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ADAPTIVE APPROACHES TO LICENSING, HEALTH TECHNOLOGY ASSESSMENT, AND INTRODUCTION OF DRUGS AND DEVICES

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Background: Adaptive approaches to the introduction of drugs and medical devices involve the use of an evolving evidence base rather than conventional single-point-in-time evaluations as a proposed means to promote patient access to innovation, reduce clinical uncertainty, ensure effectiveness, and improve the health technology development process.
Methods: This report summarizes a Health Technology Assessment International (HTAi) Policy Forum discussion, drawing on presentations from invited experts, discussions among attendees about real-world case examples, and background paper.
Results: For adaptive approaches to be understood, accepted, and implemented, the Forum identified several key issues that must be addressed. These include the need to define the goals of and to set priorities for adaptive approaches; to examine evidence collection approaches; to clarify the roles and responsibilities of stakeholders; to understand the implications of adaptive approaches on current legal and ethical standards; to determine costs of such approaches and how they will be met; and to identify differences in applying adaptive approaches to drugs versus medical devices. The Forum also explored the different implications of adaptive approaches for various stakeholders, including patients, regulators, HTA/coverage bodies, health systems, clinicians, and industry.
Conclusions: A key outcome of the meeting was a clearer understanding of the opportunities and challenges adaptive approaches present. Furthermore, the Forum brought to light the critical importance of recognizing and including a full range of stakeholders as contributors to a shared decision-making model implicit in adaptive pathways in future discussions on, and implementation of, adaptive approaches.

Keywords: Insurance, coverage*, Drug Approval/legislation and jurisprudence*, Drug approval/methods*, Licensure/legislation & jurisprudence*, Adaptive approaches

New approaches to the regulatory approval of drugs[1] and medical devices have been proposed that replace single decision points with periodic or staged assessment and re-assessment using an evolving evidence base. These proposals have been called "progressive" or "adaptive" approaches to licensing (8) and are specifically referred to by terms such as "staggered approval", "adaptive approval", "progressive licensing", and

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[1]The term "drug" is used in this paper to refer to new medicines that are either pharmaceutical or biopharmaceutical medical products.

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"progressive authorization" (8). The stated aims of these new approaches are to promote patient access to innovation, addressing clinical uncertainty, ensuring real-world effectiveness and improving the health technology development process (8).

Many of these approaches have been developed without input from health technology assessment (HTA) and coverage bodies (HTA/coverage bodies[2]) who are key players in managing the diffusion of drugs and medical devices. In parallel, HTA/coverage bodies have introduced adaptive approaches to reimbursement decision making using terms such as "coverage with evidence development, access with evidence development, and managed entry" (4). The aims of both adaptive licensing and reimbursement approaches to decision making overlap considerably, with adaptive reimbursement approaches additionally aiming to address uncertainty about cost-effectiveness.

While there are similarities between adaptive licensing and coverage approaches, there is also an increasing recognition that technology diffusion is guided by additional parties beyond HTA/coverage bodies and regulators including care providers and health system managers (collectively referred to in this study as the "health system"), as well as patients (10). The success of any adaptive approach will therefore require careful consideration of the interaction of these stakeholders and their roles in decision making.

The Health Technology Assessment International (HTAi) Policy Forum has on several occasions discussed adaptive approaches to decision making (15;16;23) along with the potential for aligning HTA evidence requirements with those of related decision-making processes, particularly licensing (14;20). Given an increasing interest in adaptive licensing and the need for multi-stakeholder input on this topic, the Policy Forum elected to discuss this topic in February 2014. The intent was to review recent developments and discuss generic solutions to adaptive decision making for drugs and medical devices. A principal focus of the discussion was the implication of adaptive licensing proposals for HTA/coverage bodies.

METHODS

HTAi is the international professional society for producers and users of HTA (18). The HTAi Policy Forum provides an opportunity for leaders and senior management of for-profit and not-for-profit organizations with strategic interests in HTA to meet with invited experts for in-depth discussions about issues of emerging interest (17). A detailed description of the Forum can be found elsewhere (17).

