Summary Report of Proceedings

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Summary

Collaborative approaches to pull v push new health technologies into health systems that potentially improve patient outcomes or health system efficiencies is now established as a conceptually preferred approach to fostering innovation through a more efficient, inclusive, de-risked pathway to expedite local and global adoption.

Companies attracted to regulatory approval as an initial focus of evidence development are likely to face significant challenges post-approval to realize adoption by health systems, which increasingly control most of the funds allocated to new approaches to clinical care. The impressive gains made by FDA in facilitating the regulatory pathway in the U.S. are laudable, though this will increase the number of companies that achieve regulatory approval without satisfying the evidence expectations of payers and health systems.

In the U.S., FDA has instituted a number of new approaches to streamline its processes and increase transparency; this is coupled with a focus on client satisfaction and is a major breakthrough in driving innovation and expediting the pathway to adoption.

In Europe, changes made by CE Mark through Medial Device Regulation (MDR) are a welcome sign of increased diligence regarding safety and performance. The approach will require more robust evidence of efficacy which represents a potential opportunity to merge regulatory with coverage considerations in evidence development. This regulatory modernization presents many complexities and challenges. Concerns were expressed that companies are caught up in a confusing transformation which could affect their viability. Among the concerns identified were the slow pace of implementation of the regulatory provisions, currently insufficient notified body review capacity and a lack of grandfathering of existing CE Mark-approved heath technologies, which will need to go through the new regulatory processes.

Payers and Health Systems (“Payers”) have until very recently been unable to have their expectations met early on in the development of new health technologies. There is increasing evidence in a number of organizations that this is changing in a significant way with the inclusion of payers upstream in the development cycle. Examples include the FDA, CMS, Blue Cross Blue Shield Association, NICE, CADTH – and EXCITE International, which was founded based on this principle. There are also welcome signs that payers and health systems are attempting to make their decision making approached more transparent through these collaborative initiatives.

Most of these upstream payer initiatives have involved providing advice following protocol review or prior to application for coverage determination. EXCITE International offers these insights across the continuum of the development cycle from proof of concept to pre-adoption. Despite initial concerns that the Payers Advisory Committee was comprised of member countries from disparate health systems, there are three important examples where this has been challenged. The first two were presented at the Summit and reflected on a PAC document

on high level guidance for coverage decision determinants and the successful involvement in upstream advice in Early Technology Review. The third example occurred during the Summit in which the payers and health systems developed consensus recommendations for protocol development based on a hypothetical case study. This augers well for continued constructive engagement towards a more transparent upstream positioning with industry.

The Industry Advisory Committee (IAC) was clear about the need for payers to be more engaging and transparent and, during a joint session with payers and health systems under PAC, there was convergence in this thinking. Industry, and especially multinationals, understand and are supportive of the evidentiary requirements of payers. In fact, examples were provided where important invasive medical technologies were withdrawn or modified following a self-initiated reviewed approach to evidence development. This early dialogue is an important forward-looking initiative EXCITE International and others will no doubt build on.

Other important areas for increasing dialogue between industry and payers considered are the inevitable transformation from fee for service to fee for value, the need for comparative effectiveness trials to understand trade-offs of interest to payers, robust estimates of downstream effects of new health technologies, early conditional adoption and ways of addressing the discontinuity in funding objectives by private payers given the transition of their members to Medicare after age 65 years in the U.S.

Scientists have an important role to play in the implementation of the transformational vision of early engagement by multiple stakeholders. Clinical trial methodologies need to address the full continuum from proof of concept to adoption and post-market. There is little clarity or consistency in the approach to early evidence development for devices in particular. This was addressed by exploring the sequential IDEAL approach to ensure safety, consistency and optimized efficacy in the use of new devices. Consistency in clinical trial end points was presented as an important consideration, since, without this, comparisons between trials on the same technologies are not possible. There is a move away from using RCTs as the one size fits all approach to evidence development. Though the RCT is essential in certain circumstances, the use of adaptive design to reflect the continuum of the technology life cycle, increasing attention to Bayesian approaches to reduce sample size and duration of studies and the use of existing patient outcomes data sets were some of the other methodological approaches discussed.

Another important scientific consideration is early health technology assessment (eHTA) and decision analysis to define the downstream effects of new health technologies. This is indispensable in a transformed evidence approach through the upstream engagement by multiple stakeholders and will become an essential component in understanding the effects of new health technologies, risks, benchmarking and defining the ecosystem in which these technologies will perform.

Patient engagement was accepted as a fundamental and increasingly important focus for technology development, evaluation and adoption. This has been recognized by the FDA which now considers patient involvement as essential. There are aspects of evidence development in which patient engagement is obvious, including selection of primary and secondary outcomes, ethical considerations, assessment of risk and benefit, the effect of urgency and acceptance of complications according to the treatment intention and monitoring patient-centered outcomes post-market. There is a rapidly developing scientific basis to patient engagement and in particular in their involvement in protocol development. A qualitative societal perspective needs to be recognized as social media continues to grow in its influence shaping opinions and perspectives. Ignoring this reality could be to the detriment of evolving new technologies.

The complexities of taking innovations along the pathway to commercialization was presented as one of the reasons innovations often fall into the "valley of death." Accelerators play a role in reducing this risk, as presented by the CIMIT approach which accelerates the healthcare innovation cycle by facilitating collaboration among clinicians, technologists, entrepreneurs and companies to create novel health tech products, services and enabled procedures.

EXCITE-like platforms have evolved in the U.S., U.K., Canada, Netherlands and Norway and form the basis for the execution of EXCITE International's activities. These are described more fully in this document and slide decks on the website at www.exciteinternational.com. These have developed based on an understanding of the local realities, programs, health systems and governance considerations and the need to protect the individuality and independence of each. Despite this, there is commonality in the collaborative pre-market expedited pathways for these platforms. Caution was expressed that focusing intensely on local priorities, professional, regulatory and coverage requirements could adversely affect attempts at global adoption – something EXCITE International was developed to avoid. Member countries continue to mould EXCITE International through active participation in its core initiatives that drive the three main offerings of ETR, protocol development and clinical trials. The Netherlands announced the recent formation of a major new initiative, Hii Holland, which is a joint development between Government and Academia working with industry to drive innovation with a portal to EXCITE International for global adoption.

