MEETING REPORT

IMI’s ADAPT SMART Draws to a Close, Outlines Path Forward for Continuing Early Stakeholder Engagement

March 23, 2018 – Budapest: On March 21\(^{st}\) and 22\(^{nd}\), ADAPT SMART held its closing meeting at the Hungarian Academy of Sciences in Budapest, highlighting the programme’s achievements and next steps for delivery after the project’s conclusion.

For thirty-three months, ADAPT SMART had been focused on developing new processes for the implementation of Medicines Adaptive Pathways to Patients (MAPPs), which aim to foster access to beneficial treatments for specific, well-defined, patient groups with a high unmet medical need at the earliest appropriate time in the product life-span in a sustainable and affordable fashion. Given the challenges of access to new medicines in Central and Eastern Europe, Hungary was chosen for the ADAPT SMART closing meeting to help put MAPPs into practice across the entire EU.

DAY 1

The conference began on the evening of March 21\(^{st}\), with an introduction by André Broekmans, the Coordinator of ADAPT SMART and a Director at Lygature, who highlighted that, “While the project had been operational for less than three years, the consortium had successfully laid the framework for the key mechanisms of MAPPs by having all the stakeholders discuss and agree on key decision points for new advanced medicines in collaboration.” This sentiment was echoed by Hans-Georg Eichler, Senior Medical Officer of the European Medicines Agency (EMA), who had also been the ADAPT SMART project leader.
He pointed out that the project had attempted to move the approval of needed medicines from a standard linear approach to, “an evolution to what Dr Richard Barker of the Centre for the Advancement of Sustainable Medical Innovation (CASMI) calls an adaptive mindset. We need to act more adaptively in consort with all the stakeholders proactively engaged to respond to the evolution of new groundbreaking therapies.”

Hans-Georg Eichler said that ADAPT SMART had successfully changed the dialogue in Europe, and the idea that patients, healthcare providers, industry, regulators, HTA bodies and payers would now discuss the merits and challenges for new therapies. “There is a consensus that working collaboratively is the way of the future,” he said. “But we also must understand this opinion is not unanimous, and that there are still concerns around, for example, the use of Real World Data (RWD) and Managed Entry Agreements (MEAs) which are not yet fully accepted. But overall, ADAPT SMART has succeeded in moving the debate forward to the eventual benefit of all stakeholders,” Hans-Georg Eichler concluded.

The evening’s keynote was called, “The ways of innovation and regulatory science”, and was delivered by Csilla Pozsgay, Director General of the National Institute of Pharmacy and Nutrition (OGYÉI), Hungary. She highlighted that regulators play a critical role in ensuring the safety of medicines, but they also must be able to respond effectively to the disruptions caused by technology that require the system to be flexible.

“In recent years, the persistence and scale of technology-induced change have led many to doubt the value and practicality of government regulation,” she said, pointing out that regulatory agencies have to identify opportunities to navigate today’s challenging landscape and prepare for the future. She concluded by saying that MAPPs are a logical response to the evolution of new innovative medicines and that regulators such as the OGYÉI would need to continue to modernise regulatory practices and increase effectiveness to respond to the demands of new technology.

After the keynote, the conference moved to a series of panel presentations and an open discussion with the various stakeholders engaged in the MAPPs project. The first presentation was by Valentina Strammiello, Programme Manager of the European Patients’ Forum (EPF). She highlighted that ADAPT SMART, from the patient’s perspective, had done much to establish trust amongst the various stakeholders and successfully put patients at the centre of the discussion as an equal partner.

However, Valentina also pointed out that the project still had gaps with regards to the collection of real world data, as many Member States lack the ability to use that data in practice, and highlighted that a key concern for MAPPs after ADAPT SMART was who will lead the project going forward. “Who
will step in to drive the MAPPs agenda?” she asked, concluding by suggesting that this was perhaps a role for the European Commission.

Francesca Cerreta, Scientific Administrator of the EMA, was the next presenter, who began by saying that opinions amongst EU regulators towards MAPPs vary. “Some say the glass is half-full, some say the glass is half-empty, others say that isn’t my order,” she said. Her presentation then outlined the current challenges as well as the evolution in the use of post-licensing evidence generation (PLEG), and how it will need to develop to support MAPPs.

