of an effective technology into the health system. In Ontario, the goal of the MOHLTC regarding innovation is not only to improve patient outcomes and the performance of health systems, but also to drive job [creation] in the province. Our role is not to support invention, but rather to drive collaboration across key players and work with small, medium and large enterprises to help them scale up in Ontario. We are also focusing on exporting indigenous companies. Partnering with MaRS EXCITE has been a successful experience for us – it's a great model for innovation." - Bill Charnetski, Chief Health Innovation Strategist, MOHLTC.

**Key messages:**

- ✓ Currently, approval and adoption of medical technology rests on an assessment cycle which happens mostly postmarket. This cycle delays the generation of evidence needed by regulators, payers and health systems, and also delays feedback to innovators, investors, industry and patients.
- ✓ If a technology is approved by the regulator but rejected in assessment, the process must begin again. Industry expends more capital and time and risks losing funding – and patients miss out on effective new treatments.
- ✓ EI's approach shifts medical technology assessment from a postmarket cycle to a harmonized pre-market model, using evidence to drive innovation.
- ✓ Operationalization of EI is currently underway.

## *PANEL 1: What Evidence Do Stakeholders Need?*

Sean Tunis, CEO of the Center for Medical Technology Policy and an EI board member, chaired a multijurisdictional panel discussion on the evidence needs of stakeholder parties in the development and uptake of new innovative medical technologies.

The discussion centered on the following three questions: *How does technology evidence fall short? What are the major barriers to evidence generation? What can EI do to help improve evidence generation?* A synopsis of the gaps in evidence generation and EI's possible role are listed below. For a full description of stakeholder responses, please refer to Table 2 in Appendix A.

| SYNOPSIS of PANEL OPINIONS: Where does evidence fall short, what are the barriers, how can IE assist? |
|---|
| ❖ The principal barriers for technology innovators are time, expense and access to quality data. Investors want to see results quickly, most start-ups and small companies have limited capital for research and innovators need access to objective data that is generated by an arms-length research enterprise. A physician/entrepreneur suggested that EI could help by providing greater consensus of the time horizon needed by payers to justify an investment. Also, in providing access to quality, affordable Clinical Trial organizations which are also able to interact with the end user, EI would help to more rapidly get studies off the ground. |
| ❖ The evidence generated is not sufficient due to the fragmentation of the current system; e.g., high quality data is generated for regulatory clearance, but may not be sufficient for adoption. In assembling a functional network of all important stakeholders, EI can develop a standard methodological framework for evaluation which covers the whole life cycle of an innovation. Further, EI can facilitate studies by using adaptive design and other variants on RCTs and by taking Big Data approaches to analysis of registries and real world data sets. |
| ❖ There is a new and emerging digital layer in all health technology – it is developing rapidly and we are not ready. EI can incorporate new technology evaluation methodologies which also have digital wraps. |
| ❖ There is a lack of transparency from most payers regarding the evidence needed for coverage and on what constitutes value. Technology innovators expressed that the transparency of EI's process and multiple stakeholder input could |

assist in clarifying payer economic targets, requirements for coverage and determinants of value (metrics, quality, outcomes). *"It should not be a pay to play system."*

- Payers and health systems report innovators are providing inadequate study designs with: Potential biases, durability issues, lack of follow-up and lack of generalizability. Further, in diseases of chronic pain and neurodegeneration, for example, outcomes measures are not sufficiently robust. EI can provide a validated inventory of outcomes (and find a way to evaluate them against each other) and clarity on statistical differences in outcomes, so that payers and health systems better understand how the technology impacts outcomes.

- There is a lack of centralized repositories of expertise for trial design; in being able to connect with experienced, high-quality researchers and scientists, EI can facilitate such a repository. CTs should be designed to generate strong data regardless of the risk.

- There is a very notable evidence gap in emerging markets (EMs). Regardless of the quality of out-of-country evidence, EM payers and regulators particularly seem to lack confidence in it and are wary of new technologies. Lacking a compensation mechanism for innovative technology, EMs generally have poor to nonexistent adoption infrastructure. Others expressed that EMs often require in-country CTs for the resulting economic benefit. Corporations are, therefore, forced to set up CRO's in those countries for trials & manufacturing. Industry feels that with EI involvement, there is the potential for a "sea change" in this space. They recommended that EI provide a transparent mechanism to bring evidence to EMs and that an EI "multijurisdictional evidence endorsement" may improve the likelihood of adoption.

- *"Regulators focus on market entry. Payers want what patients want, but also have the fiduciary responsibility for resources, which amplifies the issue."* – Naomi Aronson, Exec. Dir. of Clinical Evaluation, Innovation, and Policy, Blue Cross and Blue Shield Association (BCBSA).

- Patient representatives expressed that patient expertise is greatly undervalued and is a major value-add to protocol design. In joining the EI process, patients offer:
  - expertise in the "real life" use of technology
  - a deep experience of the qualitative aspects under study; especially for the adoption stage and in value assessment
  - the capacity to significantly and positively affect patient recruitment & retention in CTs
  - knowledge across a product life cycle in technology adoption, uptake among diverse populations and off label uses
  - education to research teams on the experience of living with a disease

- We fail to consider a technology's value capture across its entire life cycle. In order to make this possible, EI could promote novel risk sharing models in the post adoption arena (e.g., government considers a managed entry/risk sharing payment scheme to facilitate value capture throughout the product life cycle) and establish registries or other mechanisms of large data collection in electronic format to evaluate value over the full life cycle of a technology, including patient care.

- Patients are playing an increasingly greater role in their own care, have increasingly higher expectations of the health care system and are demanding greater involvement in decisions about their care. Patients report, however, that many issues of concern to them are not on the research agenda. All stakeholders alike felt patients must be an equal partner in the EI process. Patients requested:
  - to be consulted early on, in choosing priorities and determining relevance
  - that studies provide "real life" endpoints meaningful to patients which also comprehend patient values ("vs. success/ failure")
  - involvement throughout the life cycle of technology development and adoption
  - that researchers consider safety from a patient perspective; *"there is a difference between safety as a health*

*system concept and harm for an individual patient."* Patients report the term "safety" is being redefined as patients weigh in
- that patients be included in closing the loop at the adverse reporting stage of technology development
- Open Data – to improve transparency and accountability
- further exploration of patient engagement methods
- that EI create a Patient Advisory Board
- that EI promote a culture shift, fostering openness so that patients feel more equipped to participate in research teams and vice versa

❖ *"[EI needs to] be proactive at market entry. Be selective; this is not a consultation for everyone, but rather an initiative to promote game-changing technologies."* – Naomi Aronson, Exec. Dir. of Clinical Evaluation, Innovation, and Policy, Blue Cross and Blue Shield Association (BCBSA)

## *Discussion:*

During the panel discussion, stakeholders also brought forward the following issues for consideration:

1. EI's role throughout the value chain.
   *Will EI have a role in the middle stages of technology development between evidence generation and postmarket evaluation?* Several stakeholders remarked that assistance is also needed in this area; for example, EI could play a greater role in the facilitation of technology adoption.
2. Alignment across jurisdictions.
   *How will collaboration occur among Ministries of Health in the different jurisdictions participating in the EI model (including among provinces and territories within Canada)?*
   It was stated that multijurisdictional collaboration is a priority in Ontario, but that activities are limited by strategy issues and time. Les Levin remarked that every jurisdiction has its own local differences and will continue to develop and adopt health innovation within its own infrastructure. Levin added he envisions that in being a part of an international collaborative with a single protocol, jurisdictions will use their local infrastructures to leverage their strengths.
3. EI's development model in relation to Kaiser Permanente's (KP) research infrastructure and also PCORI.
   Stakeholders responded that the relationship between the EI model, PCORI and Kaiser Permanente's research infrastructure is yet to be determined.
4. The role of industry in technology adoption.
   *Can industry partner with payers to assist in the development of conditions for technology adoption?*
   Jo Carol Hiatt, Chair of the National Product Council at KP, stated that KP has partnered with industry to examine long term impacts, especially as regards value and opportunities for workflow improvement. Hiatt added that the partnership has focused less on pre-market approval. Bill Charnetski, MOHLTC Chief Innovation Strategist, observed that collaborations which would realize health system savings would be beneficial to all jurisdictions. Medtronic's Richard Kuntz reflected that if upfront discussions more routinely occurred between industry and payers, industry could use that opportunity to rethink their technology design.
5. EI – "incremental" vs. breakthrough technologies.
   *Does EI envision being involved in the segmentation of methods/approaches for the development of "incremental" technologies vs. sticking to developing breakthrough technologies?*
   A stakeholder commented that a benefit of EI's collaborative and transparent approach is that issues are on the table from the outset; such an approach might lead to the identification of projects which intrinsically should not be brought forward as well as identifying those of true value. Peter McCulloch, a surgeon at Oxford's John Radcliffe Hospital and Chair of the IDEAL initiative, stated that IDEAL is currently examining methods of assessing the value of an incremental technology upfront in order to answer the "is it worth it?" question; to this end, IDEAL is considering adding a needs assessment to the evidence review stage for incremental technologies.
6. Changes in the value of a technology over time.
   *Will EI have a role in better assessing how the value equation of a technology changes over time?*
   A stakeholder observed that after a new innovative technology comes to market, additional versions very quickly follow, changing the value equation of the original technology.
7. MNEs vs. SMEs.
   *How will EI reconcile the fundamental difference in the resource power of SMEs and MNEs?*

Stakeholders commented that SMEs typically have fewer resources than MNEs to partner with payers to deliver value. In this paradigm, SMEs are limited to their technology, whereas MNEs have the resources to involve themselves in additional elements of the care pathway and a greater threshold for experimentation. The question was raised as to how to best protect the intellectual property of SMEs, and prevent their becoming subsumed by MNEs.

8. Accelerated access for patients to effective new technologies.
   *How will the EI model accelerate access of effective innovative new technologies to patients?*
   Industry proposes that the FDA and CMS accelerate access to patients of selected breakthrough technologies through an expedited review process. It was proposed that both products that have not undergone prior FDA approval as well as those having gone through incremental changes (the 510(k) clearance process) be included. In the model, if selected products are approved and meet FDA standards, they would be awarded automatic CMS coverage for a proposed period of time. During this trial period, CMS would be authorized to inform industry of the evidence and data it needs in order to assess the provision of coverage beyond the trial in order to make a recommendation on reasonableness and necessity.
   Murray Sheldon, Associate Director, Technology & Innovation, FDA's Center for Devices and Radiological Health, commented that coverage with evidence development at the FDA is not a new concept and that programs already exist for a subset of new technologies. Murray added that the UK's Accelerated Access Review is an example of this very process at the NHS, with a current focus on regulation, reimbursement and uptake.

**Key messages:**

- ✓ The principal barriers for technology innovators are time, expense and access to quality data. A greater consensus is needed of the time horizon necessary for payers to justify an investment. Innovators would benefit from access to quality, affordable CT organizations that are also able to interact with the end user.
- ✓ The evidence generated is not sufficient because of the way the system works. Ideally, a standard methodological framework for evaluation which covers the whole life cycle of an innovation should be developed.
- ✓ Payers and health systems report innovators are providing inadequate study designs. EI can provide a validated inventory of outcomes and clarity on statistical differences so that payers and health systems better understand how the technology impacts outcomes.
- ✓ There is a lack of centralized repositories of expertise for trial design. EI can facilitate such a repository.
- ✓ There is a large evidence gap in emerging markets (EMs). EI can provide a transparent mechanism to bring evidence to EMs, improving the likelihood of adoption.
- ✓ Patient expertise is greatly undervalued; patients bring a host of knowledge to the process (see above) and should be incorporated in the EI model.

## *Panel 2: Critical Review of Explanatory vs. Pragmatic Trials*

Bryan Luce, Senior Advisor at Evidera and former CSO at PCORI moderated the multijurisdictional panel on clinical trial design. Discussion centered on the fundamental question of "what elements of trial design work for whom and under what circumstances?"

### *What are Pragmatic Trials (pRCTs) and how do they compare with Explanatory Randomized Controlled Trials (RCTs)?:*

The first RCT was published in 1948 and during the subsequent twenty years RCTs were increasingly implemented to evaluate medications. In 1967, Daniel Schwartz and Joseph Lellouch proposed that there were, in effect, two kinds of trials – "explanatory" trials (those aiming "to verify a biological hypothesis" ) and "pragmatic" trials (those aiming "to choose between two treatments").[2] Thorpe et al. expand on the statisticians' findings, describing explanatory trials (RCTs) as those designed to test causal hypotheses and pragmatic trials (pRCTs) as those designed to help users choose between options for care.[3] Schwartz and Lellouch proposed that most RCTs are, in fact, a mix of both elements. EI panelists affirmed that all randomized trials are situated on a pragmatic-to-explanatory continuum. While specific trial attributes may be more pragmatic or explanatory in nature, they should not be regarded as dichotomous. Several trial attributes are presented in Table 1.

[2] Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. J Chronic Dis 1967;20:637-48. [Reprinted in J Clin Epidemiol 2009;62:499-505.]