Development and Analysis of the Forum Discussion

Policy Forum members initially chose the topic of "adaptive licensing" early in 2013. Following a scoping discussion at a Forum meeting in June 2013, the topic was developed and a detailed meeting agenda and background paper were prepared by the HTAi Secretariat and Policy Forum Chair with input from Forum members and the Policy Forum Committee.

During development of the background paper, it was noted that others working in this field, such as the Massachusetts Institute of Technology (MIT) Center for Biomedical Innovation, had used case studies to promote informed and focused discussions (2;8). It was agreed that breakout groups in the Forum meeting should be asked to review case studies of specific drugs and devices that have already gone through existing routes for licensing, HTA, and coverage, and to consider the possible benefits and challenges that might be associated with a more adaptive approach. Table 1 provides a summary of the information presented to the Forum from one of the case studies. More information about the case studies, including the structure and process of discussion are contained in a Supplementary Appendix 1, which can be viewed online at http://dx.doi.org/10.1017/S0266462314000191.

The Policy Forum discussion of adaptive approaches to drug and medical device decision making took place on February 2–4, 2014. Invited experts included regulatory leaders from United States and Europe, a professional patient advocate, and others with top-level experience of the challenges of using data from various sources to make decisions on market access, coverage, and use of technologies. The agenda, background paper, case study exercise description, and individual case studies were circulated to attendees before the meeting, together with a study on adaptive licensing by Eichler et al. (8), who also contributed to discussions at the meeting.

This report presents the authors' views of the topic and meeting discussion. It has been informed by comments on drafts by those present, but it is not a consensus statement from the meeting, nor does it represent the views of any of those attending the meeting or the organizations that they work for. Attendees at the meeting are listed at the end of the report.

FINDINGS

Defining "Adaptive Approaches" to Drug and Device Decisions

The term "adaptive approach" does not have an agreed definition, and a range of views on what it might be taken to mean was evident throughout the discussion. The term "adaptive" has been commonly used to refer to alternative clinical trial designs (5), new regulatory licensing schemes (8), and the use of personalized medicine (11). A recent private-public sector initiative between the European Union and European Federation of Pharmaceutical Industries and Associations led to a proposed decision-making model that used the term "adaptive pathways," which incorporates each of these aspects of adaptation (21).

Another challenge with the definition is that there already exist mechanisms that might be perceived to be "adaptive." These include priority, supplementary, and conditional market

[2] By HTA/coverage bodies we mean, HTA bodies that work to advise those making decisions on coverage or payment and/or bodies making coverage decisions/payments based on HTA findings.

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Table 1. Illustrative Summary of Case Study Structure and Information Presented to Participants

Heading	European Union	United States
1. Indication	No regulations requiring indication	Edward Sapien Valve Indication
2. Pre-market Development	Description of PARTNER[a] trial	
3. Regulatory approval process (time from application to approval)	Medtronic Corevalve and Edwards Sapien in 2007. Other products from 2011 onwards	Edwards Sapien (Nov 1, 2010 - Nov 2, 2011); expanded indication (May 2, 2011 - Oct 19, 2012) and (Sep 23, 2013);
4. HTA and payer process (date)	e.g., UK guidance, Mar -2012	e.g., CMS May -2012
5. Real-world use	Germany responsible for 43% of all procedures followed by France	
6. Potential goals of an adaptive approach	*Broadening treatment eligible population* – different levels of risk as well as effectiveness in patients eligible for conventional surgery will need to be established. *Addressing AEs* – flagged by regulators and payers, were concerns about bleeds and strokes	

Note. For example, transcatheter aortic valve implantation/replacement (TAVI/TAVR).
[a]PARTNER = Placement of AoRTic TraNscathetER Valves trial.

approval mechanisms (3;6), HTA product listing agreements (4), pay for performance schemes (9), and iterative approaches to delivering care that rely on diagnostic information or response to therapy (28).

