An overview of tools and systems to guide appropriate use of medicinal products in twelve EU Member States

October 2017

The work leading to these results was conducted as part of the ADAPT SMART consortium (Accelerated Development of Appropriate Patient Therapies: a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes). For further information please refer to www.adaptsmart.eu. This paper is the result of the collective input from working group D2.07 and only reflects the views of the authors.

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1. Introduction

Background and context in ADAPT SMART

This document has been written as part of the IMI ADAPT SMART Project (www.adaptsmart.eu). ADAPT SMART was launched in 2015 as a Coordination and Support Action in the EU Innovative Medicines Initiative (www.imi.europa.eu). The objective of ADAPT SMART is to establish an enabling platform and engage a dialogue with relevant stakeholders for the coordination of MAPPs related activities. Medicines Adaptive Pathways to Patients (MAPPs) seeks to foster access to beneficial treatments addressing an unmet medical need at the earliest appropriate time in the product life-span in a sustainable fashion. The consortium's aim is to conduct a gap analysis, inform future research activities, and engage in knowledge management activities - all with a view to facilitate and accelerate the availability of MAPPs.

To achieve its objective, the consortium has identified four Work Packages (WPs), of which WP2 aims to work towards a pragmatic proposal for a future MAPPs pathway, covering all phases of development and licensing, and supporting efficient access of patients to products that address high unmet medical needs.

In the context of WP2, an important aspect of medicinal products that are approved with an initial marketing authorisation, as is the case for MAPPs, are the tools/systems that guide so-called 'appropriate use' of these medicinal products. This refers to a situation in which medicinal products with a (initial) marketing authorisation through the MAPPs pathway are prescribed, dispensed and administered to patients for which the benefit/risk profile has been demonstrated and simultaneously avoid the exposure to patients for which the benefit/risk profile has not (yet) been demonstrated. This report produced by the ADAPT SMART Workstream D2.07 from WP2 should be read alongside the report from Workstream D3.09 from WP3, that focuses on the ethical and legal challenges that arise under MAPPs relating to prescribing and use in targeted populations.

Objectives

The objective of D2.07 was to provide an overview of which tools and systems are available at the national level to guide the appropriate use of medicinal products in EU Member States. This report looks at all tools/systems for guiding appropriate use at the national level, even if these may not be directly applicable in the context of a MAPPs-type pathway.

To achieve this objective, we have conducted a survey in twelve EU Member States in the second half of 2016 to determine which tools/systems are currently available to guide appropriate use in the individual Member State, their perceived or measured impact on guiding appropriate use, and the complexity of implementing the tool/system. The survey provided input for a multi-stakeholder workshop that was held as part of the Annual Meeting of the IMI ADAPT SMART Project on 17 January 2017 in London, UK. The results of the survey and the workshop are discussed in this report. The work in D2.07 resulted in proposals for further study and in recommendations to national healthcare systems, European Commission, EMA, healthcare providers and patients.

2. Approach

Background of the survey

It is important to introduce some of the key concepts we used to explore the topic of appropriate use of medicinal products. The conceptual framework behind this survey is provided in Figure 1. As the Figure shows, before legislation or policy (as a derivative of legislation) can impact healthcare

practice, certain tools/systems must be set-up to guide and monitor the appropriate use of medicinal products by healthcare professionals and patients. It is important to note that tools/systems for guiding and monitoring appropriate use of centrally approved products can be differentiated between European regulated tools/systems and nationally regulated tools/systems. The Summary of Product Characteristics (SmPC) is an example of a EU regulated tool/system for guiding appropriate use, as it is the legal document that describes the intended use of a product in the agreed indication and target population. Another example of a EU regulated tool/system for guiding appropriate use are Direct Healthcare Professional Communications (DHPCs), which can be initiated by MAHs or regulatory authorities and provide (new) important information on the use of medicinal products directly to individual healthcare professionals. On top of EU regulated tools/systems, additional tools/systems for guiding and monitoring appropriate use can be implemented and regulated at the level of the individual Member State. These nationally regulated tools/systems can for example be additional measures based on the framework of reference provided by the SmPC that defines the appropriate use of the medicinal product. This study focuses on tools/systems that guide the appropriate use that are regulated at the national level, covering the pathway from prescribing to administering medicinal products to patients (green box in Figure 1).