Interestingly, Francesca Cerreta presented data that 4% of scientific advice interactions came with RWD support packages, but ultimately “PLEG complements pivotal RCT data, and does not yet replace it. We have some remaining uncertainties,” she said.

Wim Goettsch, the Special HTA Advisor for the Zorginstituut Nederland (ZIN), has been an early adherent to MAPPs processes through his participation in the NEWDIGS seminars at MIT’s Center for Biomedical Innovation, and was also a key member of the ADAPT SMART consortium through his previous position at the European Network for Health Technology Assessment (EUnetHTA). Wim pointed out in his presentation that, “While there was general interest in the project, the fact is the acceptance of MAPPs amongst many HTA bodies is low, and the majority of the participation in ADAPT SMART came from the National Institute for Health and Care Excellence (NICE) and ZIN.” Wim Goettsch concluded by asking the rhetorical question, “Is MAPPs deceased?”

Session moderator Duane Schulthess, Managing Director of Vital Transformation, pointed out that there are currently several bills in the US Congress pushing for the use of RWD before the Food and Drug Administration (FDA) license to have earlier stakeholder discussions with insurers. “Perhaps in Europe MAPPs is on life support, or maybe just sleeping, but it seems ADAPT SMART has had an influence internationally,” he said.

Speaking on behalf of payers in his role as the President of the Medicine Evaluation Committee (MEDEV), Ad Schuurman said that, “Many of these new therapies need us to change the way we think about our jobs, we must respond to the new technologies. I’d personally hoped we could go for one or two real pilot projects with all stakeholders around the table in ADAPT SMART, but so far none of the companies seem willing to come forward and try to do MAPPs for real.”

He continued, “I think the time has come for us to run a pilot and see what happens, but we must include a discussion on pricing too when we do, and a company will need to be brave. So far, no company seems willing to do so,” concluded Ad Schuurman.
Solange Corriol-Rohou, ADAPT SMART Deputy Project Leader from AstraZeneca, gave her presentation from the perspective of industry. She said that the consortia had, “Started with lots of excitement and uncertainties, with the goal to explore MAPPs which was, and still is, a highly sensitive and controversial concept.” She said that it was, “An opportunity to bring together all stakeholders of the health ecosystem, and that it was an evolution and not a revolution, in a very challenging environment.”

Regarding the future after ADAPT SMART, Solange Corriol-Rohou said that it was important that the participants maintain the platform for engagement, and with a nod to the comments of Ad Schuurman, “We try to have broader collaboration with payers and health care providers to enhance the acceptance of the MAPPs concept in order to enable future MAPPs pilots,” she concluded.

The final stakeholder to present was Bojan Vujkovac, a Nephrologist from Slovenj Gradec General Hospital in Slovenia, who had participated in an ADAPT SMART survey of health care professionals to determine their opinions of the MAPPs concept. “You’ve accomplished a tremendous amount and taken on an incredibly ambitious project trying to fundamentally change clinical practice,” said Dr Vujkovac. He continued, “Many people, when they try to refurbish a house, start with the roof. ADAPT SMART began by rebuilding the entire foundation, which is the harder, slower way, but it is the correct way,” he said.

Bojan Vujkovac also said that as someone who is ‘a needle doctor’, the ability to get new innovative therapies to patients is very exciting and should be fully investigated. “Anything that can help me in clinical practice for the benefit of patients must be tried,” he concluded.

The session ended with an open discussion with the audience and the panel, with an overall debate on the need for MAPPs, in order to be effective, to tackle difficult discussions on price. Richard Barker of CASMI commented that, “Perhaps we need to not only think with an adaptive mindset, but it is now imperative for us to also approach MAPPs with a collaborative mindset, then it may be possible for us to find a solution to the remaining issues hindering MAPPs.”

The first day of the conference concluded with the unveiling of the new ADAPT SMART info graphic. This new tool outlines the various component parts of MAPPs, as well as the need for stakeholder collaboration at the centre of the MAPPs process.
“Today, we are going to work,” is how André Broekmans began the second day of the ADAPT SMART closing meeting. The objective was to run a theoretical MAPPs pathway for a drug candidate targeting the condition of beta thalassemia, a rare blood disorder with an impact that varies by genetic mutation.