It was recommended that EXCITE International should hold international forums to explore concerns of mutual interest to multiple stakeholders and that these proceedings should be published and used to influence change.

Background

The second EXCITE International Summit was held on March 26th as an open session and March 27th as a closed session, the latter being designed to develop a more granular approach to defining the future direction for EXCITE International.

The intent of the open session was to define and discuss the collaborative continuum from innovation to adoption. What follows is a brief summary of key changes or emphasis that arose from both days. Presentations with more detail can be accessed from slide decks posted on the EXCITE International website www.exciteinternational.com.

The Summit provided an opportunity for stakeholders to gain a first-hand appreciation of the multiple stakeholders involved across the pathway from innovation to adoption and diffusion and how changing landscapes might affect this pathway in the short term.

As set out by Sir Andrew Dillon at the beginning of the Summit, independent assessment, understanding and sharing risk related to therapeutic benefit, harms, costs, pathway disruption and early transparent engagement between payers and companies are important predictors of successful adoption. Furthermore, health systems need to be clear about their priorities and how they value innovation. Companies face a complex challenge in trying to 'read' the ambitions of diverse global markets, while recognizing the challenges their customers face. Important consideration regarding adoption include the impact of a new health technology on infrastructure demands, inclusive multi-stakeholder involvement and flexibility in pathways to adoption. Health systems and companies need to share the risks associated with uncertainty at market launch and look for flexible and creative solutions that work in the interests of patients and the health system. This is exemplified by forward looking initiatives such as the Blue Cross Blu Shield Association Evidence Street and NICE Scientific Advice programs which provide companies an opportunity to understand how to assemble appropriate evidence to optimize their chances of a positive determination.

It is hoped that the following summary of presentations and discussions will reflect forward-looking and current important developments driving the pathway from innovation to adoption and diffusion of health technologies. In doing so, they will be informative to the multiple stakeholders who attended the Summit, in addition to helping set the next level of strategic thinking for EXCITE International. Slide decks of presentations are posted on the EXCITE International website at www.exciteinternational.com. Some comments are provided based on discussions and will be expanded on once feedback is received from those with whom this document is being shared.

1. Regulatory Considerations

New insights to the changing landscape in the U.S. and Europe are likely to affect the pathway from innovation to post-market and beyond. We must ensure that devices have true value and an acceptable benefit/risk-ratio by ensuring that the system of evaluating and monitoring innovations is developed at the front and back ends (Moons).

While there was an overwhelming consensus at the Summit that steps taken by the CDRH FDA over the last few years is regarded as being increasingly helpful in making this part of the pathway easier to negotiate, concerns were raised about the lack of transparency and

preparedness for the pending anticipated changes coming to CE Mark through new medical device regulations (MDR).

- FDA

Dr. Jeff Shuren presented on new directions in the regulation of medical devices.

Changes that have been recently introduced or are about to be implemented include:

- Early feasibility study program to encourage a continuum of regulatory involvement from proof of concept to post-market
- Formation of MDIC to further regulatory science
- New approaches to clinical trials e.g. through adaptive design
- Introduction and use of new and evolving access to real-world data sources through electronic health information, including electronic health records, claims, social media, lab and registry
- National Evaluation System for health Technology (NEST) to be ready to launch by the end of this year, currently comprising 195 hospitals and 3,942 outpatient clinics to maximize the use of data that can be used to evaluate the safety and efficacy of these technologies
- A renewed emphasis on patient preference: involvement of patients in protocol development and regulatory submissions becoming increasingly important and likely to affect regulatory approval
- Flexibility in acceptance of uncertainty. Greater willingness to accept uncertainty where appropriate, e.g. breakthrough devices, PMAs with small patient populations, de novo devices with minimal risk
- Safety and performance-based pathway. Announced February 2019 as an alternative for well-understood device types especially where the device meets FDA performance criteria
- Customer satisfaction focus by becoming more customer service oriented and working more in collaboration with industry and other customers, and through initiatives that include MDIC and NEST

Dr. Murray Sheldon elaborated on new efficiencies within CDRH FDA during his presentation in the Scientific Collaboration session:

- Opportunities intended to help patients have more timely access to certain medical devices by expediting their development, assessment and review pathways by FDA/CDRH

- FDA Breakthrough Device Program (2016) to expedite development and review of certain devices representing breakthrough technologies for unmet needs. Eligibility criteria for consideration under this program are that the technology should provide more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions; AND meet one of the following:

  - Represent breakthrough technologies
  - No approved or cleared alternatives exist
  - Significant advantages over existing approved or cleared alternatives, including the potential, compared to existing approved alternatives, to reduce or eliminate the need for hospitalization, improve patient quality of life, facilitate patients' ability to manage their own care (such as through self-directed personal assistance), or establish long-term clinical efficiencies
  - Availability is in the best interest of patients

- Orchestration by FDA/CDRH's Payer Communication Task Force between device developers and payers (CMS through parallel review and pre-submission meetings and Private Payers through pre-submission communications)to develop voluntary processes that facilitate earlier interactions with Payers about evidence needed to support coverage and reimbursement in the design of the FDA required clinical trials.

Comment: It was clear to participants at the Summit that the FDA continues to seek opportunities to constructively engage with industry and others in its attempts to encourage innovation while maintaining its (appropriately) demanding focus on safety and efficacy. Furthermore, FDA recognizes the importance of orchestrating evidence for regulatory purposes and for coverage through its parallel review and other interfaces with payers. Paradoxically, the expedited passage for health tech companies to receive regulatory approval through this welcome collaborative and helpful approach by FDA will compound the difficulties with subsequent approval by payers and health systems unless there is a well-orchestrated pre-market approach to evidence development that de-risks this scenario.

- CE Mark/ Medical Device Regulation (MDR)

Paul Brooks presented his understanding of MDR which will be implemented and come in force in May 2020. Carl Moons presented on the Netherlands health system adjustment required to fulfill some of the MDR recommendations in another session. What follows is based on both presentations in addition to input by Yves Verboven.

Medical device directives have been in place at CE Mark since the early '90's and are being replaced by more demanding regulations through the MDR. Many questions on implementation remain unanswered today and is work in progress. there will be no grandfathering meaning that existing approved technologies (CE Marked under the current directives) will need to be re-certified having a transition period till 2024 (subject to no significant changes during the interim period).