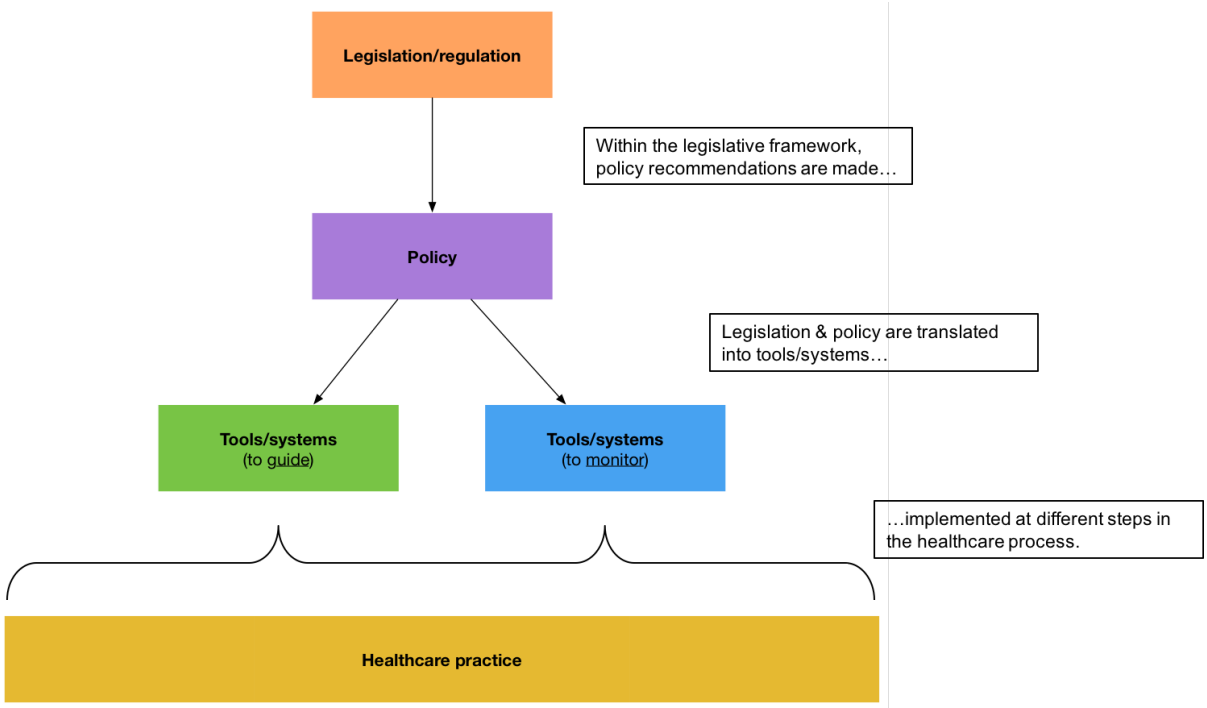

Figure 1 – The conceptual framework behind this survey. Tools/systems can be implemented to guide (green box) and monitor (blue box) the appropriate use of medicinal products throughout the healthcare process and can be regulated at the level of the EU or individual Member State. The survey focuses on the tools/systems that can guide appropriate use of medicinal products at the Member State level.

Approach

In a first step, a preliminary inquiry was performed (based on literature research) to identify tools/systems that can be available at the national level for guiding appropriate use. Based on this non-exhaustive list of identified tools/systems, a survey was developed to identify which tools/systems that guide appropriate use of medicinal products are available at the national level of different EU Member States and gather the experiences with these tools/systems regarding impact on guiding appropriate use and implementation. Respondents were able to provide additional tools/systems for guiding appropriate use of medicinal products.

We approached EFPIA member companies in twelve EU Member States (the list of companies/respondents for each Member State is included as Annex 1), who were part of the consortium and were represented in the Workstream D2.07. EFPIA member companies were encouraged to seek local expertise from the national healthcare system. Care was taken for the surveyed Member States to represent various parts of the EU, as well as Member States that acceded before and after the 1st of January 2004. An overview of the respondents can be found in Figure 2.

