EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Health systems, medical products and innovation
Medicines: policy, authorisation and monitoring

STAMP 4/23 rev.1

STAMP Commission Expert Group
10 March 2016

Subject: Real world evidence

Agenda item 4

In the previous meeting members of STAMP have raised registries and other sources of real world data as a point for further consideration by the group.

There are discussions on the use of real world data and real world evidence in relation to medicinal products. Real world data can be described as observational data that is not collected under experimental conditions (randomised clinical trials) but data generated in routine care from information related to a patient's treatment. It can come from patient registries, electronic health records, insurance data and web/social media. Real world evidence can be generated from such data sources according to a research plan. The research plan can be studies that are established to collect the data specifically for research purposes (primary data) or evidence coming from data collected for other purposes (secondary data). Examples of the use of real world evidence are: comparative effectiveness research and patient adherence studies; drug development (clinical feasibility studies, inform the design of pivotal trials); reimbursement (relative effectiveness assessment, marketing access arrangements).

In previous meetings of STAMP discussions regarding real world evidence, in particular registries, have been mainly in the context of adaptive pathways and the following questions were raised: the legal and operational issues related to the use of registries; the governance of the data; data protection issues; the purpose of the registry; data source/methodological approach for data collection; the status or type of the registry; whether the data collected is relied on to make the benefit/risk assessment; the administrative burden on the healthcare system to collect the data; who bears the cost of the registry; the readiness of Member States to manage the databases if they are relied on to judge the marketing authorisation.

The attached paper, prepared by the European Medicines Agency, gives an overview of the data sources that can be used to collect real world evidence and the potential use of the data. It outlines the ongoing initiatives to increase the utility of real world evidence; the challenges regarding the data collection and use; and gives examples of post marketing studies that have utilised sources of real world evidence.

In addition, the Italian representative will give a presentation of their experience of using registries for reimbursement purposes.

There have been various initiatives exploring the possibilities of utilising real world data to generate evidence to optimise patients' treatments. The STAMP is invited to consider the opportunities for the use of real world evidence and what are the limitations or gaps in knowledge that might need to be addressed.

The following questions are posed to help structure the discussions. Other questions or suggestions are welcome.

1. What are the views and experience of Member States in the use of real world data to support safe and timely access to medicines for patients?

2. For what purposes can real world evidence be used?

3. Are there any limitations related to the use of the data/evidence?

4. What are the barriers to generation of real world data or the use of real world evidence?

5. How could the use of real world data/evidence be optimised? What are the possibilities for cooperation?

Annex
STAMP 4/23 rev.1

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 March 2016
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Paper for STAMP meeting 10 March 2016: Update on Real World Evidence Data Collection

Summary

Big data is an umbrella term describing large data sets from any source. Real world data is a term used to describe healthcare related data that is collected outside of randomised clinical trials. In this paper we focus on real world evidence (RWE) meaning evidence coming from registries, electronic health records (EHRs), and insurance data where studies may be required by regulators through scientific advice, CHMP or PRAC and the subsequent results are used to inform regulatory and potentially HTA decision-making.

RWE is already in routine use in the EU. This is particularly true for products on the market and for safety monitoring and drug utilisation. There is increasing interest in the use of RWE for efficacy, outcomes for HTA, and for rapid cycle evaluation of medicines.

For products in development clinical trials remain the most important source of knowledge. However, RWE can inform development for example providing information on existing therapies and on the profile of patients needing treatment. Early product entry in niche indications will most likely use registries to collect effectiveness, safety and HTA information. EHR, and insurance data will become major sources of knowledge once the use of a product is more established.

There is major potential to increase the use of RWE to support lifecycle product development and monitoring and to improve decision-making for regulation and HTA. While the greatest potential is for authorised products, there is an important role in supporting innovative products and adaptive pathways.

There are challenges to realising the full potential for RWE and these include: incomplete access to electronic healthcare data from different MSs and a lack of hospital in-patient data; variable data quality and a lack of harmonisation; the need to develop methods for efficacy and HTA outcomes; and delays to start studies.