At a high level it appears that the process of assessment of classification, conformity assessment, safety and performance requirements, CE marking and post surveillance is similar to the previous medical device directive. But has become more stringent (prescriptive), notably with requirements on performance and effectiveness of IIb and III types of devices and with

increased transparency and control mechanisms. It should be noted that re-certification following a certain number of years is still required.

Under MDR, manufacturers conduct the clinical investigation for the purpose of establishing safety and verification of what the technology is designed to do (intended purpose) within the defined population and the clinical benefit claimed. For selected new Class III, IIb implants and some drug delivery technologies and some drug delivery technologies, an independent EC expert panel will have the option to review the clinical evaluation and provide an advice on the appropriateness to the Notified Body. As with all clinical evaluations this will include consideration of currently available alternative treatment options for that purpose, if any.

Class III, IIb and implantable devices may claim equivalency based on another similar MDR-approved device provided by the manufacturer if the latter is prepared to share data, which is probably unlikely, unless being continuous innovation by the original manufacturer. Annual post market clinical follow up (PMCF) is required for all Class III and implantable devices, designed and reported on by the manufacturer. In addition, a post market surveillance system proportionate to the risk of the device and a periodic safety update report are required to include PMCF, volume of sales, population of users, and frequency of use.

While tightening regulatory requirements is an important objective, there are implementation issues that are of concern. There is uncertainty, ambiguity, lack of guidance and changing requirements in addition to the following concerns regarding implementation of MDR:

- Effects of Brexit
- Slow pace of progress in formulating necessary implementing acts
- Slow pace of certification of notified bodies, with just over one year left before the MDR deadline, only 1 notified body has been certified
- Lack of notified body capacity – it does not appear that the reduced number of notified bodies that will be able to conduct all of the necessary (and increased complexity and number) reviews in advance of the deadlines
- Managing economic operators – contract revisions
- Designation of notified bodies which will be strictly controlled and certified
- Notified bodies being restricted in sharing expectations (until designation) and best practice (clinical strategy services) with Class IIa, IIb and III required to provide sufficient evidence assessed by independent panels for Class IIb and III. There is ambiguity regarding these evidence requirements
- Legacy devices (particularly clinical evidence) will need to re-certify; estimated by some authorities to be approximately 500,000 devices that will be required to be ‘re-CE Marked’. Concerns regarding lack of grandfathering existing compliant devices were raised by Summit attendees
- Understanding the Competent Authorities for Medical Devices roadmap and arrival times
- Regulation extension – business decisions made now cannot easily be reversed
- Impact on registrations elsewhere

- Clinical evidence – there is lack of consistent understanding of 'sufficient' & 'equivalent' – how much data is enough?
- What evidence or type of studies suffice for which types of devices?
- 'Combination' devices
- Lots of uncertainty, ambiguity, lack of guidance, changing requirements, and expectations

The effect of uncertainty and current lack of engagement with companies seeking CE Mark under the current legislative MDD, AIMD is putting at risk bringing products to market which in turn could result in financial pressures for SME.

If more research is required to meet increased expectations of CE Mark, premarket studies that address expectations of payers at the same time will be highly attractive. Both are likely to become more client/patient need-focused than technology need-focused.

A technology insert card will be expected and this will include risk/benefit information, which will require more evidence, as exemplified by the Hii Holland-EXCITE model. Furthermore, medical technologies will be tracked through the European Database for Medical Devices (EUDAMED) which is an important part of Europe's new MDR regulations. EUDAMED is a database that will be used to monitor the safety, performance and effectiveness of devices under the Medical Devices Regulation (MDR 2017/745) and the In Vitro Diagnostic Medical Devices Regulation (IVDR 2017/746). Its constituent parts include an E-system for registration of devices using a unique device identifier, registration of manufacturers, databases, notified bodies and issued certificates, past and ongoing clinical investigations, a summary of safety and performance and post-market surveillance. This will place a demand on each EU member country which The Netherlands has responded to through mandatory registration of all implanted devices.

2. Hub Development

Hubs have been established in all EXCITE International member countries; all differ in construct and are completely independent. Each represents locally established processes, programs, organizations and governance. Membership with EXCITE International provides an international portal for jurisdictional initiatives and an opportunity to influence the ongoing development of EXCITE International through involvement in key committees and participation in all offerings including Early Technology Review, Protocol development and participation in clinical trials.

Each Hub is a neutral space that allows for a single-entry point for industry and represents an opportunity to collaborate with regulators, payers, health systems, patients, and clinical trialists in order to navigate the complex pathways to adoption. They provide an opportunity to drive innovation and for multifaceted input into the innovation pipeline, in addition to providing an interface with EXCITE International as active participants. In this context, these interfaces with industry allows for pre-selection of potentially relevant/impactful technologies while also providing feedback to industry. The resource implications of running a Hub should be covered

by existing funding provided by each jurisdiction in addition to opportunities for engaging with EXCITE International through finder fees, overhead applied to cost per case funding for clinical trials and a share in any downstream excesses based on willingness to pay a membership fee.

The Hub is a pull model and is designed to expedite access by patients to evaluate impactful technologies. While final EXCITE International products are designed to inform jurisdictional decision makers on adoption, there can be no guarantee regarding final adoption since these decisions are the sole responsibility of each payer/health system. EXCITE International works with its Hubs to optimize chances of successful coverage/adoption but cannot guarantee this.

The Hub development parallel session demonstrated how these jurisdictional initiatives can learn from each other and a recommendation was made that they should meet by teleconference on a regular basis to update experiences. What appears below is a composite of what was presented and discussed during the Summit parallel closed session and the open session.

External sources have been identified by each Hub. EXCITE International might be of some assistance through administration overhead built into cost per case funding for clinical trials, finder fees for access to its offerings and a share in any future excess funding following front-ended investment into EXCITE International as has occurred in the case of MaRS EXCITE and the Netherlands.

There was agreement that implementation was essential to adoption but the meeting was cautioned regarding the complexity of this process according to principles of implementation science. It is unlikely that implementation guidelines will be of interest to EXCITE International at present as it has a policy of not interfering with jurisdictional approaches to adoption and diffusion while still providing evidence to help inform these decision-making processes. However, an EXCITE International approach to promulgating a generic approach to implementation science might be considered if member countries would find this useful. The Hub decision to become involved in implementation is a local preference in partnership with payers and health systems, as is occurring with MaRS EXCITE (see below).