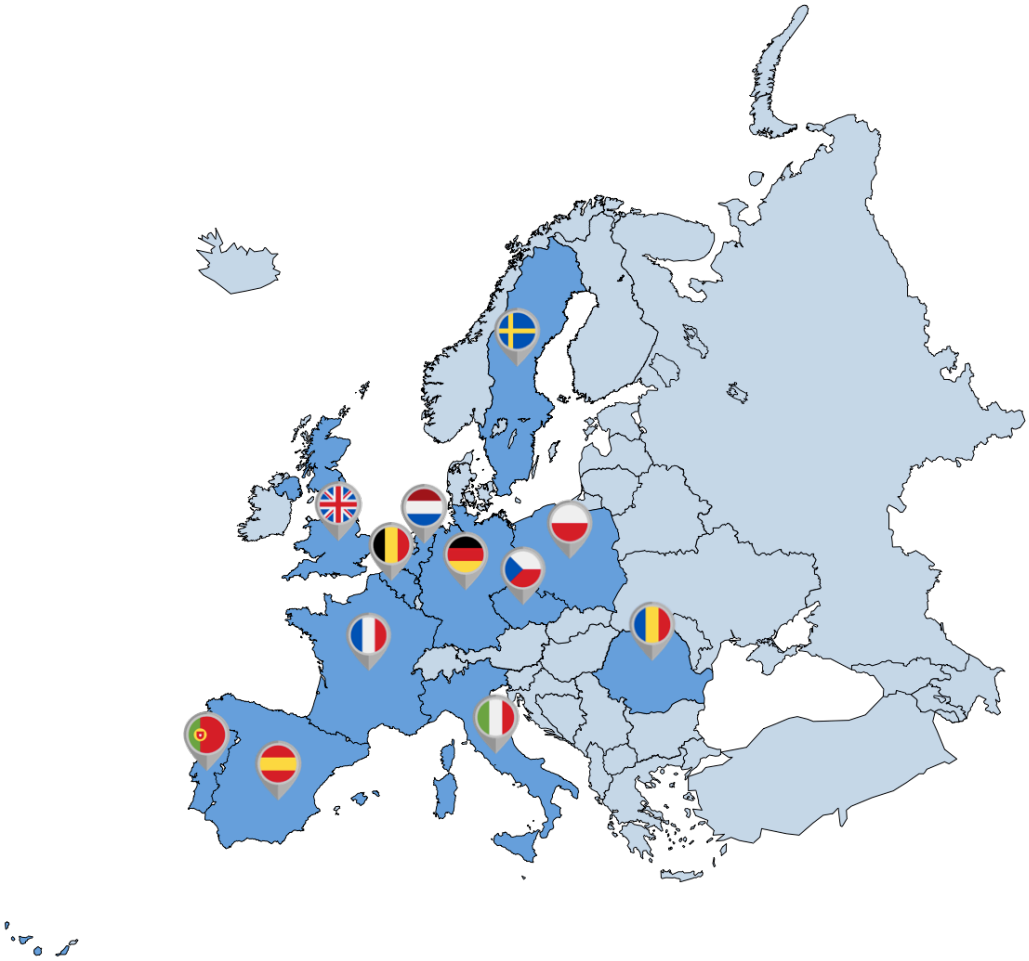

Figure 2: Respondents to the survey: Belgium, Czech Republic, France, Germany, Italy, The Netherlands, Poland, Portugal, Romania, Spain, Sweden and the United Kingdom.

Survey structure

The survey is structured along different levels of tools/systems identified in the preliminary inquiry based on where in the healthcare process they may guide appropriate use. The survey contains the following pre-defined levels and their corresponding tools/systems:

1. At the level of providing information to prescribers, e.g.:
    - *Treatment guidelines*: offer advice to prescribers for making treatment-decisions for specific clinical circumstances. Treatment guidelines can focus on the (appropriate) use of specific medicinal products for a certain disease;
2. At the level of assessing/diagnosing patients, e.g.
    - *Diagnostic tests:* diagnostic tests focus on biomarkers related to a disease (e.g.

plasma levels of specific markers, genotypes, metabolite levels etc.) and are used to determine whether specific medication is appropriate.
    - *Assessment of prior history:* This assessment can be important to evaluate any prior association with a disease that could predispose the patient to medical emergencies during treatment. This could also be the assessment of whether recurrence of a disease is occurring or prior treatment has already been received.
    - *Assessment of the patient's demographic characteristics:* This assessment can be important to determine whether the patient fits the targeted patient population. Such demographic characteristics include for example age and sex;
3. At the level of prescribing medicinal products;
    - *Restricting prescriber speciality:* Appropriate use can be guided by restricting the prescribing of specific medicinal products to specialized prescribers experienced in the diagnosis and treatment of the disease. For example, use of certain treatments could be restricted to board certified oncologists or cardiologists.
    - *Certification for prescribers:* Appropriate use can be guided by restricting the prescribing of certain medicinal products to qualified prescribers that have received additional certifications, e.g. through educational programs. As an example, we refer to the FDA REMS program, which can require that healthcare professionals complete a training module before they are allowed to prescribe certain medications, and EU RMPs [a] [b].
    - *Site approvals:* In addition to the certifications for prescribers mentioned above, appropriate use can also be guided by restricting prescriptions to healthcare settings that are specially certified allowing them to perform specific medical care based on the presence of certain equipment or quality systems (e.g. nationally registered centers of excellence).
4. At the level of the use of medicinal products:
    - *Patient support program (PSP):* A PSP comprises of a set of activities organized by a marketing authorisation holder involving direct interaction of healthcare professionals with patients, with the purpose of providing healthcare services to patients related to the use of medicines (especially in chronic disease states). The underlying objective may be for example to help patients better manage their disease and their medication regimen, reduce the burden of treatment, improve medication adherence, collect information, and reduce complications and costs
    - *Registry:* Registries are organised systems that use observational methods to collect quality data on real-life clinical use and play an important role in monitoring the safety of medicines. Use can be restricted to patients that are enrolled in a registry.