Guiding the discussion were Mark Trusheim, the Strategic Director of MIT’s NEWDIGS, and Ariel Stern, Assistant Professor of the Harvard Business School. The meeting attendees were guided through a MAPPs case study including a development pathway and evidence plan for beta thalassemia, but interspersed in the discussion was a series of polls to determine the various points of alignment and disagreement between the stakeholder groups in attendance, which nicely fostered a lively discussion.

Broadly in Europe, all stakeholders agree that MAPPs is appropriate for new transformative therapies to address a clear unmet medical need, but one of the challenges is the lack of a single agreed definition for (high) unmet medical need. It is for this reason that multi-stakeholder dialogues are vital in ensuring that all stakeholders agree on the MAPPs engagement criteria, and an assessment can only be defined on a case-by-case basis.

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<th>Which stakeholder benefits the LEAST from MAPPs?</th>
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The challenge to finding consensus was made clear when the session participants, 43% of whom were from industry, said in a survey that they felt that the stakeholders who could potentially have the most downside in a MAPPs pathway were payers. Session moderator Mark Trusheim disagreed with the participants by saying, “I actually think it’s possible that, over the long-term in a well implemented MAPPs pathway, payers could benefit the most. A payer gains commitments that they only pay for
the eligible population, and that evidence for clinical and cost effectiveness will be collected post-market. This is certainly an improvement compared to the way things are done today. We find at NEWDIGS that concerns about MAPPs are also often expressed by industry, as it commits them to a smaller first population that begins the 10 year exclusivity period which could reduce total revenues over time and that it commits them to that evidence generation over the long-term.” said Trusheim.

Ad Schuurman from MEDEV responded by saying, “It’s a nightmare if products come into our system and we can’t control them anymore. It’s very important that we can monitor and control the access and measure the response from the very beginning. We need an agreement to make sure we have transparency over the process and benefits for entry and exit. That’s crucial for us.”

He continued, “If this was done correctly with good data collection and controls on prescribing and pricing, then yes, it’s possible that payers would have the greatest benefit in MAPPs.” “However,” he qualified, “The problem is that currently, this is only theoretical, and until we actually test this, we don’t know if this is true or not. It’s just a theory,” Ad Schuurman concluded.

Responding to the issue of data collection, Jacoline Bouvy of NICE commented that, “We need to recognise that the responsibility of collecting the data will fall to healthcare professionals, and they are already saying they are over committed for time and resources.” This opinion was echoed by session co-moderator Ariel Stern, who pointed out that, “In all of our courses we run for practitioners at the Harvard Business School, we are told in no uncertain terms, ‘don’t make me do anything extra in my workflow,’ we understand that this is an enormous issue and barrier that will need to be overcome.”

Richard Barker of CASMI commented that, “Far too often the solution is a product registry, as that is what is needed for licensing. However, if we were to focus instead on disease registries, this would have far greater benefits beyond only the reimbursement of the therapy, and generate significant benefits to the healthcare system as a whole. Frankly, I don’t understand what the resistance is to this solution, it seems painfully obvious to me.”
When asking who could benefit the most from the use of MAPPs, the session participants were far more unified with 75% agreeing that ultimately, patients would have the greatest benefit.

The beta thalassemia case study outlined that the disease is an inherited, recessive genetic blood condition and that the average patient lives to nearly 50 years of age. An alternative allogenic stem-cell treatment currently exists, but finding a match is challenging, and according to Mark Trusheim, “Only 25% of patients can find a match for a stem cell donor.”

The current treatment regime for the majority of patients then is a lifelong monthly red blood cell transfusion plus iron chelation therapy to circumvent iron overload. While marginally effective, it is accompanied by a plethora of potentially life-threatening complications including severe anaemia, liver cirrhosis, liver fibrosis, liver cancer, heart failure, growth impairment, diabetes and osteoporosis.

The theoretical new product in the case study, the eponymously named Budapest Bio’s MAR-18 Gene Therapy, presented Phase 1 trial data that had shown safety and potential efficacy in 10 patients. The question presented by Ariel and Mark was, “is this a good candidate for MAPPs?” The survey results were interesting, as most in attendance agreed that it was probably a good candidate, but it was a qualified result.