[3] Thorpe KE, Zwarenstein M, Oxman AD, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. J Clin Epidemiol. 2009;62:464–475.

| Table 1: Attributes of Pragmatic Trials (pRCTs) and Explanatory Randomized Controlled Trials (RCTs) | |
|---|---|
| Pragmatic Trial (pRCT) ⟷ | Explanatory Randomized Controlled Trial (RCT) |
| Tends toward measuring effectiveness | Tends toward measuring efficacy |
| Goal: choosing among alternatives in a real world situation; usually designed with this goal in mind | Goal: measuring the causal relationship between an intervention and a specified outcome |
| Usually designed to maximize generalizability | Usually designed to optimize internal validity; less concerned with external validity |
| The intervention is generally:<br>✓ flexibly applied in "usual care" | The intervention is generally:<br>✓ optimized through study design and monitoring |
| Inclusion criteria tend to:<br>✓ emulate the real world - participants, practitioners and institutions are typical of the range reflected in usual conditions of health care delivery<br>✓ not monitor or correct participant adherence | Inclusion criteria tend to:<br>✓ eliminate poorly adherent participants and/or comorbidity, both of which act to dilute the effect of the intervention |
| The trial is typically conducted in "usual care" | The trial is typically conducted in optimal conditions to "control" the behavior of the patient and maximize the effect of the intervention |
| Generally focused on evaluating outcomes of importance to patients, funders and health care practitioners (e.g., quality of life, long term survival, severe morbidity); typically not focused specifically on regulatory requirements | To the extent they are focused on regulatory requirements, outcomes of interest may not be fully oriented to outcomes of primary interest to patients, funders and health care practitioners |
| Major Benefit:<br>✓ tend to be widely generalizable (based in usual care and real world situations) | Major Benefit:<br>✓ lack of bias |
| Limitations:<br>✓ there is a widespread belief (but little evidence) that there is modest reduction of effect size in comparison with more explanatory trials<br>✓ there is a belief (but no evidence) that pragmatic trials are more biased as a tradeoff for wider real applicability | Limitations:<br>✓ lack of generalizability (results cannot necessarily be extrapolated to the wider population) |
| Trialists and policy makers alike must recognize that what constitutes "real life" and "usual care" in one jurisdiction may be different in another | By design, there is typically no attempt to match conditions found in the real world |

## *A regulatory challenge – lack of high-quality evidence:*

Rod Taylor, Professor of Health Services Research, University of Exeter Medical School and NIHR Senior Investigator, was previously part of a large European research consortium (MedtecHTA) conducting a cross country analysis of health technology assessment (HTA) for medical devices. Taylor reported that delays in medical technology funding and patient access are often the result of shortfalls in clinical evidence generated to respond to regulatory requirements, making it difficult to conduct a health technology assessment.

MedtecHTA compared regulatory practices in the US and in Europe and found that while approaches differ as concerns their mandates, organization, pre- and postmarket evidence requirements and the transparency of their processes, both jurisdictions share similar challenges in getting safe and effective medical devices to market, monitoring use in the real world and exchanging device information with patients and clinicians. As a result, reforms of the regulatory process have been implemented or are being considered in each jurisdiction, including improving postmarket oversight through better surveillance systems and boosting the traceability and monitoring of devices.[4]

[4] Sorenson C, Drummond M. Improving medical device regulation: the United States and Europe in perspective. Milbank Q. 2014 Mar;92(1):114-50.

Taylor stated there is a need for innovative models of collaboration between regulators, HTA, and reimbursement agencies and that EI could be instrumental in this area. Taylor expressed that efforts at regulatory reform fall short of stakeholder needs and recommended they also include:

- requiring pre-approval evidence to match the potential risk of a new device
- requiring companies to provide clinical trials for the efficacy & safety of a high-risk device
- greater centralization of regulatory approval across jurisdictions, with common risk classification rules
- better links between device identifiers and data collection (EHRs)
- greater use of registries to ensure safe use of devices in the real world
- enhanced surveillance at post-market, providing real world data (e.g., effectiveness, user learning curve, organizational impact, etc.)

*Discussion:*

Peter Juni, Director of the Applied Health Research Centre, St. Michael's Hospital and U. of T. Professor reminded stakeholders of the importance of including patient perspectives in trial design. Juni remarked that outcomes important to trialists are often not the outcomes which are important to patients. Juni urged researchers to innovate in finding methods to answer and more quickly report on questions of relevance to patients.

Stakeholders had several suggestions regarding gathering patient-focused evidence:

| In generating patient-focused evidence, how can we? | Solution |
|---|---|
| ❖ produce patient focused outcomes | ✓ overlay large trials with smaller patient studies |
| ❖ more rapidly answer patient focused questions | ✓ incorporate simple examples of electronic case report forms in trials (eCRFs) |
| ❖ investigate why some patients do well in a trial and others do not | ✓ nest small qualitative research studies in the pRCT design |
| ❖ disseminate patient experience | ✓ add a patient focused section to published papers |
| ❖ satisfy the market's demand for fewer outcomes, not more | ✓ conduct a patient survey for desired outcomes & incorporate results in study design |
| ❖ engage physicians, who play a key role in user adoption of new technologies | ✓ engage physician associations (e.g., the UK's NICE has incorporated the Royal College under their umbrella & focuses on a full set of indicators including economic value)<br>✓ include patients in clinical guideline development |

Considerations and suggestions were raised regarding trial methodology:

| pRCT methodological consideration | Solution |
|---|---|
| ❖ how does industry address diluting effect of heterogeneity in pRCTs | ✓ current evidence that heterogeneity of trials (i.e., more pragmatism) dilutes effect size is mixed. If lack of association between pragmatism and effect size is confirmed, this fear may be unfounded. Repeats of this work on medical technologies need to be funded using standardized methods<br>✓ Create a common framework for payer expectations of trials and for communicating those expectations to industry. (For example, BCBS is piloting a new product called Evidence Street: "Where the Market Meets Evidence." Industry will have access to the evidence reviews used by the 36 BCBS Plans, representing 106 million members. Industry will also have access to a framework of evidence expectations and gaps analysis.) |
| ❖ how does industry address methodological challenges such as:<br>• blinding | ✓ if effect size is large enough – make case that blinding may not be necessary, even with "humanistic" outcomes |

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| • measurement of subjective endpoints<br>• placebo & Hawthorne effect<br>• demand for large quantity of data – culture of "needing to keep to status quo," even though FDA is increasingly working on pRCTs and "lean" studies | ✓ obtain clarity on payer specifications for "minimally important differences"<br>✓ use of PROs vs. "hard" outcomes when appropriate: *"if bias is introduced, it is usually on the part of physicians, not patients"*<br>✓ consider the use of an adaptive clinical trial design *"EI could pilot an adaptive process whereby we start with a traditional explanatory approach and over time adapt to a more pragmatic design at the postmarket stage. This model would include the input of stakeholder parties and describe a continuous process from concept through to post adoption."* Bryan Luce |

**Key messages:**

- ✓ Explanatory Randomized Controlled Trials (RCTs) tend to measure efficacy, Pragmatic Trials (pRCTs) tend to measure effectiveness.
- ✓ The goal of pRCTs is usually to choose among alternatives in a real world situation, the goal of RCTs measuring the causal relationship between an intervention and a specified outcome.
- ✓ pRCTs are typically conducted in "usual care."
- ✓ pRCTs are generally focused on evaluating outcomes of importance to patients, funders and health care practitioners.
- ✓ The major benefit of pRCTs is that results tend to be widely generalizable – the disadvantage is a belief (but no evidence) that pRCTs are more biased [than RCTs] as a tradeoff for wider real applicability.
- ✓ Currently, evidence generated frequently does not meet regulatory needs, making it difficult to conduct HTAs. EI could help by creating innovative models of collaboration between regulators, HTA, and reimbursement agencies.
- ✓ There is a need for more patient input and patient focused outcomes. EI could include both in their model.
- ✓ pRCTs present methodological challenges. EI could help by piloting alternative adaptive clinical trial design schemes for medical technology evaluation.