An overview of the structure and the predefined tools/systems can be found in Figure 3.

For each tool/system we requested respondents to indicate whether a tool/system is used in the Member State for guiding appropriate use of medicinal products, what its impact has been on guiding appropriate use and how challenging it was to implement. To each of the categories respondents could add other tools/systems that guide appropriate use of medicinal products that were not included in this survey. Moreover, for the tools/systems that are available, we requested information on any enforcement mechanisms or consequences for non-compliance to the tool/system. These could include:

- Reimbursement restrictions;

[a] FDA REMS program: https://www.accessdata.fda.gov/scripts/cder/rems/)
[b] EU RMP: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000360.jsp

- Disciplinary procedures;
- Non-dispensing of the medicinal product;
- Other.

If a tool/system is not available in a Member State, we requested respondents to indicate what the underlying reasons were (e.g. political, social, technological, economic or legal barriers) and whether, in the opinion of the respondents, the tool/system could be implemented in their country.

The survey consisted of a mix of multiple-choice and open questions. Respondents were asked to elaborate on their answers where possible. All questions referred to the situation at the time of the circulation of the survey (October 2016). A follow-up survey was created to collect missing information on tools/systems after the deadline of the initial survey had passed.

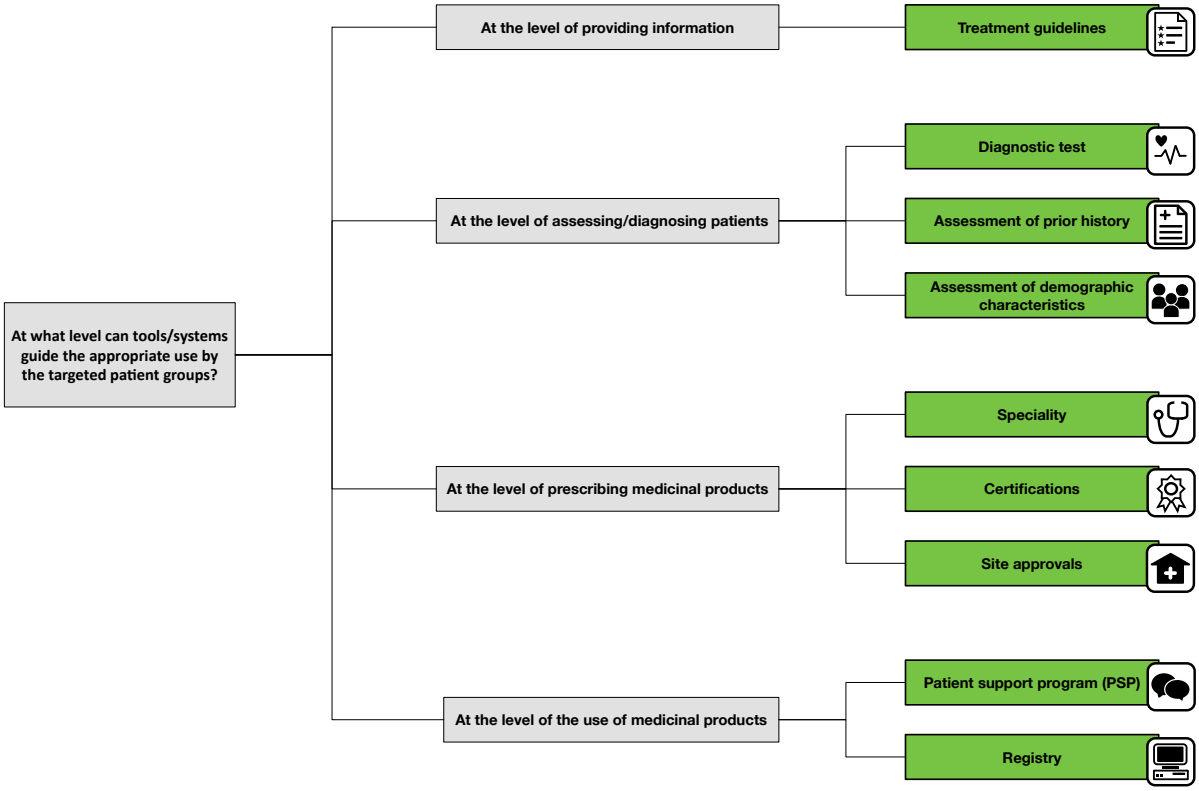

Figure 3: Structure of the survey.