The discussion turned immediately to the issue of unmet medical need, the key entry criteria for a MAPPs pathway. Brigitte Bloechl-Daum from the Medical University of Vienna and a member of the EMA’s Committee for Orphan Medicinal Products (COMP) asked, “Does this new treatment really meet the definition of unmet medical need? We have a stem-cell treatment for 25% of the patients, and a transfusion therapy for the rest?”
Christian Andriciuc of the Romanian Federation of Diabetes Persons' commented that, “With all the complications and only living until you’re 40 or 50, this is not a life.” He broadly supported the MAR-18 Gene Therapy as addressing an unmet medical need.

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(Adapted from Modell 2010, Table XVI)

Zoltán Kaló of Eötvös Loránd University (ELTE) highlighted that the genetic mutations of the disease were not distributed evenly, with Mediterranean countries having a much higher rate of incidence. “Quantifying unmet medical need with this treatment is challenging, as the regional distribution of the disease is not equal. Also, its rate is highest in areas where we know that the country’s ability to pay for very expensive treatments is already limited. It’s a good example, but certainly not a perfect one,” he concluded.

Hans-Georg Eichler, the Senior Medical Officer at the EMA pointed out that, “In this case, we really need to consider exactly what the life of the patient is. If you live with that disease, if you have complications from iron overload, liver cancer, etc., it’s worse than a death sentence for some of them,” he said.

The debate turned to the issue of access options based on a pre-agreed evidence plan. What would be the metrics and data package that would be agreeable to HTAs and payers that would allow for the reimbursement of MAR-18? The case study outlined that the proposed plan would be based on the secondary endpoint of reduced transfusions, as this would be an easy data point to track by EU payers.
After presentation of a theoretical evidence plan made by Hans-Georg Eichler, Mark Trusheim outlined the detail of the study design for MAR-18 to the group. “In this single-arm study, the protocol is to take the patient history for 12 months, as they will need to have a year’s data before they can enter the trial. This gives a baseline to determine the number of transfusions before the infusion of MAR-18, and when a person became transfusion free. Being transfusion free is easy to track, as that data will be in the payer records,” Trusheim said.

Anthony Barron from the contract research organisation Charles River Associates made the point that, “This approach probably provides enough evidence for regulatory approval, but when you’ll take this to an HTA body, that probably won’t take you over their evidence hurdles. Most payers will want a comparator, and with this you won’t have evidence of value addressed all the way through the HTA process.”

Wim Goettsch from ZIN concurred by saying, “With Advanced Therapy Medicinal Products (ATMPs), you see that there is a generally clear regulatory path within the Committee for Advanced Therapies (CAT) at EMA, but the number of positive assessments for cell and gene therapies when you get to the Member States is low. We have to think very carefully how to design this,” he said.

Richard Barker of CASMI highlighted that there have been many single-arm studies that have seen a path to regulatory approval in Europe. “Nobody asked for an RCT in Ebola, it’s a dialog based on principles of unmet need and proven safety,” he said. This opinion was expanded upon by Francesca Cerreta of the EMA, who said that, “Patients are often very good controls for themselves. If we see a high cure rate, if we see that the drug is very effective without many complications, there won’t be any questions. It’s the value and effectiveness of the drug that is ultimately important.”
Pall Jonsson of NICE said that he was also less pessimistic. “Open-label, single-arm studies are in principle not controversial; there may be ethical or practical reasons why a randomised trial is not feasible, for instance for very rare diseases or in well-defined populations with a high unmet medical need and limited treatment options. At NICE, we’ve seen many of these studies in oncology, and yes, we do need to match the comparator populations very carefully – but there are ways to do that,” he concluded.

Michael Ermisch of the German state health insurer GKV-Spitzenverband made the point that, “There are four categories where we can make an assessment of value, and those are mortality, morbidity, quality of life, and adverse events. Quality of life has value; it is worth something in the German system. Rather than simply present the secondary endpoint of transfusions, I agree with the concept of converting the transfusions to a quality of life measure, maybe this would be the best available evidence?”