## *Panel 3: Leveraging data for HTA Evaluation – pre- & post-adoption*

Joseph Ross, a member of the Center for Outcomes Research & Evaluation (CORE), Yale-New Haven Hospital, moderated a panel discussion on leveraging existing data to evaluate health technologies in the pre- and post-adoption stages of development.

### *Background:*

Since the implementation of the 1976 Medical Device Regulation Act in the US, manufacturers have been required to register their product with the FDA and follow quality control procedures. The Act specifies three classes of devices: Class I - General Controls - devices considered as low risk for human use; Class II - Performance Standards - devices considered as moderate risk for human use; Class III - Premarket Approval - devices considered as high risk for human use. In this way, some device types are required to undergo premarket approval by the FDA to assure safety and effectiveness; others are required only to meet performance standards before being marketed.

There are currently two traditional pathways toward FDA approval – the 510(k) Pathway for clearance of moderate risk devices and the Premarket Approval Pathway (PMA) for clearance of high-risk devices. The vast majority of medical devices and diagnostic tests classify for the 510(k) Pathway. This clearance process does not require clinical evidence of safety and effectiveness, but requires instead evidence that the new device is "substantially equivalent" to another device already on the market (a "predicate" device). FDA expectations for medical and diagnostic tests differ. The PMA pathway requires clinical testing that provides "reasonable assurance" that the device is safe and effective for its intended use.

Currently, the 510(k) process is flawed in that any new 510(k) submission, used when a moderate-risk device undergoes initial clearance or modification, such as a labeling change, technology or performance specification change, or materials change, does not require submission of clinical evidence. The safety and effectiveness of a device is better assessed in an integrated pre- and postmarket regulatory framework which evaluates these elements as long as a device is in use. The FDA is increasingly moving toward a total life cycle approach of evaluation in order to accelerate patient access to new technologies.

In the case of high-risk devices, the FDA can require additional clinical studies in the post-approval stage as a condition of PMA approval.

The generation of evidence through clinical trials, while essential, is costly and time consuming. Further, there are concerns that some clinical studies supporting FDA approval for high-risk devices are not sufficiently rigorous and suffer from bias. A recent analysis of the characteristics of clinical studies conducted over the total product life cycle of high-risk therapeutic medical devices receiving FDA PMA approval in 2010 and 2011 found that "evidence generation varied in both the number and quality of premarket and postmarket studies, with approximately [only] 13% of initiated postmarket studies completed between 3 and 5 years after FDA approval."[5]

It is a fact that in addition to evidence generated by clinical trials, high quality clinical and real world data exists in many forms and is being increasingly generated. Ross and Nihar Desai (also a CORE member) proposed that in leveraging these secondary forms of data in the postmarket space, it is possible for industry and researchers to examine outcomes of importance to patients, providers, manufacturers, payers and policymakers/regulators. In the total life cycle paradigm of evaluation, studies conducted postmarket will increasingly influence FDA decisions. If these studies, using secondary data sets, not only complement clinical trials but also generate accurate, meaningful evidence in a timely manner, patients will gain access to effective treatments sooner.

### *New Evidence Generation*

There are three elements which are necessary for leveraging existing data:

- A unique device identifier (UDI) designed to identify every device through distribution and use, in a standard format, and in a form that uses automatic identification and data capture (AIDC) technology
- Reliable and complete data
- Robust statistical methodology

Ross and Desai described secondary data sets and several statistical methodologies, their advantages and disadvantages and examples where they have been implemented. For a detailed list of these data sets, please refer to Table 3 in Appendix A.

Secondary data analysis can play an important role in postmarket technology evaluation, but requires investment, infrastructure and ingenuity. The issue of confounding is critical because of the heterogeneity of the data. These issues will hopefully lead to the further development of analytic and statistical frameworks for secondary data analysis. "We desperately need to reimagine the way evidence is generated to support the needs of patients, providers, payers, and regulators/policymakers. There is no simple solution." Joe Ross and Nihar Desai, CORE.

Several stakeholders raised the issue of randomization and its possible use in secondary data sets. Peter McCulloch (Surgeon and Chair, IDEAL) stated that while randomization is difficult and expensive, there exists no substitution for it.

**Key messages:**

- ✓ There are two traditional pathways toward FDA approval – the 510(k) Pathway for clearance of moderate risk devices and the Premarket Approval Pathway (PMA) for clearance of high-risk devices. Most medical devices and diagnostic tests classify for the 510(k) Pathway.
- ✓ The PMA pathway requires clinical testing that provides "reasonable assurance" that the device is safe and effective for its intended use. The 510(k) Pathway does not require clinical testing but requires evidence that the new device is "substantially equivalent" to another device already on the market.
- ✓ The FDA is increasingly moving toward a total life cycle approach of evaluation in order to accelerate patient access to new technologies, assessing the safety and effectiveness of a device in an integrated pre- and postmarket regulatory framework which evaluates these elements as long as a device is in use (total life cycle).
- ✓ High quality clinical and real world data exists in many forms and is being increasingly generated. This data can be leveraged for use in pRCTs and complement RCTs conducted for initial approval.
- ✓ In order to use secondary data sets, three elements are essential: reliable and complete data, robust statistical methodology and UDIs. UDIs are necessary so that devices can be identified and evaluated as long as they are in use.
- ✓ EI can assist by helping to clarify definitions of "reasonable assurance" and "substantially equivalent"; by helping to generate high-quality evidence which supports the "total life cycle" approach to evaluation; by supporting the development of new statistical methodologies and collaborations in order to leverage secondary data sets, by

[5] Rathi VK, Krumholz HM, Masoudi FA, Ross JS. Characteristics of Clinical Studies Conducted Over the Total Product Life Cycle of High-Risk Therapeutic Medical Devices Receiving FDA Premarket Approval in 2010 and 2011. JAMA 2015;314(6):604-612.

supporting the generation of robust UDIs in all devices, and by supporting transparency into all clinical research efforts supporting medical product evaluation.

**About EXCITE International (EI):**
EI is a coordination of emerging global efforts to solve a known and frustrating health technology problem: existing approaches to driving disruptive new innovations across the trajectory from development to evaluation, adoption and post-adoption evaluation are fragmented, inefficient, counterintuitive, unnecessarily convoluted and expensive. EI's mission is to improve well-being and create value by accelerating the adoption of disruptive health technology innovations into more markets, with greater certainty, at a lower cost. EI's founding Chair is Richard Kuntz, Senior Vice President and Chief Scientific, Clinical and Regulatory Officer, Medtronic. EI's Chief Executive and Chief Scientific Officer is Les Levin.