There are already many national and EU initiatives ongoing to strengthen RWE. Through good coordination and a cross-stakeholder collaborative approach we can address the challenges and realise the full potential of RWE in supporting product development, monitoring and decision-making.

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Introduction

The use of real world evidence (RWE) in the support of drug regulation was last discussed on 20th October 2015 in the context of the EMA Adaptive Pathways Pilot. At the time it was agreed that a survey would be conducted, the results of which are the subject of a separate paper and presentation. This paper provides a high level overview of the utility of RWE across the life cycle of a medicine including its contribution now and in the future to STAMP (Safe and Timely Access to Medicines for Patients), an update on EU initiatives relevant to RWE and in a discussion of the gaps and opportunities.

What are we talking about?

Big data is an umbrella term describing large data sets from any source. Real world data is a term used to describe healthcare related data that is collected outside of randomised clinical trials. In this paper we focus on real world evidence (RWE) meaning evidence coming from registries, electronic health records (EHRs), and insurance data where studies may be required by regulators through scientific advice, CHMP or PRAC and the subsequent results are used to inform regulatory and potentially health technology (HTA) decision-making. Annex 1 provides a graphic to help visualise RWE as a subset of big data relevant to healthcare.

For the vast majority of products RWE will not replace the gold standard evidence for pre-authorisation development derived from randomised controlled trials (RCTs), however RWE has significant potential to support drug regulatory and HTA decision-making by providing information on a medicine's use, effectiveness and safety in real world environments with a particular utility in monitoring authorised medicines on the market. The term can encompass data collected during the course of routine clinical care (for example electronic health care records, hospital data, health insurance data, sales data and spontaneous reports of adverse reactions) or prospectively as part of patient registries (drug or disease registries) or biobanks. In addition to these more traditional sources in current use today, the growth in digital technologies in relation to health status opens the possibility of using more innovative datasets to inform regulatory decision making in the future. The integration of these multiple sources in the future will realise the full power of RWE in monitoring drugs and in decision-making for regulators, HTAs and payers.

Place of RWE in supporting life-cycle medicines development and STAMP

Current use of RWE

Benefit-risk decisions are already based on a combination of clinical trials data, with their excellent control for bias but the associated inherent uncertainties with regard to real world applicability, and RWE which mainly stems from post-authorisation data and where most experience comes from observational safety studies. Clearly the balance between RCTs and RWE swings from RCT dominance at initial authorisation (and for extensions of indication) to a much greater use of RWE post-authorisation.

Currently, RWE is used by some companies to support decision-making during drug development (burden of disease, patient profiles, existing therapies), and in the regulatory environment most newly authorised medicines have observational studies either imposed as a condition of the marketing authorisation, or as a requirement in the risk management plan. The large majority of these studies

are post-authorisation safety studies, including drug utilisation studies, imposed using the tools of the EU pharmacovigilance legislation. They are frequently registries or use well established pharmacoepidemiological methods based on secondary use of healthcare data. In addition RWE can be used to measure the background incidence of adverse events so that suspected adverse reactions reported in the post-authorisation phase can be put into perspective (observed vs. expected).

There is great potential to extend such approaches to study use of medicines more systematically, looking to see how efficacy performs in real-world use and to rapidly and iteratively monitor (rapid-cycle evaluation) the use, safety and efficacy of new products. There is also great potential to support HTA by looking at patient outcomes relevant to healthcare utilisation.

Place of RWE

RWE is pertinent in meeting the challenges posed by innovative medicines including for approaches such as adaptive pathways which aim to facilitate the timely access of patients to new medicines. The latter allows for early and progressive patient access to a medicine but requires the benefit-risk balance of a product, following initial approval, to be confirmed via the collection of data from real-world use.

RWE can support access to novel products by providing information across the life cycle of a medicine from development through to HTA. For example RWE could support product development by providing information on the natural history of the disease and the unmet need, an understanding of resource utilisation and current standards of care, patient recruitment and potentially differential benefit-risk profiles in targeted subpopulations. Following the initial approval, patient registries (including registries linked to and enriched by existing data from real world use), electronic health records and established pharmacovigilance tools will be critical in ensuring products authorised through adaptive pathways are closely followed for their use, effectiveness and safety.