3. Results

3.1 Availability of tools/systems for guiding appropriate use

The survey was sent to selected EFPIA company affiliates in twelve EU Members States (see Section 2). Companies were requested to involve all relevant internal and external expertise in completing the survey. All twelve EFPIA company affiliates have completed the survey.

Availability
Table 1 provides an overview of the tools/systems for guiding appropriate use of medicinal products and their availability in twelve EU Member States that participated in this survey. Four tools/systems were indicated by all twelve Member States to be available in their Member State for guiding appropriate use:
treatment guidelines, diagnostic tests, restrictions by prescriber's speciality and *registries*. Eleven out of twelve respondents indicated that *assessment of prior history* and *patient support programs* are available in their Member State for guiding appropriate use of medicinal products. It must be noted however that it was not clear to the Italian responder if and to what extent *assessments of prior history* are used as a tool/system for guiding appropriate use of medicinal products in Italy.

Certifications for prescribers are not very common in the twelve surveyed EU Member States when it comes to guiding appropriate use. Only four Member States (33%) have indicated that *certifications for prescribers* are available in their Member States.

In general however, the tools/systems included in the survey were widely available throughout the twelve Member States. In the few cases that a respondent has indicated that a tool/system is not available in their Member State, no underlying reasons were provided.

Consequences
Table 2 provides a summary of the potential consequences that are in place if prescribers are not complying to the tools/systems to guide appropriate use available in their Member State.
The four most common responses were:

- *no consequences,*
- *reimbursement restrictions,*
- *disciplinary procedures,*
- *and non-dispensing of the medicinal product.*

Differences can be observed between individual tools/systems when it comes to consequences for non-compliance. For example, for not complying to *treatment guidelines and registries*, most respondents indicated that prescribers are not confronted with any consequences. However, for *restricting prescriber speciality* as a tool/system for guiding appropriate use, reimbursement restrictions and disciplinary procedures are the most frequently provided consequences for non-compliance. Non-dispensing of the medicinal product is a potential consequence that plays only a minor role in the twelve Member States.

Differences between Member States can also be observed; for example in Germany, it was indicated that no enforcement mechanisms or consequences are in place for prescribers for not complying to the tools/systems that are available for guiding appropriate use. Yet, responders indicated that Spain, Italy, France and Poland implemented enforcement mechanisms in the form of reimbursement restrictions for the same tools/systems.

Additional tools/systems

Some respondents have named a number of additional tools/systems for guiding appropriate use:

- *Therapeutic plan [Italy]:* Therapeutic plans are regulatory instruments with the objective of ensuring the appropriateness of use of medications (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4221088/)
- *Circulars [United Kingdom]:* Communication channel/tool to prescribers that is integrated into the prescriber modules in the patient management software used at the clinics.

These specific national tools are not discussed further in this report as we did not find specific evaluations of the impact of these two tools on guiding appropriate use.

Table 1 – Overview of the availability of tools/systems for guiding appropriate use in twelve EU Member States

		(BE)	(CZ)	(FR)	(GE)	(IT)	(NL)	(PL)	(PT)	(RO)	(SP)	(SW)	(UK)	Availability
	Treatment guidelines	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	**100%**
	Diagnostic test	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	**100%**
	Assessment of prior history	☑	☑	☑	☑		☑	☑	☑	☑	☑	☑	☑	**92%**
	Assessment of demographic characteristics	☑			☑	☑	☑	☑		☑	☑	☑	☑	**75%**
	Speciality	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	**100%**
	Certification	☑				☑	☑	☑						**33%**
	Site approval		☑		☑	☑	☑	☑		☑				**50%**
	Patient support program	☑		☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	**92%**
	Registry	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	☑	**100%**

"☑" = tool/system available in Member State to guide appropriate use

Table 2 – Assessment of the consequences for not following the tools/systems for guiding appropriate use in the EU