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## *Acronyms:*

ACO - Accountable Care Organization
AHRQ – Agency for Healthcare Research and Quality (US)
AIDC - Automatic Identification and Data Capture [technology]
ARTIC - Adopting Research to Improve Care (ON, Canada)
CDRH - Center for Devices and Radiological Health (FDA) (US)
CEO – Chief Executive Officer
CER – Comparative Effectiveness Research
CMS – Centers for Medicare and Medicaid Services (US)
CORE - Center for Outcomes Research & Evaluation, Yale-New Haven Hospital (US)
CRO – Contract Research Organization
CSO – Chief Scientific Officer
CT – Clinical Trial
eCRF – Electronic Case Report Forms
ECRI – ECRI Institute (US)
EHR – Electronic Health Record
EI – EXCITE International (Excellence in Clinical Innovation and Technology Evaluation)
FDA – U.S. Food and Drug Administration (US)
HTA – Health Technology Assessment
IDEAL - The IDEAL Collaboration (Idea, Development, Exploration, Assessment, Long-term study) (UK)
IHS - Integrated Health Solutions [at Medtronic] (US)
MDIC – Medical Device Innovation Consortium (US)
MDMA – Medical Device Manufacturers Association (US)
MNE – Multinational Enterprise
MOHLTC - Ontario Ministry of Health and Long-Term Care (ON, Canada)
NHS – National Health Service (UK)
NICE – National Institute for Health and Care Excellence (UK)
NIHR – National Institute for Health Research (UK)
NOCRI - NIHR Office for Clinical Research Infrastructure (UK)
PCORI - Patient-Centered Outcomes Research Institute (US)
PMA – Premarket Approval (US)
SME – Small- and Medium-sized Enterprises
UDI – Unique Device Identifier

***APPENDIX A:***

| TABLE 2: Session Comments – Stakeholder Evidence Needs | | | |
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| Stakeholder | How Evidence Falls Short | Barriers Encountered | What Can EI do? |
| **End Users** | | | |
| Physician/Entrepreneur (Canada) | | • Need access to quality, objective data that is generated by an arms-length research enterprise<br>• Time is of the essence - investors want to see results quickly<br>• Expense – most start-ups have limited capital for research | • Provide access to arms-length, quality, affordable clinical trial organization, able to interact with end user to get the study off the ground |
| Surgeon/IDEAL Chair (UK) | 1. Adequate evidence on safety (Regulators)<br>2. Evidence on relative efficacy (Purchasers)<br>3. Evidence on cost-benefit (Purchasers)<br><br>Above are separate groups with specific data needs | *The nature of complex invasive therapies means:*<br>• Refinement is often possible and desirable after first-in-human use<br>• A learning curve for implementation/delivery is often present<br>• Complexity prevents standardization of delivery and requires pragmatism in evaluation<br><br>*The nature of the Regulatory and Purchasing landscape means:*<br>• It's a 2-target problem: Low bar for marketing approval, higher bar for purchasing<br>• Neither bar is based on a consistent set of methodological requirements<br>• Both bars are based on a Yes/No decision model, not graded acceptance | • Assemble a functional network of all important stakeholders<br>• Develop a standard methodological framework for evaluation which covers the whole evolution of an innovation:<br>• Radboud model of pre-clinical prioritization<br>• IDEAL model of pre-RCT or non-RCT clinical studies (Development and Evaluation stages)<br>• Innovative use of adaptive design and other useful variants on RCTs<br>• Intelligent use of Big Data approaches to analysis of registries and Real World data sets<br>• Offer this as the basis for rapid, impartial, expert third party evaluation which will meet all foreseen evidence needs |
| **Industry** | | | |
| VP – Global Strategy & Analysis (US) | Evidence gap in Emerging Markets (EMs) | • Lack of confidence by payers and regulators, due to perspective<br>• Wary of new technologies<br>• Many EMs lack a compensation mechanism for innovative technology or it is underutilized - therefore lack infrastructure for adoption | • Provide a transparent mechanism to bring evidence to EMs who are less familiar with innovation, may have a less developed health care system and less academic infrastructure<br>• EI multijurisdictional "endorsement" may improve the likelihood of EM adoption<br>•"Potential for a sea change" in this space |
| CEO & Chair, Industry Association (Canada) | Real world & Pragmatic trials are increasingly offered – but lack the | • In Canada, independent decisions by different regions, provinces and even | • Clarity, transparency and timeliness of EXCITE model can addresses the barriers in Q1 |

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| | economic or other components of an evidentiary package | institutions – can be arbitrary or have different timelines<br>• After a positive HTA decision there is often no good pathway to support adoption | • Assist following a positive decision regarding coverage, thereby de-risking investment in the EXCITE study |
| CEO, Industry Association<br>(US) | 5 years ago the focus was Regulatory & FDA; now the focus is on narrowing gap between Regulatory & Reimbursement.<br>E.g., CMS – 180 days to review a technology | • Lack of transparency from most Payers regarding evidence needed for coverage – some private Payers are transparent & public<br>• For small companies lack of funding to develop evidence for coverage; (dearth of VC financing for small and medium enterprises (more IPOs that series A Financings))<br>• Time horizon – we do not look at technologies' value capture/profile across entire life cycle | • Multiple stakeholder input can help narrow gap between Regulatory and Reimbursement<br>• Provide greater consensus on how to define value (which metrics, quality, outcomes)<br>• Provide greater consensus on time horizon needed by Payers to justify an investment<br>• Provide greater transparency from Payers on requirements for coverage and determinants of value – what is the economic target?<br>"Should not be a pay to play system"<br>• Can EI promote novel risk sharing models in the post adoption arena? (E.g., government considers a managed entry/risk sharing payment scheme to ensure value capture across technology life cycle) |
| Director, corporate R & D<br>(Canada) | 1. Evidence generated not sufficient due to current fragmented system. E.g., high quality data for Regulatory clearance, but adoption not guaranteed<br>2. Historically CTs designed to support registration of product & not designed to show value of the product over time. Currently the goals of getting product to market quickly but also meeting Payer evidence bar is a major tension<br>3. Int'l evidence; jurisdictions don't accept outside data despite its quality. Want CTs run in-country/for country for the economic benefit. As a result, corporations have to set up CRO's in those | | • Get regulators and provinces [in Canada] to work together to clear technologies<br>• Use processes to facilitate diffusion (E.g., ARTIC) & drive change management with front line workers<br>• Models to bring technology to market both quickly & with high evidence bar will be invaluable (E.g., MDIC). Possible to include conditional acceptance – real world evaluation<br>• Could EI leverage GE's existing int'l methodology centres (E.g., China)?<br>• Incorporate new technology evaluation methodologies which also have digital wraps – developing quickly & we are not ready<br><br>"GE very pleased to hear about EI forum/model – similar to what happened 20 years ago when pharma transitioned from how they measured things in the past to outcomes measured (had to convene stakeholders to conclude what changes were needed)" |