Adaptive licensing was formally defined as a "prospectively planned, flexible approach to regulation of drugs and biologics" with "iterative phases of data gathering and regulatory evaluation" (8). While no formal definitions exist for the broader concept of a more holistic *adaptive approach* to the introduction of new drugs and medical devices, it was defined for the Forum discussion as one that is: (i) flexible and prospectively planned within and between key decision makers, (ii) intended to reduce uncertainty progressively to inform ongoing decisions on appropriate patient access and care, (iii) intended to promote informed choices and improved outcomes and use of resources.

Issues and Solutions

After reflecting on presentations and completing the case study exercises, ensuing discussion highlighted several issues that need to be addressed if adaptive approaches are to be understood, accepted and successfully developed and implemented (Table 2). A general observation was that many issues are not unique to an adaptive versus traditional approach but may be exacerbated or become of greater importance if an adaptive approach is used. For example, adaptive approaches highlight the need for early engagement and dialogue about evidentiary and performance standards – although such dialogue is needed and exists today, the increased complexity of an adaptive approach suggests a need for additional planning and effort.

Some Forum members wondered what the specific problem was that adaptive approaches were seeking to address. Eichler et al. originally proposed the following goals for adaptive licensing: reducing uncertainty around surrogate end points; broadening the treatment-eligible population; reducing statistical uncertainty; enabling development of new drug with new drug new combinations; reducing uncertainty due to study designs; ensuring "real-world" effectiveness; and addressing rare adverse events (8). The implication is that current binary approaches to decision making are not as effective at achieving these goals. Much of the initial discussion at the Forum meeting focused on the single goal of progressively broadening treatment-eligible populations. Many of those present seemed to believe that this goal could already be addressed by existing mechanisms, and questioned whether truly novel approaches were required.

Solutions to issues identified generally focus on opportunities to improve coordination of key stakeholders to ensure prospective study protocols for specific products are adequately planned and organized, and on generic work needed to ensure that study designs, data capture systems and analytic methods are adequate to support decision making. Specific issues and proposed solutions are described in detail in the remainder of this section:

Defining the Goals of Adaptive Approaches. Any work toward further developing adaptive approaches to decision making that addresses health technology development, assessment, approval, and diffusion will require an explicit description of the overall goal. Given the discussion, a proposed goal of adaptive approaches on which it might be relatively easy to get agreement is that of improving patient outcomes by providing more appropriate patient access to promising technologies, through more coordinated approaches and building on existing processes in regulatory and coverage systems.

Setting Priorities for Applying Adaptive Approaches. Whether an adaptive approach involves new mechanisms or more coordinated application of existing mechanisms, there was agreement that not all drugs and devices may be amenable to an adaptive approach or there may be resource constraints on the number of technologies that can be managed in this way; therefore, there will be a need for a system for selection or priority setting. For example, some participants suggested adaptive

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Table 2. Description of Key Issues with Adaptive Approaches Identified by the Forum

Issue	Description of Issue
Defining the goals of adaptive approaches	Are there broader goals to having more coordinated approaches that are not met with existing mechanisms?
Setting priorities for applying adaptive approaches	Are adaptive approaches feasible for all drugs and medical devices or a particular subset of them?
Data: availability, interpretation, and reliability	Are decision-makers prepared or willing to rely more on observational data for evidence collection?
Roles and responsibilities of stakeholders	Is it possible to renew our current social contract—shifting current roles, obligations and responsibilities of patients, the public, clinicians, regulators, payers and industry in regards to drug and medical device diffusion?
Implications for current legal and ethical standards	Are we able to revisit and change the current overlapping legal and ethical responsibilities of industry, regulators, CBs, those conducting clinical research, and those providing care?
Costs of adaptive approaches how they will be met	How will costs shift or change with these approaches and will there be willingness to pay for additional costs?
Drugs versus devices	Will different models need to be adopted when approaching drugs versus medical devices due to existing differences in regulatory approval and coverage?

approaches might be best suited to therapies for rare and very rare disease with a known and predictable natural history where direct harms are not reasonably expected to outweigh benefits. Others suggested adaptive approaches might be better suited to situations of high regulatory or payer uncertainty or where payer and regulator uncertainty overlap. Another proposal was targeting those technologies with high costs of development and high unmet need to improve incentives for innovation in such situations. Some medical devices may be also be less amenable to these approaches as they do not represent significant patient risk and/or may not be directly intended to improve health outcomes, while others (e.g., innovative and potentially life-saving devices) could be more amenable.