		(BE)	(CZ)	(FR)	(GE)	(IT)	(NL)	(PL)	(PT)	(RO)	(SP)	(SW)	(UK)	O	€	✖	⊘
	Treatment guidelines	O		€	O	O	O	€/✖	O	O	€	O	✖/⊘	7	3	2	1
	Diagnostic test	O		⊘	O	€	O	€/✖	O	€		O	✖	5	3	2	1
	Assessment of prior history	O		€	O	N/a	O	€/✖		O	€	O	✖/⊘	5	3	2	1
	Assessment of demographic characteristics	€	N/a	N/a	O	€/⊘	O	O	N/a	O	€	O	✖/⊘	5	3	1	2
	Speciality	€/✖/⊘		€/✖	O	€/⊘	€	€/✖/⊘	O	€		✖		2	6	4	3
	Certification	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
	Site approval	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
	Patient support program	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
	Registry	O		O	O	€	O	O		O		O	O	8	1	0	0

"O" = No consequence; "€" = reimbursement restrictions; "✖" = disciplinary procedures; "⊘" = non-dispensing of the medicinal product; N/a = Consequences are not applicable for this tool/system

3.2 Impact of tools/systems on guiding appropriate use

Table 3 gives an overview of the scores that were provided by the respondents on how the impact of each tools/systems for guiding appropriate use was rated.

The impact of the speciality of the prescriber on guiding appropriate use was rated with the highest average score of 4.7 (with 5 being the highest possible score representing a high impact), followed by assessments of prior history (4.5) and diagnostic tests (4.3) [c]. Reasons for the high impact of the speciality of the prescriber are the fact that the speciality of the prescriber is a clearly identifiable part of a legal framework and healthcare practice and has been in place for many years. The speciality can easily be linked to enforcement mechanisms such as reimbursement criteria, as indicated by some Member States. For the diagnostic test and the assessment of prior history, respondents indicated that these assessments are already part of standard care and play a fundamental role in deciding on the right treatment.

[c] The impact of certifications for prescribers has been scored by only two respondents, therefore left out in the further analysis

Table 3 – Impact assessment of the tools/systems for guiding appropriate use

		(BE)	(CZ)	(FR)	(GE)	(IT)	(NL)	(PL)	(PT)	(RO)	(SP)	(SW)	(UK)	Total impact score
	Treatment guidelines	+	+	+	+	+/-	+	+	+	-	+	+	+	**4.0**
	Diagnostic test	+	**0**	+	+	+	+	+	-	+	**0**	+	+	**4.3**
	Assessment of prior history	+	+	+	+	N/a	+	+	+/-	+	+	+	+	**4.5**
	Assessment of demographic characteristics	+	N/a	N/a	-	+/-	+	+/-	N/a	+	+/-	-	+	**3.4**
	Speciality	+	+	+	+	+	+	+	+	+	+	+	+	**4.7**
	Certification	+	N/a	N/a	N/a	**0**	+/-	+	N/a	N/a	N/a	N/a	N/a	**4.0**
	Site approval	N/a	+	N/a	+/-	**0**	-	+	N/a	+	N/a	N/a	N/a	**3.6**
	Patient support program	+	N/a	+	+	+/-	+	+	+	+	-	+	+/-	**3.9**
	Registry	+	-	+/-	+	+	-	+	+	+	+/-	+/-	+/-	**3.7**

"+" = High impact; "+/-" = moderate impact; "-" = low impact; "0" no score provided (e.g. impact not known or tool/system not available in Member State); "N/a" = not applicable (tool/system not available in Member State); Impact: 5 = high; 1 = low

3.3. Implementation of tools/systems for guiding appropriate use

Table 4 presents the findings from the implementation analysis of the tools/systems. Three tools/systems (speciality, assessment of demographic characteristics and assessment of prior history) obtained the lowest average scores (1.5, 1.6 and 1.8 respectively), showing that the implementation of these tools/systems is/was relatively easy. In comparison, Certifications for prescribers, PSPs and registries have obtained the highest average scores of 3.5, indicating that these tools/systems require a relatively larger effort for implementation.