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| | countries for trials & manufacturing<br>4. New digital layer on all medical technology | | |
| Payers/Health Systems | | | |
| Executive Director, Clinical Evaluation, Innovation & Policy - Technology Evaluation Centre [at Insurer] (US) | Inadequate Study designs with:<br>• Potential biases<br>• Durability issues<br>• Lack of follow-up<br>• Lack of generalizability<br><br>Further, in diseases of chronic pain, neurodegenerative etc.:<br>• Gaps in robustness of outcomes measures<br>• Validated inventory of outcomes so we can understand how the technology impacts outcomes<br>• Clarity on statistical differences in outcomes | "We have to think about strategies for managing a condition – technologies are a component, but should not be the focus. In the US, strategies are more directed to the approach to care & management of a condition. E.g., Knee Replacement Therapy (KRT), a very effective procedure, has changed what aging means for people – they are no longer impaired for life. KRT becomes more effective in high volume centers; setting & delivery systems are hence important for the performance of technology. But there are controversies: should it be done sooner vs. later, what are the value & cost/benefit trade-offs?"<br><br>"The importance of Open Science: it's an opportunity to aggregate more insights not only on technologies, but also on clinician [practices] & management of the disease. [We then] have a coherent view; this is hard to measure when the outcome is not as simple as 'survival,' but when it is the 'plagues of our time' – harder to measure outcomes." | • Be proactive at market entry<br>• Be selective; not a consultation for everyone, but rather to promote game-changing technologies. "If we can push another 'knee replacement' through EI it will have delivered on its mission."<br>• Collaboration should improve quality of information available while also reducing barriers to positive change<br><br>"Regulators focus on market entry. Payers want what patients want, but also have the fiduciary responsibility for resources, amplifying the issue." |
| Chief Health Innovation Strategist – MOH (Canada) | Evidence too narrowly focused or hard to translate into the system: "so what?" often missing; ministry needs to better articulate what it is looking for<br><br>The Executive Summary of an HTA is often not clear to a decision maker – does not provide the clinical utility and value profile of the technology | • Payers need to better articulate the [health] system's priorities<br>• Then articulate what evidence they actually need from a technology<br>• Price sensitivity is often missing in the decision making stage of a technology – contrast with how pharma embeds this in their go-to-market model<br>• Silos are an issue – when the technology delivers benefits in a different place | • Provide a consulting service abroad to ensure that the types of thinking/clarity of thought from the experts in the consortium are exported to all the key markets – helping small companies, such as those in Canada, to export internationally<br>• Provide methodology for getting the technology over the finish line after positive HTA –i.e., how to get it into the marketplace and diffused through the system<br>• Help Payer articulate needs so that "If you exceed the milestones you are in [the health system]" |

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| | | from where the buying occurs | • Help drive economic industrial policy<br><br>"The international collaboration between Ministries of Health regarding adoption & economic policy will be key." |
| Chair, National Product Council & Chair, Inter-Regional New Technologies Cmte – [Insurer]<br>(US) | 1. Adequate evidence on safety (Regulators)<br>2. Kaiser HTA group has very strong standards for "good evidence," & therefore very little evidence makes it through.<br>"But there are also pragmatic issues surrounding evidence for adoption of new technologies: e.g., when the Da Vinci robot was approved, my concern was how to hire enough urologists."<br>3. Registries unit – share their data and results internationally<br>4. [Importance of] ECRI collaboration:<br>"When there were claims about a device for a surgeon doing minimally invasive procedures Kaiser could test some features in their ORs & have surgeons trial it. But ECRI could test it in the human factors lab & found environmental impact issues which Kaiser would have never identified (E.g., increased CO2 in the atmosphere when the laparoscopic device is used) which, of course, affects decision making."<br>5. Trials: Populations restrictive | • Interest in participating in protocol design (have not been very involved in Phase 3 - no medical school until now & research infrastructure is fragmented)<br>"Getting an inter-region thing moving is very hard, e.g., no central REB); & evidence review boards reject studies sponsored by suppliers."<br><br>• Involvement in study design is constrained by resources and processes<br>• Published evidence & literature of an HTA sometimes does not match the workflows and union environment | • A full [company] hub commitment difficult as are not yet "one KP"<br>• EI could find physician champions to lead key studies – [company] could then add a substantial infrastructure and population to some of the studies |

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| | 6. Levels of compliance which will never reach what could be reached in the real world<br>"Baseline does not always match Kaiser's baseline: E.g., the VA started from "doing nothing" in remote monitoring for CV, so they saw a huge lift compared to what Kaiser would have." | | |
| Representative, Health Technology Advisory Cmte<br>(Canada) | Regarding Ministry decision making:<br>1. Post-market, key focus is on whatever science is available. The science has to focus on effectiveness, costs, & cost-effectiveness<br>2. Value: "Is it worth it?" Question is very important for systems & society & not being discussed<br>"Minimal gains are possible at enormous costs – no one is systematically dealing with fundamental challenge of evidence and technology [cost]." | • Science stops after HTA; context then becomes locally influenced. There is a need for local contextualization (cost effectiveness, patient input, public input, quality of evidence ranking outside of scientific factors) | • Help local jurisdictions with "template" enabling input in protocol design<br>• Localize issues related to cost effectiveness: E.g., affordability, feasibility (for different population size & characteristics)<br>• Help with collaboration and coordination, e.g., "NIMBY"<br>• Address the broader societal question of "is it worth it?" for incremental gains with high price tags |
| Chief Clinical Officer and SVP – Health care advisory services firm<br>(US) | Clinical trial outcomes need to be designed for the convenience of investigator or sponsor: E.g., for rehab of spinal cord injuries it's really hard to come up with an evidence table given how many variables each study design could have<br><br>Evidence is important but is not going to get us all the way to the end; reminder that when Congress founded medicare they did not say "if it works for patients, pay for it."<br>The role of evidence becomes simply a | • US is in transitional stage of payment systems from fee for service vs. value based. So there are currently a mix of methods available for market access<br>• Incremental improvements from technologies: health care is both far from perfect and also far from awful. Currently we have a lot of good medicine, and some less "sexy" technologies might be "good enough." A lot of incrementalism is driven by low event rate – is a large and long trial necessary to get data of significance? Is the RCT paradigm becoming | • Identify a common taxonomy of preferred outcomes. Find a way to evaluate them against each other. Obtain consensus and agreement across jurisdictions, and include patient input<br>• Critical stakeholder community for EI will be commercial payers – it's very hard to get them to the table; even BCBS is not one entity, it is many entities<br><br>"Metaphor - we are [currently] like a new school board trying to design a new curriculum and evaluation system, while also trying to ensure our own students place 1st." |