Whatever the basis used, it was believed that some systematic approach to the application of adaptive approaches was needed because making decisions on a product-by-product basis for all new market entrants would be resource intensive and introduce further uncertainties for those developing technologies. Forum participants suggested that prioritization should involve upfront agreement among stakeholders building on existing mechanisms. For example, there are regulator-driven approaches that give new drug applicants opportunities to have an expedited review based on the need and disease burden associated with a new therapy (6). These mechanisms could be modified to additionally consider patient and HTA/coverage bodies' views on the potential for improving the quality and efficiency of care.

Data: Availability, Interpretation, and Reliability. Adaptive approaches link decision making to an evolving evidence base, parts of which are frequently seen as being derived from analyses of observational data gathered from sources such as electronic medical records, registries or administrative databases. Acceptance of such evidence is an important issue—regulatory authorities and payers are currently prepared to accept observational data to support manufacturers' efficacy/effectiveness claims only in limited circumstances (30). This probably reflects a range of factors, including differing views in the scientific community on the validity of using these data (7). Some of those at the meeting with the widest experience saw this as the biggest issue to be addressed if adaptive approaches are to be more widely accepted and implemented in practice.

Many believed a promising approach to evidence collection was to make better use of registries which have become increasingly important in HTA processes. For example, the Agenzia Italiana del Farmaco has conditionally reimbursed numerous drugs with the associated collection of real-world data through Web-based registries (31). Registries are also being increasingly designed and implemented through patient groups. Numerous cystic fibrosis (CF) registries have also been developed internationally to track disease burden, medication use and other key metrics associated with CF diagnosis and treatment (32). Registries such as these could play an important part in adaptive approaches based on linking patient characteristics with treatment outcomes.

Another issue is that observational studies may need to be very large to provide valid findings about treatment outcomes for decision making. This could require linked datasets and multinational studies. Even if there were agreement on what data sources are appropriate, available comparators and care pathways would be expected to be highly variable across jurisdictions creating challenges. This issue already exists in the clinical development of new medicines but could be more challenging if planning for an expanded range of studies through an adaptive approach. Nonetheless, where multiple registries exist, an approach similar to the U.S. FDA Sentinel initiative, which attempts to bring together existing data sources to increase analytic power, could be explored (34). Another approach would be to develop common templates for the development of registries across different jurisdictions.

Roles and Responsibilities of Stakeholders. Adaptive approaches require a "systems" approach to address the balance between the need for early patient access and evidence (36). A true whole system approach suggests a renewed

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social contract—a recognition that all parties are important contributors to shared decision making and that the goals and benefits of adaptive approaches require a shift in the roles, obligations and responsibilities of patients, the public, clinicians, regulators, HTA/coverage bodies, and industry, because each independently influences the diffusion of health technology and may unintentionally undermine the efforts of others.

Specifically:

- For *clinicians:* there may be a need to accept some degree of loss of freedom regarding choice of new drugs or devices, where regulators allow early access only for tightly defined indications, and introduce measures to curb off-label prescribing. Although there may be a case for changing regulatory legal frameworks for off-label use, clinical autonomy is still seen by many as key to patient-centered health care and driving innovation.
- For *patients:* there may be a need to understand and accept a greater degree of personal responsibility (in discussion with their clinician) for assessing the personal benefit/harm profile of a product, and in some cases also accept more restrictions on what clinicians may be able to prescribe for them.
- For *HTA/coverage bodies,* there would be a need to join discussions about clinical development programs for products being considered. There may also be a need for more upfront commitment and clarity about what aspects of value will be considered for reimbursement, and how data will be assessed.
- *Industry* may need to accept more binding requirements for delivery of downstream data agreed as a condition for early market access.
- The *public* will need to understand and support these changes as a better way of balancing the potential for benefit and harm from innovation.
- *Regulators* will need to work with all these groups.