It was suggested that Hubs declare a common interest and end-goals regarding their local and international connections through EXCITE International.

The status of each Hub is presented below:

i. Netherlands

a) Platform

Hii Holland, recently announced, aligns closely to an EXCITE Platform. It is a fit for device (innovation) approach to the complex pathway to adoption for medical (non-drug) innovations

, orchestrating the pathway of the evaluation (evidence collection) of the specific innovation, in such a way that it satisfies expectations of Users (eg. Healthcare providers and patients), Regulators and Payers at the front end.

Hii Holland has been funded by the Dutch Government, in association with four academic centers, including Radboud umc which was the original Netherlands connection for EXCITE International, UMC Utrecht (Carl Moons), UMC Groningen (Erik Buskens) and UMC Maastricht (Manuela Joore). Maroeska Rovers and Carl Moons are the assigned "ambassadors" for Hii Holland. Consultants have been hired to develop the organizational and governance infrastructure and processes that will drive this important initiative. It is also likely that government and agency funding for healthcare innovation and corresponding research will be re-channelled through Hii Holland once it is up and running – expected to occur in the fall of 2019. Hii Holland will use EXCITE International as its international portal and is expected to play a significant role in the further development of EXCITE International through a close partnership that continues to evolve.

Hii Holland represents an important opportunity for other Hubs to learn from the linkage of innovation funds to the platform, academic leadership and strong government support.

It was suggested that the Hii Holland model be used as an example and as a suggested way for other Hubs to leverage their resources as part of their developmental process.

b) Functional Considerations

Carl Moons presented on the interface between MDR (CE Mark) and health systems in Europe and some of this is reflected in the section dealing with European Regulation. The Netherlands is preparing for implementation of MDR since CE Mark will expect more evidence of effectiveness and performance and annual or biennial re-certification. This means that the performance of health tech will need to be closely monitored through EUDOMED (See section under European Regulation). The Netherlands is preparing for this by mandating that each implantable medical device be followed on a registry which went into effect in January 2019. This will allow long-term complications and real-world performance to be monitored by tracking safety in recipients in addition to estimating the impact of complications at a healthcare level. This data will be linked to other patient outcomes data sets, such as EHR.

ii. MaRS EXCITE

a) Platform

MaRS EXCITE is a Canadian hub which has been in existence since the inception of the EXCITE model. This pre-adoption partnership was formed in November 2011 between government, HQO/OHTAC, the health system, regulators, academia, clinicians and industry, allowing for early selection by the health system and protocol design by all. It was the first attempt in Canada to

meet regulator and coverage expectations through a single premarket approach and was set up as a collaboration between eight methodology centers working with 24 research hospitals in Ontario.

MaRS EXCITE operates within a large incubator/accelerator MaRS program that it is able to feed off in capturing impactful technologies coming down this pipeline.

b) Functional Considerations

There has been an increasing emphasis on post-market barriers to access studies for industry and implementation of new health technologies, in addition to premarket collaborative approaches to evidence development. These two additional offerings consist of contextual evidence development and implementation navigation through an analysis of opportunities and identification of barriers to access, resulting in a proposed pathway to uptake and diffusion.

The use of barriers to adoption analysis by MaRS EXCITE has been useful to companies whose products have not been adopted despite a convincing high-quality evidence base of improving patient outcomes or health systems efficiencies and/or satisfactory diffusion in other jurisdictions.

The use of anecdotal evidence based on patient experience to drive adoption was presented as a useful tool. While unlikely to be of relevance in the U.S. market, other member countries might wish to consider this approach.

Examples of companies that have engaged with MaRS EXCITE were presented. Eighty percent of companies engaging in this program are SMEs with $10.2 million of contracts executed with industry.

Advice to other Hubs included:
- Make sure companies understand the perspectives of professional associations and other jurisdictions before undertaking an evaluation at a local level
- MaRS EXCITE is available to discuss Hub development with other jurisdictions, given the extent of their experience in developing a successful model

iii. Norway (Kathrine Myhre, Per Olav Vandvik and Stig Slørdahl)

a) Platform

The Norwegian Hub has developed around the successful incubator-accelerator – Norway Health Tech - which has championed and led a strong innovation ecosystem. This has included interactions between academia, industry, Innovation Norway and the Government. The involvement of Government continues to develop and made it possible to welcome the involvement of Stig Slørdahl.

One unique approach by Norway Health Tech is to work with other Hubs and non-EXCITE countries such as MaRS EXCITE and Singapore. This is especially advantageous in broadening test sites at the proof of concept phase of development with the caveat of ensuring that lessons learned in (ii) above are considered.

The Norwegian Hub continues to develop and now includes involvement by government. It was noted that a champion in government as is the case with Hii Holland and MaRS EXCITE, is the quickest way to successful and meaningful platform development. A full-time person responsible for developing and running an EXCITE-like platform and interacting with EXCITE International is being considered.

At a health systems level, Norway is part of a Nordic collaboration of health systems *Nordic Proof,* which includes a clinical trials network aligned to EXCITE International.

Shortly after the Summit ended, the Norwegian government published a white paper in which it supported an investment in health tech innovation. It is hoped that this will result in the formation of a Norwegian platform with which EXCITE International will develop an interface.

b) Functional Considerations

Evidence-based guidelines based on the GRADE hierarchy of evidence, followed by decision aids, adaptation, integration into the EHR and revisions based on new evidence is being introduced through the MAGIC process. This assumes adoption by decision makers based on evidence. Underpinning decisions based on cost-effective thresholds has been used by many European countries mainly for medicines.

In this process, the desired maximum timeline set is 45 days for completion of systematic review and 90 days for issuance of guidelines as per the BMJ rapid recommendations.

It is envisaged that the loop from evidence generation to guidance development, and implementation monitoring through EHR will become operational in the winter of 2019.