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| | common starting point to inform decisions, and the starting point will differ by jurisdictions | incompatible with the nature of technologies?<br>• Reminder: disruption theory expects disruptive technologies to be lower-tech and cheaper. Why do we expect that new technologies will need to be higher-tech and more expensive? | |
| Patient perspective | | | |
| Patient Advocate (US) | Patients want innovative technologies that do not become museum pieces | • Tension in CT development when endpoints are designed to answer Regulator questions as well as HTA and private payer questions – latter are becoming increasingly key to decisions | • Include patients in protocol development – they often understand HTA and reimbursement processes and pricing<br>• Include patients in design of qualitative issues<br>• Include patients in CT patient recruitment & retention<br>• Design value-based pricing models – beginning with oncology<br><br>"EI should not be the exception, it should be the rule - for now it is the best practice - a multinational, multi-stakeholder initiative." |
| Patient (Canada) | Expertise of patients is essential, but not respected | • To date, patients not at the table, but patients are playing an increasingly greater role in their own care, patient expectations are higher than before<br>• Disruptive technology will only happen if it is driven & led by patients – they uniquely represent continuity in health care<br>• Too little transparency & accountability | • Give patients & carers power to "pull" innovation into the system; allow patients to codesign the process - 85% of the questions raised by patients are not on the research agenda or in the pipeline: e.g., study populations, exclusion criteria [in relation to "real life"], meaningful end points demonstrating patient values vs. "success or failure"<br>• Respect the essential expertise of patients<br>• Involve patients early on in choosing priorities & determining relevance<br>• Co-produce with patients across life cycle of technology development & adoption<br>• Consider safety from a patient perspective; there is a difference between safety as a system concept vs. harm for individual patients – the term is being redefined as patients are weighing in<br>• Include patients in closing the loop at the adverse reporting stage of development<br>• Patients can be valuable across the product life cycle in helping with technology adaptation and adoption, uptake among diverse populations, off label uses<br>• Insist on open data - will improve accountability |

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| | | | • Appoint a "Chief Patient Experience Officer"<br>• Create an EI patient advisory board |
| Patient Representative (UK) | 1. CT design – safety & efficacy<br>2. Cost assessment horizon is too short with too little information – hard to extrapolate accurately across the full life cycle<br>3. Small cohort studies with short time frame not "reliable" – lead to cherry picking & "hope" that product is cost-effective | • Fear of failure due to time and money invested in CTs<br>• High level of pressure leads to looking at easy options for success | • Treat patients as an equal partners<br>• Include patient priorities – they rarely match CT outcomes<br>• Select an appropriate comparator that is "real world" – not just catering to the lowest common denominator<br>• Proving incremental benefit is attractive as 1st to market takes most risk & 2nd to market meets corporate profit requirements – but this approach stifles innovation |
| Scientific Advisor – HTA (Canada) | | | • Engage patients as experts/users of technology<br>• Explore patient engagement methods<br>• Operationalize: patients as committee members in developing trial protocols<br>• Enlist patients in educating research teams regarding what it's like to live with the disease<br>• Enlist patients in trial design – systematic review shows recruitment rates increase & attrition rates decrease as a result<br>• Promote culture shift & foster openness; typically patients don't feel equipped to participate in research team & vice versa<br>• Expand concept of evidence to include qualitative considerations/research methods, especially in adoption stage & value assessment –adds relevance |
| Regulators | | | |
| Associate Director, Medical Devices Bureau – Government (Canada) | 1. Poorly designed medical and clinical testing from: single innovator, physicians Class II, through to global manufacturer Class IV<br>2. Lack of centralized repositories of expertise for trial design<br>3. SMEs not spending time designing pre-clinical studies; information missing, procedures not well described<br>4. Fewer RCT in Class | • Funding & cost<br>• Time to market<br>• Endpoints occur to ≤ 1 year; HC trying to adapt – instead of saying no, issuing more licenses with conditions (this information is public to be accountable) | • Design CT to generate strong data regardless of risk<br>• Make primary endpoints clinically significant<br>• Provincial initiatives<br>• Harmonize appropriate infrastructure in hospitals for CTs if costs can be reduced, transferred to manufacturers<br>• Establish / designate common electronic data capture system in Ontario/Canada (E.g., "Approach" in Alberta – outcomes in coronary artery disease)<br>• Improve integrity of longer term outcome data |

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| | III-IV, single registry arm<br>5. Performance usually primary focus, then data messaged to suit stakeholder needs | | |
| Associate Director, Technology & Innovation, Center for Devices & Radiological Health – Government (US) | 1. Lack of appropriate CTs<br>2. Lack of quality of data needed for regulatory decision making<br>3. Small, innovative developer is siloed in their thinking, i.e., first I'll do what FDA needs, then what payer needs, then what is needed for adoption - makes process long & time-consuming<br>4. Data – while CTs produce much information, it is not necessarily related to how the technology will perform in the real world - makes it difficult for payers and providers to incorporate devices into daily care. *See recommendation regarding registries*<br>"FDA recognizes that regulatory decision making is only the beginning of a long pathway; FDA is very concerned with the remainder of the pathway – coverage, uptake and active surveillance" | • Resources not realistic<br>• Small & innovative companies lack the time & money to go through the linear process & keep project going – therefore innovation is stifled<br>• Above causes shortfalls in quality & relevance of data<br>• Larger companies have time and money, but most innovation comes from smaller companies<br>• Transparency from the Regulator AND the Payer as regards evidence needs - (e.g., FDA has worked with CMS in giving input into evidence needs, as well as participation in parallel reviews)<br>• Need early input from private Payers given their scope (now starting to get private Payer input into design of phase 3 of CTs)<br>• Take into account patient perspective – FDA is looking to partner more with patients & develop patient perspective platforms<br>• Overall barrier – lack of trust amongst stakeholders in realizing they are on the same page | • Establish registries or other mechanisms of large data collection in electronic format to evaluate technology over full life cycle, and evaluate the value of device in patient care<br>• Provide a platform to engage all the stakeholders to help address the barriers<br>• Facilitate by jurisdiction given each local set of frameworks |

TABLE 3: Secondary Data Sets and Statistical Methodologies

Ideally, data sets should be:
- ✓ Rich, with detailed clinical information - contain full array of outcomes, including patient-reported measures
- ✓ Representative, Timely, Longitudinal
- ✓ Integrate with existing systems
- ✓ Take minimal resources to achieve data collection

| Data source | Characteristics |
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| **REGISTRIES:**<br><br>AHRQ website – registry of registries | • heterogeneous<br>• numerous |
| **Selected CLINICAL REGISTRIES (meant for illustrative purposes):**<br><br>❖ NCDR (National Cardiovascular Data Registry)<br>Hospital registries for the in-patient setting:<br>✓ ACTION-Registry GWTG<br>✓ AFib Ablation Registry<br>✓ CathPCI Registry<br>✓ ICD Registry<br>✓ IMPACT Registry<br>✓ LAAO Registry<br>✓ PVI Registry<br>✓ STS/ACC TVT Registry<br>Outpatient registries for the ambulatory care setting:<br>✓ Diabetes Collaborative Registry<br>✓ PINNACLE Registry<br><br>❖ Swede Heart<br>❖ AJRR – American Joint Replacement Registry | **Advantages:**<br>• detailed clinical information<br>• opportunities for advanced patient phenotyping<br>• established by professional societies<br>• available for many health care technologies & conditions<br><br>**Disadvantages:**<br>• costly data collection on parallel system<br>• rarely include longitudinal information<br>• seldom include spectrum of patient centered outcomes<br>• may or may not be representative<br>• established by professional societies & often with manufacturer support, limiting true CER<br><br>**Example of use:**<br>• Ranasinghe I, et al. Long-Term Risk for Device-Related Complications and Reoperations After Implantable Cardioverter-Defibrillator Implantation: An Observational Cohort Study. Ann Intern Med. Published online, 3 May 2016.<br>• Kadakia MB, et al. Use of anticoagulant agents and risk of bleeding among patients admitted with myocardial infarction: a report from the NCDR ACTION Registry--GWTG (National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network Registry--Get With the Guidelines). JACC Cardiovasc Interv. 2010 Nov;3(11):1166-77. |
| **ADMINISTRATIVE CLAIMS DATA:**<br><br>❖ Centers for Medicare and Medicaid Services<br>❖ OptumLabs - health services platform for United Health Care; brings together vast data assets<br>❖ Premier, Inc. - health care alliance of over 3,500 hospitals and 100,000 providers | **Advantages:**<br>• ease of data collection<br>• (relatively) inexpensive<br>• representative<br>• longitudinal information<br>• integrates with existing data platforms<br><br>**Disadvantages:**<br>• absence of detailed clinical information<br>• most have significant time delays<br>• concerns about adequate risk adjustment<br>• if outcomes are available, quite limited |