Regulators and coverage bodies have also on occasion made decisions to restrict, delay or deny access of a previously approved technology to patients as a result of concerns or uncertainty about safety, relative effectiveness or cost-effectiveness. These decisions may become more frequent with an adaptive approach and this requires acceptance by all parties if these approaches are to be successful. There will be a need for heightened coordination between payers and regulators to ensure this works well.

The general view in the Forum meeting appeared to be that, at a minimum, further development of adaptive approaches requires stakeholders arriving at a shared understanding of their roles and responsibilities within such approaches, as a means of minimizing misunderstanding and promoting coherence. Even small changes in roles and responsibilities may not be easy. For example, HTA/coverage bodies may find upfront commitments (on how value will be assessed and rewarded) challenging if policies governing drug and device reimbursement change with political leadership. Industry will also have to be more prepared to say in advance what its development plans are and to comply with requirements to provide further data after being granted market access. Despite good agreement that more explicit prospective planning and agreement between regulators, HTA/coverage bodies and manufacturers is required, there was recognition that all parties might wish to maintain their right to change their views and plans as time passed.

Once this is achieved, there may be opportunities to build on existing systems to develop some of the key processes required for an adaptive approach. For example, the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) host hundreds of engagement and public consultations processes involving industry and occasionally other regulators to discuss evidentiary requirements, process issues, and quality assurance requirements. These discussions could in theory be expanded to include other stakeholders, such as HTA/coverage bodies, clinicians and patients, though there are concerns about the capacity of HTA/coverage bodies to join a significant number of discussions of this kind—emphasizing the need to focus adaptive approaches as discussed previously. The challenges of systematically introducing the concerns of HTA/coverage bodies into discussions of this kind and reconciling differences in evidentiary standards (e.g., efficacy versus effectiveness) have already been documented in existing work on "joint scientific advice" (33), and will be amplified if these approaches are applied to more technologies.

Implications for Current Ethical and Legal Standards. Earlier access to treatments with ongoing collection of evidence tied to regulatory, HTA/coverage body and health system needs may present issues for current ethical and legal standards related to provision of care and oversight of research. Granting early access to treatments offering promising but uncertain benefits may heighten perceived risk for patients, and satisfactory information sharing about clinical uncertainty needs to be communicated and informed patient consent obtained (27). The type of consent sought from patients currently depends on whether the treatment is considered as "research" or "routine use," and under an adaptive approach this boundary becomes blurred. As one Forum participant observed, this distinction might be seen by some to suggest that the regulator "assumes a measure of ethical responsibility for the welfare of study participants."

Adaptive approaches may also require an increased number of post-market studies to be conducted simultaneously and governed by decision rules that amplify current issues with patient recruitment. For example, post-market research already increases the need for adequate informed consent based on an acceptable level of exposure to risk (25). It may also amplify issues of jurisdictional differences regarding ethical standards. One Forum participant observed definitions of informed consent are based on "what would a reasonable patient want to know," determined by a jury of peers, in some jurisdictions, and "what do doctors usually do" in others.

The discussion revealed the need for payers and producers to work more closely with existing ethical governance mechanisms (jurisdictional ethics review and consent standards) to help re-define rules around the use of technology in treatment and research. It is not clear who could best facilitate this change. One option is to have the regulator, payer(s), patient

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association(s), or manufacturer spearhead the process. For example, the recently announced EMA-led European adaptive licensing pilot highlights the regulator's relationship with clinical, regulatory, ethics oversight and HTA communities as a catalyst for bringing parties together.

The current overlapping legal responsibilities of industry, regulators, payers, those conducting clinical research, and those providing care may also require reconsideration. For example, adaptive approaches challenge the notion of strict legal requirements regarding what public or private insurers must cover in benefit plans for patients (35). There may also need to be required shifts in legal responsibilities and arrangements for indemnity for non-negligent harm associated with technology. Ultimately, there may be a need to review who is legally responsible during different points in an adaptive pathway.