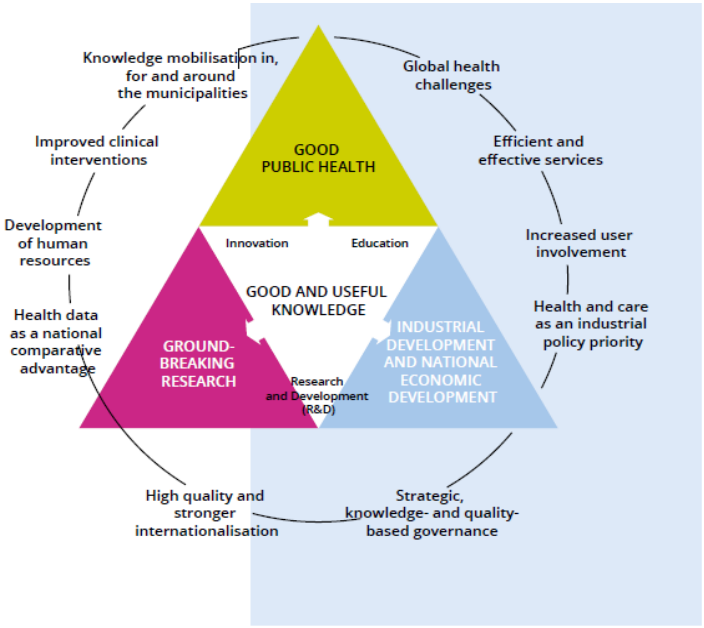
Comment: this evidence-based approach to adoption characterises most health systems in EXCITE International member countries, though MAGIC is a more integrated holistic approach with the potential to track patient outcomes based on EHR. This approach is also a reminder that premarket engagement by EXCITE International, FDA and NICE will take time to introduce and post-market approaches will continue for a while. High-quality patient outcomes data could be of benefit to the evaluation of new technologies in the future.

Norway accepts health technology as an asset to improve patient outcomes, reduce patient harm and reduce waste but insists that evidence show that the technology is a value-add based

on HTA and comparative effectiveness. National initiatives to support the adoption of impactful health technologies in specialist health care include:

- assessments of added therapeutic value
- a coordinated decision body
- procurement
- implementation of decisions based on relevant national guidelines

The adoption pathway for new health technologies is based on HTA and priority setting (policy). The emphasis on a quality health system and its inter-relationships with other national priorities in research and industry was presented in the diagram below:



While the current emphasis from a policy perspective are at the early pre-launch phase, in the future more emphasis will need to be placed on pre- and post- market phases such as identifying unmet patient needs, tracking outcomes and understanding values in clinical practise.

iv. U.K. (Nina Pinwill (NHS), Pall Jonsson (NICE)

a) Platform

There have been promising developments in the U.K. based on the Accelerated Access report which gave rise to an Accelerated Access Partnership for which NICE has a secretariat role. The intent is to facilitate the adoption of U.K. technologies by the NHS. This is considered by EXCITE

International as a potential point of intersection with the U.K. The key components of a loose platform in the U.K. consists of NHS, NICE, NIHR and the Association of British Health Tech Industries, all of which are represented on the EXCITE International Payers' Advisory Committee, Advisory Council, International Scientific Collaboration, and the Industry Advisory Committee.

b) Functional considerations

There are three key U.K. initiatives, established to promote adoption of impactful health technologies:

- Accelerated Access Partnership
  Aims to get transformative technologies to patients and health system quicker, cheaper and easier for innovators and the NHS through horizon scanning, generating real-world data and clinical trials, negotiating price flexibility earlier and supporting adoption and diffusion through Academic Health System Networks and the Pathway Transformation fund. Twelve adopted technologies that are not diffusing well to optimize patient outcomes were selected in 2018 for consideration under this program
- NICE Office for Market Advice
  Explores the broad and focused ecosystems relevant to the technology, the most appropriate pathway into the health system and the value proposition
- NICE Scientific Advice
  Reviews the company's clinical, evidence and economic plans premarket to recommend an approach that aligns with NICE's expectations, cost-effective analysis and health system and patient perspectives

There is a continuum from evidence development by NICE to adoption by the NHS. An example of the adoption of a complex new technology, CAR T-Cell therapy was presented to demonstrate how this continuum from evidence development to implementation works:

- This therapy consists of genetically modified T (immune) cells to attack tumour cells with recognizable unique antigens. CAR T-Cell therapy was approved by NICE for refractory B-cell lymphoma and for refractory B-cell lymphoblastic leukemia in 3-25-year-old patients
- There was residual uncertainty regarding comparator studies, lack of maturity of clinical evidence, precision around curative effects and prolongation of life, costs of side effects and generalisability. Furthermore, clinical studies were single arm with short-term evidence
- For these reasons, based on the NICE recommendation, the NHS opted for evidence generation through managed entry to make the technology available under controlled conditions. This therapy is now available for the described indications in nine centers across England
- Implementation of this complex treatment was overseen by NHS working with the Joint Accreditation Committee and Companies to ensure hospitals were prepared to deliver the treatment and that providers adhered to safety and quality standards. While capacity and

increasing access may not be at desired levels initially a National CAR T-Cell therapy Clinical Panel has been set up to prioritise access

- In summary, this example of coverage with evidence development shows how the process needs to be established through establishing standards, working with key partners, managing demand and capacity and developing processes to collect evidence for more definitive decision making

Additional note, based on the CAR T-Cell therapy experience there are over 850 trials of gene and cell therapies currently underway worldwide covering a wide range of clinical indications, half of which are cancer-related. These are likely to be disruptive and will require thoughtful approaches such as those applied to CART T-Cell therapy.

v. U.S.A

a) Platform

While the U.S. is the largest health tech market and at first pass appears to be the most complex, the pivotal role of payers and health systems in adoption through defined policy processes makes it easier to understand the adoption process. The U.S. has 6-7 very large health systems or funding agencies, all of which are underpinned by evidence linked to direct funding which can be adjusted to facilitate adoption or withdrawal of health technologies based on performance.

Given the above considerations there is no single U.S. EXITE International Hub, though discussions are underway to secure a central focus through an existing organization with existing relationships with a disparate group of health systems and funders.

b) Functional Considerations (Tamara Syrek-Jensen)

CMS is one of the largest healthcare payers in the world. There are two coverage options open to med tech companies, through national (CMS) and local determinations. There are 10 groups that provide access to local determinations, though none of these undertake CEDs. Companies may choose which of these processes to follow depending on their commercialization strategy.

Coverage decisions through national determination used to have high response rates due to uncertainty regarding effectiveness. To overcome this, coverage with evidence development (CED) was introduced and is being used increasingly. CED allows for the conditional adoption of technologies for which there is some uncertainty in evidence. It is offered through national, not local determinations. It was pointed out that CED is an admission of failure by companies to meet expectations of payers based on inadequate evidence development, often designed to satisfy regulatory purposes but not relevant to coverage decision making.