Table 4: Implementation score of tools/systems to guide appropriate use

		Implementation score (# of respondents)
	Treatment guidelines	2.8 (11)
	Diagnostic test	3.2 (9)
	Assessment of prior history	1.8 (8)
	Assessment of demographic characteristics	1.6 (7)
	Speciality	1.5 (10)
	Certification	3.5 (2)
	Site approval	3.0 (5)
	Patient support program	3.5 (12)
	Registry	3.5 (10)

Difficulty to implement: 1 = Easy; 5 = hard

4. Outcomes of the discussion during workshop, STAMP and future research

The survey described in the previous sections of this report aimed to provide insights into the tools and systems to guide appropriate use that are currently available in the EU Member States that were included in this study. As such, this survey was meant to provide input for the achievement of the objectives of D2.07 of IMI ADAPT SMART, which is to provide proposals for further study and recommendations to the national health systems, EMA, the European Commission, healthcare providers and patients. For these proposals and recommendations, a workshop on the 17th January of 2017 was organised at the EMA in London, which was attended by experts from different stakeholders such as European regulators, Health Technology Assessment (HTA) bodies, the pharmaceutical industry, patient organisations, healthcare professionals and academia. This section reflects the discussions at the workshop and draws some general conclusions based on the survey and the workshop discussion.

General discussion

As the survey shows, in general, there is already a large concurrence of tools/systems that are used to guide appropriate use in the EU. Most tools/systems are being used in all surveyed Member States. Tools/systems that are used less extensively are certification for prescribers and site approvals. In the survey we asked participants to provide us with additional tools/systems in case they were missing. Although some specific tools were mentioned from Italy and the UK, we received no information that indicated that there were broad categories of tools/systems that we had missed. Two additional topics were highlighted in the discussion at the workshop. First, the use of registries provides a potential to monitor the use of medicines, and also create the possibility to capture other relevant data, such as data on patient reported outcomes and patient views. Registries were included in the survey, but their use could be explored in more detail in future activities. A second tool that was mentioned was to monitor dose adherence ("Is the indicated dose being used?").

With regard to impact of the tools/systems, the survey respondents indicated that restrictions at the level of prescribing have the highest impact. In general, limited evidence is available on the impact of tools/systems that are used to guide appropriate use as well as on cost-effective measures for influencing prescriber, pharmacist and patient behaviour is limited [d]. This would be a strong recommendation for future EU research projects. At this moment, this area of research is underserved, especially in light of the economic and healthcare relevance. Future research should also expand the survey conducted here to other Member States.

Notwithstanding, in EU Member States a general principle of therapeutic freedom to prescribe for physicians exists. This means that use of medicines can only be restricted to the extent that it does not result in an unreasoned limitation of the access to possible treatment to patients [e]. Considering the very specific and unique challenges presented by MAPPs, i.e. a restricted indication, limited population, and objective need for careful and controlled post-marketing authorisation (post MA) data gathering/analysis, it is crucial that this "freedom of prescribing" is more closely monitored for MAPPs. It is important to note here that MAPPs is not a separate regulatory pathway, and makes use of the existing procedures and legal routes for, e.g. approval under conditional-, or exceptional conditions (including orphans). However, some additional (national) elements may need to be put in place in agreement with all stakeholders to ensure both appropriate use and further data gathering

[d] Lee et al. International experience in controlling pharmaceutical expenditure: influencing patients and providers and regulating industry - a systematic review. J Health Serv Res Pol 2015;20:52-59.

[e] Belgian Health Care Knowledge Centre. Towards a better managed off-label use of drugs. https://kce.fgov.be/sites/default/files/page_documents/KCE_252_Off-label%20drugs_Report.pdf

for later analysis. Post-MA data collection on each and every patient receiving a medicinal product approved under MAPPs is recommended where feasible.

The results in the context of STAMP

An important point for discussion is how this report should be considered in the context of the Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP). At the STAMP meeting in December 2016 results were presented on a broad survey conducted by the EMA on prescription control to the initially licensed population[f]. Individual responses from countries were not available to us, so we could not compare these responses with the results presented here. Also, it was not clear how many countries filled in the survey. However, this important report highlighted a few items: the importance of the SmPC wording and communication to prescribers, the value of electronic prescription and electronic data capture, the use of registries and stakeholder engagement. The report highlighted the differences between Member States, and that the potential to control prescribing may depend on the therapeutic area. The report puts a lot of emphasis on the potential use of registries and pay for performance schemes, especially based on the experiences in Italy and Finland. The report also discussed how real-world data could be extracted from such registries. The STAMP report did not detail the availability of tools in different Member States and their potential impact. This report, therefore, is complementary to the STAMP report and supports some of it main conclusions.