Changing roles may also require specific legislative mechanisms to align incentives. For example adaptive licensing could build on or use legal provisions in some jurisdictions that disallow public funding or adjust prices of health technology with the potential for significant opportunity cost (12;29). Laws such as these may regulate technology more effectively than relying simply on clinical practice guidelines or consumer choice and will require buy-in from patients and the health system. Whether these additional measures would be required may depend on each jurisdiction assessing the effectiveness of its existing mechanisms to manage health technology.

Despite these issues, Forum members believed at least some aspects of adaptive approaches could probably be made to work within existing legal frameworks if the issue above were addressed.

Costs of Adaptive Approaches How They Will be Met. Adaptive approaches have resource implications for regulators, payers, health care providers, public research funders and industry. For example, the need for more upstream planning will require further upfront investment by various parties and it remains to be seen if this will reduce or increase downstream costs or lead to improvements in efficiency or quality of care. In addition to these costs, there are larger questions of who pays for the data infrastructure required to support decisions. For example, electronic medical records are currently funded by health systems while proof-of-concept clinical trials are funded by industry. If there is to be an increased use of observational studies, how costs will be shared between different parties will have to be determined.

There are also costs related to paying for technology itself, which currently shifts from industry pre-market to coverage bodies post-market. How this two-stage model will be further adapted to multiple stages in widening indications will have to be determined. Simulation modeling provides a good way to explore the implications of adaptive pathways for drug development costs, pricing, revenue, health gain, and health system budget impact. This approach can help all parties understand the potential benefits and costs to patients, health systems and companies, and help companies understand whether and where upfront investment is justified. The MIT initiative is developing a simulation tool for adaptive decision making that could serve as the basis of a more robust cost analysis (1).

Beyond the decision to use or not use a health technology (or in what population to use it) are industry and coverage body decisions regarding the price charged and paid for the individual product. There was considerable discussion at the Forum meeting and a wide range of views about pricing in the context of an adaptive approach. Coverage bodies might want to see low initial prices if there is a wide degree of uncertainty about value, while industry may seek higher prices to provide adequate early revenue from a relatively small initial patient population. In theory, if prices reflect value, then prices should change as value becomes clearer, but several of those at the meeting questioned the feasibility of implementing "adaptive pricing" of this kind. For manufacturers, dynamic pricing may be difficult if price then varies widely and does not give producers a predictable revenue stream from which to calculate return on investment and inform research and development decisions (26). It may also heighten the need for confidential pricing agreements in an environment of international reference pricing (22). Many manufacturers are skeptical about the likelihood of coverage bodies agreeing to an increase in price if increased value is clearly demonstrated.

What is clear from this discussion is that adaptive approaches require some further thinking from coverage bodies and industry about price and that there is much to be explored here. Progress may depend upon a better mutual understanding of how prices should be determined (e.g., value-based pricing) and what is amenable to negotiation. A starting point could be to extend current mechanisms for conditional pricing and reimbursement to adaptive approach-based mechanisms.

Drugs versus Devices. Some of the basic issues raised by applying adaptive approaches to medical devices are similar to those for drugs, but there are also important differences relating to the nature of the technologies and differences in current regulatory and reimbursement pathways. Many drugs are already introduced using a staged approach—an initial indication for one population followed by additional indications and more often planned by product innovators—while in contrast, in many jurisdictions, medical devices are introduced with fewer formal restrictions. Data collection by drug versus device manufacturer also occurs at different points with drug companies focused on pre-market data collection and device companies interested in post-market data collection. The formal requirements for evidence will also differ across different classes of devices (usually according to risk), and may also vary according to jurisdiction. The types of study designs possible with devices also differ from drugs, given in some cases difficulty with blinded treatment allocation or adequate controls.