3. Payers Advisory Committee (PAC) (Closed Parallel Session)

The PAC met separately prior to a joint meeting with the Industry Advisory Committee to go through a hypothetical case study and to discuss ways in which the PAC might consider appropriate outcomes that are unique to their needs and expectations. The following overarching high-level observations relating to the case study specifically were made:

- It is important to establish who the target payer is for a particular technology. This may be confusing and merits discussion to ascertain whether the technology is to be deployed in a hospital, in the community or a specialized clinic
- The ecosystem in which the technology will be used needs to be defined and driven by, for example, an understanding of whether it is an adjunctive, additional, replacement or novel technology; the demonstrated value-add to patient outcomes and economic considerations currently required by many jurisdictions and increasing in others
- Single arm observational studies will not be seen as persuasive by payers
- It is important to focus on targeted populations such as diabetes or varicose ulcers
- A clear description of effectiveness needs to be established. For this reason, appropriate comparators from the PAC perspective need to be identified early on, probably at proof of concept studies. Therefore, comparative effectiveness studies are likely to be important to payers/health systems to inform decision-making
- Within the context of comparative effectiveness from the payer's perspective, a comparator of *usual care* sets a low evidence bar compared to *optimal care*
- This technology is seen as an adjunct to debridement which should be included in both arms of the study
- The setting of care should be standardized e.g. wound clinic versus community-based care. Human resource impacts should be included in study design
- In terms of outcomes, complete healing would be most useful from a payers' perspective. Durability of effect is important to track. The inclusion of patients with more than one ulcer may become a confounder if treated differently. Drop-out rates should be monitored
- Opportunities for cost shifting should be included in the study design
- Attention was made to the possible overstatement of effect of an innovation when examined in a specialized clinic

Comments: The PAC has produced a document which considers decision determinants at a high level. Despite the discrepant health systems represented on the PAC, it was possible to arrive at a common position. This was in itself an important first step to a consistent transparent approach to payer/health system decision making. The exercise described above posed a challenge to PAC members working to arrive at a broad-based approach providing their perspectives in protocol development for hypothetical technology. This 1.5 hour exercise was reassuring in the depth and breadth covered and the common purpose and experience of the group in setting out their expectations which would be included in the protocol. In the EXCITE International protocol development process approximately 9 hours is set aside for Panel members including PAC. The interplay among the multi-stakeholder Panel will be interesting

when this is attempted in September 2019. This dynamic interaction has already been shown to be constructive and informative for Early Technology Reviews completed to date.

4. **Industry Advisory Committee (IAC) (Open and closed Sessions)**

There is an obligation by industry to exercise due diligence in securing a robust evidence base. Examples of an early supposed effect for renal denervation and laser angiogenesis subsequently demonstrated that more careful attention to elimination of bias, and Hawthorne and placebo effects added greater precision resulting in a re-evaluation of effectiveness. Validation can be achieved through larger sample sizes to examine subset effects, using double blinding, and sham controls as appropriate. Longer term effects, both positive and negative, should be examined possibly post-market.

While there is increasing clarity of requirements of industry to satisfy regulatory expectations by FDA, this is not the case for payers and health systems. In fact, the presence of multiple hurdles to adoption and unpredictable results makes it difficult for industry to negotiate the pathway. A more transparent and consistent approach to coverage/adoption was urged by the Industry Advisory Committee. The easier it gets for companies to satisfy regulatory requirements, the more companies will face the disappointment of failing to satisfy coverage decisions unless these two processes can be aligned more closely in the premarket space with greater transparency by payers/health systems. A playbook by payers/heath systems was recommended to fill existing gaps, these being:

- Defined prioritized endpoints through transparent processes
- How industry can work with payers/health systems to fill these gaps
- Define the criteria/role for end-users in coverage and reimbursement determinations

Industry understands at a high level what is required to satisfy requirements by decision makers but SMEs in particular lack the resources to undertake these complex studies. One approach recommended is to use the neutrality and multifaceted input through premarket approaches, such as the EXCITE International Early Technology Review to de-risk investments and in so-doing facilitate appropriate studies to improve the chances of successful adoption. An example of this approach was shared with Summit participants.

5. **Joint Meeting of IAC and PAC (Closed Parallel Session)**

This joint meeting was to discuss areas of mutual interest and made the following observations and recommendations:

- A dialogue is needed to examine the value stream for medical technologies. It is highly likely that most health systems will increasingly move away from fee-for-service models to alternative financing models. The rewarding of value was discussed which raised the question on the perspective taken when defining value. While the rewarding of value and

value driven agreements should be considered, metrics used to underpin value-based pricing requires further discussion. For example, the use of the QALY to define price levels will not be likely to be supported. Moreover, QALYs may apply to therapeutic devices, but not easily to non-therapeutic (e.g. diagnostic, prognostic, monitoring) devices.

- An understanding of payer trade-offs for technology as an overarching consideration and the uncertainty of the benefits for patients and , depending on the payer, economic consequences of the use of individual technologies for the population covered drives the need for comparative effectiveness or performance studies. This is especially relevant for therapeutic technologies which require additional funding and reimbursement that cannot be covered within the existing system.
- The need for full examination of the downstream effects of a technology – either therapeutic or non-therapeutic - from the perspectives of patients, citizens, industry and health systems need to be examined. The example provided was a closed-loop system of insulin delivery in type 1 diabetes; does the incremental cost result in better glycemic control than multiple daily injections (MDI) and if not, what are the additional benefits to the patient such as reduced hypoglycemic events, quality of life, and adherence to treatment regimen within the specific population covered?
- A stepwise approach of addressing initial access and partnerships demonstrating the full value was positively received. This, in addition to building in a phase of intermediate financing schemes while addressing uncertainties, given the complexities of unraveling the desired effects of a new technology. More attention needs to be paid to schemes like coverage with evidence development (CED) models to accommodate these changes.
- In the U.S., the current funding model of transferring payment for treatment to Medicare after age 65 could affect funding for treatments further upstream. This could affect the costs of medical care later in life as there is no incentive to avoid paying for downstream consequences. However, uncertainty of the value within the population currently covered is likely to be a more immediate issue to address.
- It was recommended that EXCITE International should hold open international forums to explore concerns of mutual interest to multiple stakeholders and that these proceedings should be published and used to influence appropriate changes.