Mark Trusheim interjected in the debate that in MAPPs, it’s an agreed principle that efficacy needs to be transformative. If the product only has a minor impact, it won’t pass the hurdles. Further, he said that, “In many ways, we’ve fallen into our old traps. This isn’t a single magic moment, in MAPPs we have an iterative development plan, this first license occurs in the context of an entire iterative series of evidence generation; we’re still only focusing on one magic entry point for approval.”

There was general agreement by the participants that if the stakeholders are aligned, and if this wasn’t simply done for negotiation positioning, there would be a consensus on next steps. The process of MAPPs requires and demands that discussions between the regulator, HTA bodies, payer, industry, and patients have gravitas.

Ultimately, the key question of the afternoon was can you develop the evidence required for MAPPs in which all stakeholders will have confidence?

Andrew Bate, Pfizer’s Senior Director of Epidemiology said, “Yes, absolutely.” He pointed out that Pfizer were currently using Real World Evidence (RWE) through the US FDA’s Sentinel, the Patient-Centered Outcomes Research Institute (PCORI), claims data, and various electronic health record (EHR) systems, and that this approach has changed enormously over the last five years. “The use of RWE enhances all of the aspects of research, reporting, prospective trial design, and market access,” he said.

There was a general agreement that many HTAs are willing to use RWE to make assessments, but others are not. This was outlined by Wim Goettsch of ZIN who said, “We’ve had many experiences where we’ve asked companies for RWE and the data we get is not what we wanted. For MAPPs to work, the data needs to be addressing the endpoints where we expect evidence.”

Anthony Barron from Charles River Associates made the point that MEAs are one way to mitigate the uncertainty of the process, but there is a cost to collecting this data and evidence. “Payers are saying these are great, but they are also a costly hassle, why wouldn’t I do an agreement to solve this problem?” He concluded by saying, “Either we make the HTAs much more flexible, or we move into a contracting mode where we share the risk as well as the cost of collecting that evidence.”
The final session of the meeting began with a survey question, “Do you believe that MAPPs will be in use within 24 months?” Despite all the challenges, 60% of the attendees agreed that MAPPs would be put into practice.

In the last presentation of the meeting, Solange Corriol-Rohou, ADAPT SMART Deputy Project Leader from AstraZeneca, outlined that the ultimate objective of ADAPT SMART was to release recommendations and proposals for future research projects. ADAPT SMART, as opposed to other IMI projects, was not expected to do research, but work on the MAPPs concept.

**CONCLUSIONS:**

What came out of the two-day conference in Budapest was a series of Action Points in order to move MAPPs forward effectively:

1. Address the cost and methods of data/evidence collection
2. Facilitate context specific discussions
3. Increase and augment transparency
4. Develop targeted workshops to address gaps in payment methodology
5. Bring payers more actively into the consortia
6. Run MAPPs pilots, i.e. use MAPPs-y approaches to outcomes and methods

Based on these Action Points, Mark Trusheim pointed out to the attendees that, “ADAPT SMART has taken the stakeholder discussions that were previously happening behind the scenes and has brought them out in the open in an adaptive mindset. Building the forum where this collaborative legacy can occur is one of the great deliveries of the project.”

Hans-Georg Eichler closed the final ADAPT SMART meeting by saying, “In the words of Victor Hugo, nothing is more powerful than an idea whose time has come. We’ve great enablers, products and the financial and demographic pressures that will be sure to drive the need for the products to force MAPPs to move forward.”
The ADAPT SMART Coordination and Support Action (CSA) acts as a neutral collaborative framework to establish the platform that will engage with all relevant stakeholders, including patients, industry, SMEs (Small and Medium sized Enterprises), regulators, health technology assessment bodies (HTAs), payers (national and European Networks), clinicians, governments/policy makers (national authorities as well as European Commission’s DG SANTE and DG GROW, and European Networks). In addition to engaging in a dialogue with relevant stakeholders, the ADAPT-SMART consortium aims to align understanding of the impact of MAPPs, to share findings between all stakeholders, and to allow the field to actively work towards MAPPs implementation.

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115890. This Joint Undertaking receives support from the European Union’s Horizon 2020 research and innovation programme and EFPIA.