Also, unlike outpatient drugs, decisions or recommendations to use devices do not always occur at a National level and

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for many jurisdictions are made in hospitals or local health authorities. Both sectors have examples of adaptive approaches but may have different perspectives on their expansion: for the device sector this may be seen as a providing more restrictions on technology diffusion than exist currently, while for drugs it may be seen as more flexible. This again suggests that adaptive approaches would have to be developed differently for pharmaceuticals and medical devices and taking into account regulatory, HTA/coverage body and health system differences.

Designing an adaptive approach will need to reflect these differences and may mean different adaptive processes would also have to be created according to the unique requirements of medical device class. Despite rich discussion regarding the issues posed by medical devices and drugs at the Forum, there will clearly be more need for further discussion about the feasibility of adaptive approaches recognizing these issues and possibly identifying others.

Stakeholder Perspectives

Identification and exploration of the issues at the meeting revealed that an adaptive approach has different implications for different stakeholders. These include:

- *Patients* would most likely welcome arrangements that provide earlier, appropriate access to treatment. However, adaptive approaches involve potentially greater risks for patients, so patient groups need to be actively involved in deciding when and how they are applied. Patients groups are increasingly involved in helping regulators determine what is acceptable risk and providing input to HTA bodies (24), and a new access paradigm will require extending these efforts to allow patients to become partners in various other stages in the process. Adaptive approaches will also require individual patients to be more actively involved in providing truly informed consent to both treatment and research in an environment that blurs traditional lines between them. Patients may be challenged to accept restrictions on off-label prescribing.
- *Regulators* already have several tools at their disposal that allow for an adaptive approach, and there appears to be a range of views in the regulatory community on the extent to which new mechanisms are needed. Regulators concerns about increased adaptability include (i) the extent to which industry will deliver requested data, and (ii) the extent to which clinicians will adhere to initial narrow label indications if more adaptive approaches are implemented. Some regulators seem to accept the need to coordinate adaptive approaches with payers, but many have doubts about the capacity for other stakeholders to consistently engage in discussions. Some regulators see a major potential benefit of working more closely with HTA/coverage bodies as the incentives they can put in place to manage clinician prescribing.
- *HTA/coverage bodies* also have various tools at their disposal that allow for adaptive approaches, as noted above. These bodies may be concerned that more adaptive approaches to regulation may increase the pressure to cover treatments with what they see as low or uncertain value, especially if they are not involved in early discussions about evidence development plans. HTA/coverage bodies may also have concerns regarding how much planning and coordination is necessary and feasible given a limited capacity to engage as well as the weight that will be given to their interests during discussion of data requirements.
- *Health systems* will ultimately be responsible for real world data collection, with the use and application of electronic health records, registries, and other data collection tools. Heath system decision makers may be concerned that regulators and coverage bodies have unrealistic expectation about (i) routine information and patient management systems, (ii) the extent and speed with which they can be developed, and (iii) the additional resources required to do so. Adaptive approaches may also create a shift from voluntary to mandatory use of these datasets and place extra demands on those delivering care, for example increased human resource capacity to ensure adequate data capture. Health system administrators and managers responsible for local decisions may further be concerned that adaptive approaches will lead to increased pressures on them to invest in high cost new treatments of uncertain value, and more work to manage patient expectations, treatment and recruitment to studies.
- *Clinicians* will be wary of any development that threatens clinical autonomy and freedom to prescribe off-label. They may also be concerned about the time and resources needed to explain benefit-harm profiles to patients, to seek informed consent to treatment with less certain benefit-harm profiles, or to recruit patients into studies required for adaptive approaches.
- *Industry* would welcome approaches that allow earlier patent access and support innovation. Like the regulatory community, some in industry seem to believe that existing regulatory and coverage tools already allow for a good degree of adaptability. Despite a general desire for adaptability, there are concerns regarding what is feasible given current separate regulator and HTA/coverage body environments. There is also concern that uncoordinated development of new approaches across jurisdictions will lead to an even-wider variation in evidence requirements—suggesting that there needs to be an even greater focus on harmonization and agreement on methodology. Although industry welcomes coordination of regulators and payer expectations, companies may be wary of getting tied down to long-term evidence development plans that may not prove feasible or make commercial sense in the light of developing circumstances. As noted above, industry is also skeptical about payers' willingness to pay for value once demonstrated, and particularly their willingness to increase prices when greater value is proven. Device manufacturers will want to see careful consideration about the different regulatory and payer environments for drug versus device manufacturers, and have concerns about the development of a one-size-fits all approach.