6. Patient Engagement (Open Session)

There is a pressing need to recognize the increasing role patients should play in the development and evaluation of new health technologies. This is emphasized as an important requirement by FDA through attention to patient preferences and reflected in initiatives such as the MDIC patient centered risk benefit project. In addition, patients need to be inserted in the pathway from innovation to adoption at the discovery and ideation phase through articulation of patient informed needs, in clinical trial design and in particular in the identification of appropriate outcomes, in the determination of the balance between acceptable risks and benefits to patients across the full life cycle and in monitoring patient centered outcomes post-market.

It is important to engage with patients as part of the iterative process of development and evaluation and not at the end of this process. This approach is seen as beneficial to the speed and ease of product development, evaluation and launch.

Trade-offs by patients in terms of accepting uncertainty and adverse events depend on where in the stage of disease the technology is being used, in addition to the intent to control adverse effects of the disease or to cure. For example, uncertainty and risk of complications might be more tolerable if there is intent to cure than at end of life. Patient urgency, the need for new therapeutic options and tolerance of uncertainty could impact design and sample size for clinical trials. This has been demonstrated for Parkinson's disease in which patient engagement may drive product development and expedite adoption for sub-populations.

The involvement of patients in all EXCITE International offerings was emphasized and is viewed as essential by the organization. The challenge will be how to include patients across the broad spectrum of medical technologies in a meaningful way and on a continuous basis. A preliminary recommendation is to consider having expert patient representatives on all EXCITE International committees to ensure that their perspectives are considered at all levels. Other considerations will be the development of a core group of experts to drive this process and explore the most useful and meaningful way of soliciting patient input according to the technology being considered.

7. **Scientific Collaboration (SC) (Open and Closed Sessions)**

The Scientific Collaboration is responsible for providing the methodological base that allows multiple stakeholder expectations to be reflected in EXCITE International offerings. These stakeholders include payers, regulators, expert end-users, industry and patients. The SC also has a focus on methodological considerations that expedite the pathway from innovation to adoption. It provides the scientific basis for Early Technology Review, advice on proof of concept trials and protocol development for pivotal clinical trials. Further information on these EXCITE International offerings can be found on its website at www.exciteinternational.com.

It was emphasized that different methodological approaches are required for different technologies and end-points and that adaptive design across the continuum from proof of concept to post-market surveillance should be considered. Where post-market surveillance is considered as part of evidence development, this should be decided at the beginning of the evidence development strategy in conjunction with payers/health systems. These different approaches are usually driven by whether the technology is high or low risk in addition to the nature of the technology, such as whether it is characterized by being diagnostic, digital, biotechnology or device. Furthermore, the IDEAL framework (see below) should be considered especially for high risk technologies between the proof of concept and pivotal stages.

The role of the Scientific Collaboration was discussed with a focus on whether it serves to inform decision makers or to help companies bring their product to market. These may not be

discrete considerations if the intent is to accelerate the adoption of impactful technologies that improve patient outcomes and/or health system efficiencies in which case, both objectives are important.

A number of key presentations were invited by the Scientific Collaboration as being topical and a focus for further consideration. See slide decks at www.exciteinternational.com.

- The need for consistency in outcome measures needs to be addressed and EXCITE International could play an role in this regard. Elise Berliner provided examples:

- Different criteria used in multiple trials to assess depression as the basis for measuring responses to repetitive transcranial magnetic stimulation making it impossible to compare studies undertaken for this treatment of drug-resistant depression. This was presented as a concern given the high prevalence of depression with one in eight people over the age of 12 years taking anti-depressants in the U.S. as reported in 2012 by CDC
- 74 outcome measures reported in 11 studies for retinal prosthesis and failure to measure the effect in Medicare patients with ultra-low verses low vision

- An iterative approach to the early development of new medical devices was presented according to IDEAL guidance. This is important as there are no other clear methodological pathways for the development of medical devices. Furthermore, there is no process for advancing a device from conceptual to proof of concept stage and to the point where it is sufficiently developed for a pivotal clinical trial. This includes detailed technical details, criteria for patient selection, an accounting of all patients studied consecutively and a description of all modifications and reasons for these. This also should assess values and preferences by patients and clinicians.

  Stages of the IDEAL process appearing in the table below (McCulloch) require small sample sizes, should be quick to complete and can be regarded as an approach to proof of concept.

IDEA (Stage 1)	DEVELOPMENT (2A)	EXPLORATION (2B)	ASSESSMENT (3)	LONG TERM STUDY (4)
Initial report	"Tinkering" (rapid iterative modification)	Technique now more stable	Gaining wide acceptance	Monitoring late and rare problems, changes in use & quality of surgical performance
Innovation may be planned, accidental or forced	Small experience from one centre	Replication by others	Considered as possible replacement for current treatment	
Focus on explanation and description	Focus on technical details and feasibility	Focus on adverse effects and potential benefits	Comparison against current best practice (RCT if possible)	
		Learning curves important		
		Definition and quality parameters developed		

- eHTA (Presenter Maroeska Rovers)

Approximately 80% of innovations fail to reach commercialization and of those that succeed, 70% fail to establish themselves post-market. Early HTA should become an essential part of the tool kit available to innovators to better inform them and de-risk the pathway to successful adoption.

Early HTA, defined as: *Methods to inform industry and other stakeholders re- potential value of medical products in development, including methods to quantify and manage uncertainty (IJzerman et al, 2017),* aims to provide insight in the potential value of an innovation in its intended context.

The eHTA/decision analysis process involves an examination of existing pathways, evidence analysis, assumptions derived from multiple sources, and weighing advantages, risks and costs. The aim is to provide:

- Insight in the size and uncertainty of the potential cost-effectiveness
- Inform how the innovation could be further developed or should be positioned to maximize its value for money
- Steer further research, with specific recommendations made for endpoints, types of studies and target populations

EXCITE International includes eHTA/decision analysis in all its offerings (Early Technology Review, protocol development and clinical trial analysis,) recognizing that the precision in determining downstream effects of the technology increases with the development of data from proof of concept and pivotal trials. The information is considered an essential part of the

evidence base that informs companies in benchmarking their technology and determining their strategic direction in addition to informing payers and health systems in their decision-making on adoption.