Both this report and the STAMP report clearly indicate that investing in evidence on successful tools/systems can help to identify which strategies are most suitable for a MAPPs context. However, it has to be acknowledged that these tools/systems operate within a very diverse environment. For example, possibilities to curtail the freedom to prescribe for doctors may be very different in Germany compared to The United Kingdom. The diversity of enforcement mechanisms can also be seen in the results of the survey and may pose challenges when implementing a universal approach for guiding appropriate use throughout the EU. Moreover, (restrictive) policy measures existing on paper may be only a limited explanation for medicines use in practice[g]. The scope and resources for this survey did not allow us to explore the diversity in detail. We recommend national health systems and the European Commission to further explore a number of these tools/systems, for example in the STAMP working group or in future IMI projects. A particular topic of interest is how cross-border data collection and research can be strengthened. During the workshop, the challenges to make progress in this area were recognized (e.g. investments to set-up the registries, lack of cross European platforms for registries, how to compensate/motivate physicians for using a registry, how to assure the robustness of (real-world) data, how to avoid misuse and how to assure interoperability in different regulatory environments). However, the potential value of such cross-border data collections is expected to outweigh the barriers that have to be overcome, according to the experts in the workshop. Learning from existing EU experiences (e.g. in Italy) seems key here. Furthermore, the work on registries in the EU should take place in close coordination with various EMA initiatives.

Limitations and recommendations for further research

There are a number of limitations that apply to this study. First, the questions relating to the impact and implementation of tools/systems to guide appropriate use of medicinal products are subject to judgement and local expertise of the responder. This could therefore introduce bias to the responses collected. We therefore urge readers to put the overall results on impact and implementation into perspective, as measurable impact or data on implementation was often not available.

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[f] European Medicines Agency. Prescription control to the initially licensed population. https://ec.europa.eu/health/sites/health/files/files/committee/stamp/2016-03_stamp4/5a_adaptive_pathways_stamp_questionnaire_summary_of_responses.pdf

[g] P Stolk et al. Variable access to clopidogrel in a harmonized EU market. Value Health 2008;11:989-995

Another limitation of this study was the sole inclusion of EFPIA member companies in this survey. In light of the scope and the limited resources of the ADAPT SMART we were not able to extend the survey to other stakeholders. However, due to the exploratory nature of this study, we believe that the inclusion EFPIA member companies, with their national expertise and access to the local healthcare network, was regarded a valid approach to address the objective of Workstream D2.07. Nonetheless the authors recognize that in order to increase the scientific impact, this study needs to be extended with views and experiences from other stakeholders (e.g. regulators, healthcare professionals, payers etc.).

Finally, it was mentioned during the workshop that the survey could benefit from an extension to more EU Member States. Although the level of agreement among responders seen the results is already pointing towards a sufficient responder-sample that was currently included in the survey, as well as a representable mix of Member States was included, additional Member States may always be providing new valuable information.

The questions in the survey relate to the general situation in a Member State. Within the context of the discussion about the implementation and feasibility of MAPPs pathways, arrangement will often have to be 'tailor-made' for a specific type of medicine, disease or patients. Moreover, it could be argued that tools/systems that are used to guide appropriate use should be an integral element for an approval under MAPPs. Therefore, we would recommend designing scenarios for different types of products and asking Member States (including Central and Eastern European countries) how they would manage appropriate use in this specific case. This could also be part of a future IMI project. This scenario could also build on the experience in simulation studies in projects such as ADAPT SMART (see for example the joint GetReal/ADAPT SMART workshop in June 2016). It could also be relevant to involve prescribers and patients in such simulations, as this may help to design systems that will work in practice and create a political will for solutions.

In conclusion, the results of the survey indicated a certain level of agreement between Member States with regard to the availability of tools and systems to guide appropriate use, for example, treatment guidelines, diagnostic tools and restricting prescriber speciality are available twelve surveyed EU Member States. However, there are also some differences observed when it comes to the availability of tools/systems, especially for certifications and site approvals. Overall the highest impact of the tools/systems on guiding appropriate use was indicated for restricting prescriber specialty, assessments of prior history of the patient and diagnostic tests. A diversity of enforcement mechanisms can also be seen in the results of the survey when it comes to non-compliance. Further research and designing scenarios could help identifying tools/systems to guide appropriate use in the MAPPs context.

Annex

Annex 1: Overview of the EFPIA member companies for each of the twelve surveyed EU Member States.

Member State		**EFPIA affiliate**
Belgium	(BE)	UCB Pharma
Czech Republic	(CZ)	Novartis
France	(FR)	Astra-Zeneca / Servier
Germany	(GE)	Merck Sharp & Dohme (MSD)
Italy	(IT)	Amgen
Netherlands	(NL)	Sanofi
Poland	(PL)	Sanofi
Portugal	(PT)	UCB Pharma
Romania	(RO)	Sanofi
Spain	(SP)	Novartis
Sweden	(SW)	Merck Sharp & Dohme (MSD)
United Kingdom	(UK)	Ipsen