POTENTIAL NEXT STEPS

It is clear from this Policy Forum discussion that there is a range of views and fair degree of skepticism about the feasibility and desirability of increasing the use of adaptive approaches to decision making beyond current practices. What is known about adaptive approaches suggests that, while they may be of theoretical benefit under certain conditions, they raise several significant concerns and empirical evidence of benefits in the real world is scarce.

There was agreement that further discussion is needed between all the stakeholders involved, and that retrospective or prospective case study exercises provide a good foundation for an understanding of the likely implications and outcomes of new approaches. Progress can be achieved through international collaboration, as exercises such as the Green Park pilot initiative have shown (13), but are also associated with considerable challenges . As more information comes available, feasible proposals to address the many issues raised will hopefully emerge, along with insights into good practice.

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There has been a recent increase in international initiatives to promote regulatory and payer interaction (19;33). Given limited resources, potential next steps may be to (i) use the outcome of this Forum discussion to further develop potential solutions where adaptive approaches are being proposed; and (ii) to consider how to share learning from these deliberations across jurisdictions. At minimum, continued discussion should be informed by intelligence from formal analysis and modeling of case studies, and by piloting of some real world examples. This should address the issues around need and justification for adaptive approaches and the revised "social contract" that is needed to underpin them, as well as the technical issues of how to do it.

A key next step will be the development and assessment of the recently announced EMA adaptive license pilot project (10). The project is committed to working with all parties affected by changes to decision making and has already committed to working closely with the European HTA community, including the European Network of HTA producers, EUNetHTA.

CONCLUDING REMARKS

As in previous Forum discussions, for many of those present, the key outcome of the meeting was a clearer understanding of the issues relating to the topic being discussed—in this case, adaptive approaches and the opportunities and challenges they present for the various stakeholders involved in health technology decision making.

There was general agreement that the active involvement of HTA/coverage bodies in discussions intended to further explore or develop adaptive approaches is key, that clearer agreement is needed on the goals of adaptive approaches and the nature and extent of the problems they aim to address, and that consideration of real world case examples is a good first step toward better understanding the implications of these approaches.

There was also general agreement that involvement of the full range of stakeholders is essential to future discussions on, and implementation of, adaptive approaches. These discussions will need to arrive at clarity on the implications for the current roles and responsibilities of all stakeholders, and on how changes in these will be managed. Given the emphasis to date on adaptive licensing proposals and the work of regulators and industry, it is particularly important that payers, patients, clinicians and providers are now brought into the mainstream of these discussions. This wider engagement will recognize that all parties are important contributors to the shared decision-making model implicit in adaptive pathways, and therefore needed to develop a renewed "social contract" regarding the provision of drugs and medical devices.

SUPPLEMENTARY MATERIAL

Supplementary Appendix 1:
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CONFLICTS OF INTEREST

Don Husereau received payment from HTAi for drafting and revising the manuscript. Jamil Jivraj is employed at Health Technology Assessment International, and has participated in preparation of the manuscript in this role. Chris Henshall receives an honorarium from HTAi as Chair of the HTAi Policy Forum, including time spent in preparation of the manuscript: In addition he declares membership of the Board in Alberta Research and Innovation and Authority; consultancy for WHO, Brunel University, IHE Edmonton, CMTP Baltimore, RAND Europe, AstraZeneca, GlaxoSmithKlyne, Eli Lilly, MEDEC Canada, Medtronic, MSD, and Pfizer; he has received payment for lectures including service on speakers' bureaus, and payment from organizations listed above for manuscript preparation, development of educational presentations, and travel/accommodations/meeting expenses from National University of Singapore.

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