- Use of real time patient outcomes data (Dr. Jeff Popma)

New devices that result in change in clinical practice require large scale clinical trials with "hard" clinical endpoints. However, device iteration, indication expansion, accessory devices, and post-market studies may require less rigorous endpoints including device success, surrogate endpoints (e.g. reduction in mitral regurgitation), or leverage of "real world" clinical data.

Real world data from existing data sources like CMS, TVT registry, claims based data, MD EpiNet, NEST, OHDSI and PCORNet demonstrate close alignment between data collected from established data sources such as with clinical endpoints for transcatheter aortic TAVR and mitral valve replacement. These approaches may be of special relevance to indicate expansion regarding the use of TAVR in lower risk populations, building on results from high risk patients established through large pivotal studies with hard end points.

The NEST project is an important attempt to explore the utility and accuracy of using patient outcomes and a submission has been made by the Baim Clinical Research Institute to explore this by using multiple existing data sets for outcomes of death and stroke in addition to other outcomes such as cognitive impairment following TAVR. Through this approach, it is hoped that relevant prospectively collected data contextualised for relevance by payers through EXCITE International's Payers Advisory Committee.

8. Innovation to Adoption – the Consortia for Improving Medicine through Innovation and Technology (CIMIT) Model: An example of driving innovation towards commercialization

CIMIT was started in 1998 through an academic collaboration centered around Harvard and its associated teaching hospital and has expanded to include other partners including NHS and Oxford University. Its premise is that innovators are not well positioned to move their technologies to commercialization. They are often not prepared for multiple steps and barriers and don't have the band width of expertise and capabilities to move along the pathway.

Its aims are to accelerate the healthcare innovation cycle by facilitating collaboration among clinicians, technologists, entrepreneurs and companies to create novel health tech products, services and enabled procedures.

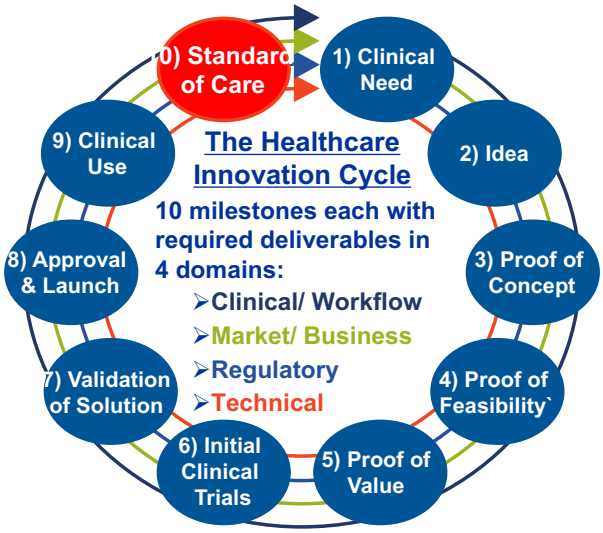
A CIMIT approach was developed, following an examination of over 600 projects for statistical correlates of success and failure as the basis for hypotheses to test and share. Publicly funded research is least likely to become commercially viable, whereas privately funded innovation to

meet an existing need are most likely to do so. Facilitation along the way with experts improves the commercialization rate. A diagram summarizing the CIMIT approach appears below:

Codifying Experience: **Prevent "unforced errors" and de-risk by proceeding in 4 key domains in sequence.**

Key Concepts

1. Keep a focus on the Standard of Care
2. Follow a sequence of milestones
3. Synchronize work by completing deliverables at each milestone in four key domains
4. Start anywhere, but backfill to manage risk
5. Use best practices to complete each required deliverable



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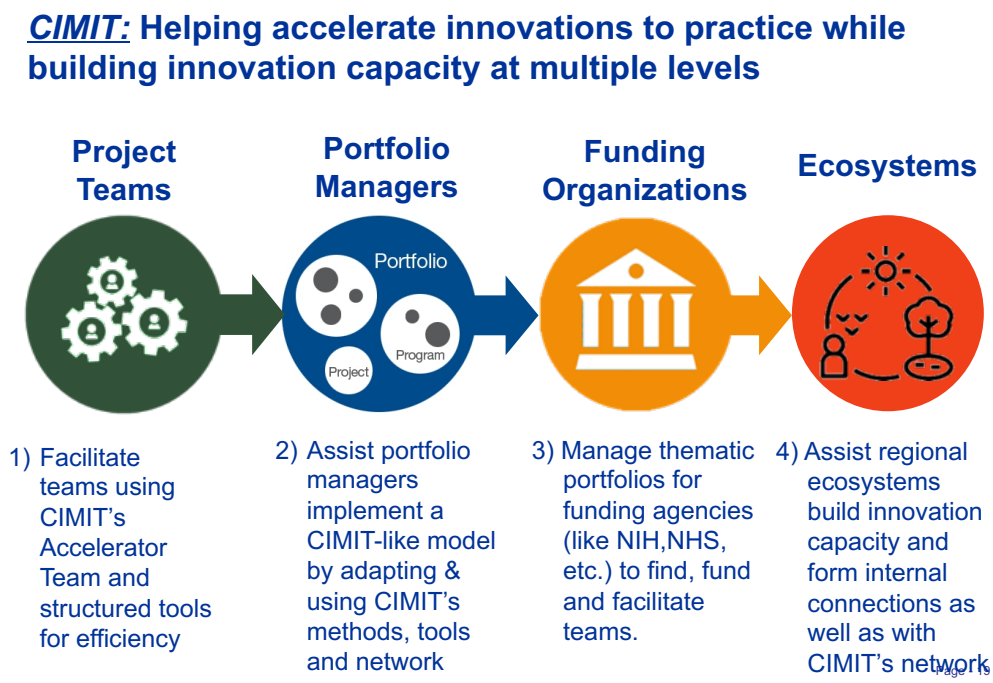
A diagrammatic description of the CIMIT process presented by John Collins appears below:



Comment: Incubators and accelerators continue to be important catalysts in the development of new health technologies and CIMIT is an excellent example of this. They are most effective at the front end of technology development and the CIMIT approach is a reminder of the need to identify elements that are most likely to translate into successful commercialization. There is a need for the back end of this model to take off where accelerators end in terms of moving to adoption by engaging regulators and payers/health systems, patients, and clinical trial methodologists in multi-faceted protocol development as is occurring with FDA, NICE, CADTH and EXCITE International.