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| | • may be quite costly to access<br><br>**Example of use:**<br>• Desai N, et al. Patterns of initiation of oral anticoagulants in patients with atrial fibrillation- quality and cost implications. Am J Med. 2014 Nov;127(11):1075-82. |
| **ELECTRONIC HEALTH RECORD DATA:**<br><br>❖ EPIC EMR<br>✓ Costs (Strata)<br>✓ Quality<br>✓ Clinical resource manager<br>✓ Registries<br>✓ National Death Registry<br>✓ External Claims<br>✓ Hadoop (Bedside Alarm, Streaming Vitals, Genomics, Social Media, Allergy/Weather, Traffic) | **Advantages:**<br>• detailed clinical information<br>• opportunities for advanced patient phenotyping<br>• longitudinal information if remain in system (e.g., VA vs. private)<br><br>**Disadvantages:**<br>• lack of interoperability<br>• EHR platforms have been built on prior existing patchwork systems so data can be scattered<br>• not representative<br>• can be cumbersome from an analytic standpoint & are mostly limited to structured fields (vs. free text)<br>• issues ascertaining outcomes & seldom include patient centered outcomes<br><br>**Example of use:**<br>• Starling RC, et al. Unexpected Abrupt Increase in Left Ventricular Assist Device Thrombosis. N Engl J Med 2014; 370:33-40. |
| **MINI-SENTINEL:**<br><br>❖ FDA initiative in which collaborating institutions enable access to data via structured queries for centralized analysis | |
| **ACTIVE SURVEILLANCE SYSTEMS** | **Advantages:**<br>• rapid<br>• minimal marginal cost<br>• longitudinal information<br>• may or may not be representative<br><br>**Disadvantages:**<br>• absence of detailed clinical information<br>• may neglect disparities in utilization<br>• requires standardized event terms, methodology must be developed<br>• limited to tracking products that are billed for<br><br>**Example of use:**<br>• Southworth MR, et al. Dabigatran and Postmarketing Reports of Bleeding. N Engl J Med 2013; 368:1272-1274. |
| **Emerging Technologies:**<br><br>❖ Wearables, Smartphone Apps such as Hugo<br>❖ Pcornet - a collaborative to transform the manner in which evidence is generated & translated | **Advantages:**<br>• detailed information<br>• opportunities for advanced patient phenotyping<br>• longitudinal information<br>• ability to capture patient reported outcomes |

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| | **Disadvantages:**<br>• may or may not be representative<br>• infrastructure, legal & privacy considerations<br>• not integrated into health care data platforms<br>• may not capture all outcomes of interest |
| **Existing Data (Data Sharing Platforms):**<br><br>❖ Yale Open Data Access (YODA) project enables data holders to share data through a learned intermediary (e.g., worked with Medtronic, Johnson & Johnson and other companies to facilitate access to investigators who are interested in conducting secondary analyses to advance science)<br>❖ ClinicalStudyDataRequest.com is similar, but in contrast to YODA where Yale has full jurisdiction over the data & works with investigators, CSDR is run by companies themselves | **Advantages:**<br>• momentum for greater sharing & transparency<br>• detailed clinical information<br>• opportunities for advanced patient phenotyping<br>• relatively inexpensive<br>• can conduct systematic reviews & comparative effectiveness studies<br><br>**Disadvantages:**<br>• slow<br>• limited by outcomes captured by clinical trial (seldom patient centered outcomes)<br>• likely not representative<br>• requires a parallel system |
| **Registry or EHR Based Randomized Trials** | **Advantages:**<br>• methodologic rigor<br>• (can) minimize confounding<br>• cheaper than RCTs<br>• faster than RCTs<br>• more representative (maybe)<br><br>**Disadvantages:**<br>• one simple hypothesis<br>• only work for certain endpoints<br>• limited monitoring<br>• [lack of] data completeness & validity can be limiting<br><br>**Example of use:**<br>• Fröbert O, et al. Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction. N Engl J Med 2013; 369:1587-1597. |
| Statistical Methodology | |
| **Propensity Score Matching**<br><br>(Instead of looking at entire study population, take a subset that have similar characteristics & examine their outcomes) | **Advantages:**<br>• fairly simple from an analytic standpoint<br>• can be updated with new data<br>• high dimensional clinical data to address confounding<br>• matching vs. non-matching can boost power<br><br>**Disadvantages:**<br>• can never be sure about residual confounding<br>• datasets without robust clinical data can lead to erroneous results |

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| | **Example of use:**<br>• Lagerqvist B, et al. Long-Term Outcomes with Drug-Eluting Stents versus Bare-Metal Stents in Sweden. N Engl J Med 2007; 356:1009-1019.<br>• Mauri L, et al. Drug-Eluting or Bare-Metal Stents for Acute Myocardial Infarction. N Engl J Med 2008; 359:1330-1342. |
| **Advanced Modeling of Heterogeneity**<br><br>❖ ePRISM (individualized estimates at point of care) | **Advantages:**<br>• extends from clinical intuition<br>• can enumerate risks & benefits<br>• uses hierarchical modeling which does not neglect interactions<br><br>**Disadvantages:**<br>• relies on completed RCTs<br>• model can be over-fit and may not be generalizable<br>• can be challenging to deploy in routine practice<br><br>**Example of use:**<br>• Wiviott SD, et al. Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes. N Engl J Med 2007; 357:2001-2015. |
| **Big Data and Advanced Analytics**<br><br>(e.g., Cluster Analysis – an unsupervised learning task of grouping a set of objects in such a way that objects in the same group are more similar to each other than to those in other groups) | **Advantages:**<br>• embraces high dimensional, complex data<br>• statistical & analytical power<br><br>**Disadvantages:**<br>• requires infrastructure<br>• data quality, "missingness" can be crippling<br>• signal : Noise<br>• over-fitting<br>• no clear validation |