RWE therefore has the potential to significantly enhance decision making across the spectrum of drug regulation and throughout the life cycle of a medicine. Consideration of the appropriateness of RWE, particularly compared to RCTs, needs to take place during the lifecycle and will be critical in Scientific Advice and during the assessment of the Marketing Authorisation Application. Post-authorisation, RWE can contribute to decision-making by providing an understanding of how efficacy established within the clinical trial environment translates in the real world, a characterisation of the real-world safety of a product and oversight of how the product is used in practice (indications and populations). In addition, widespread access to RWE would be invaluable in providing information on long-term outcomes, national differences in drug utilisation patterns across the EU, the place of the medicine in the standard of care armamentarium and how these aspects impact upon benefit risk. RWE can also contribute significantly to health technology assessments by providing information on healthcare resource utilisation, patient compliance and the real world effectiveness of new medicines in comparison to existing treatments.

Ongoing Initiatives

EU level initiatives to increase the utility of RWE (mainly ongoing) include:

- initiatives on patient registries (such as PARENT Joint Action, ENCR - European Network of Cancer Registries, Eurocourse and the EMA Initiative on Patient Registries);
- initiatives on electronic health records (such as EH4CR, EMIF, EU-ADR Alliance, RD-Connect, epSOS, EuroRec);

- initiatives aimed at establishing methods and platforms to enable and facilitate data access, analysis and collaboration (such as IMI GetREAL, IMI PROTECT, IMI ADAPT SMART, IMI ADVANCE, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance - ENCePP);
- initiatives on HTA (EUnetHTA JA3 aims to conduct pilots on post-launch evidence generation and to develop a tool to support permanent collaboration on post-launch evidence generation);
- approaches aimed at the exploitation of social media (IMI WebRADR).

In addition some Member States have funded national initiatives aimed at harmonisation RWE such as the Farr Institute in the UK and the national EHR systems in Denmark, Finland, and Sweden which aim ultimately to capture the EHRs of their entire population.

Registries

The overall objective of the PARENT Joint Action was to support the EU Member States in developing comparable and interoperable patient registries in fields of identified importance (e.g. chronic diseases, medical technology) with the aim to rationalize the development and governance of patient registries and enable analyses of secondary data for public health and research purposes in cross-border settings. The consortium has produced guidance on methodology and recommendations for the efficient and rational governance of patient registries in addition to a web based inventory, the Registry of Registries (RoR). It will be important to determine if such guidelines can be implemented by other consortia such as the ENCR whose aim includes the promotion of collaboration between cancer registries and the definition of data collection standards in order to provide improved information on the burden of cancer in Europe. In 2015, in recognising the important role that registries can play in monitoring the safety of medicines, the EMA established an initiative to encourage better use of existing registries and facilitate the establishment of high-quality new registries (if no existing source is appropriate). As part of the initiative the EMA aims to deliver guidance around the common data elements, standard methods and governance principles for registries which will build upon the technical guidance provided by PARENT JA. Further details are provided at Annex 2.

Electronic Health Records (EHRs)

There have been a number of initiatives aimed at increasing the accessibility and utility of EHRs across multiple Member States for both clinical research (EHR4CR, GetREAL, EMIF, epSOPS) and drug safety (EU-ADR, PROTECT, ADVANCE). It is critical that the promising work delivered by these initiatives feeds into future work. For example, EHR4CR, which finished in 2015 aimed at providing adaptable, reusable and scalable solutions (tools and services) for reusing data from EHR systems for Clinical Research. The resultant EHR4CR platform due to be launched later this year will provide secure access to multiple hospital EHR systems and clinical data warehouses across Europe, to enable a trial sponsor to predict the number of eligible patients for a candidate clinical trial protocol, to assess its feasibility and to locate the most relevant hospital sites. As an illustration of the potential value, the Salford Lung Study provides the first example of a Phase III trial involving the use of EHRs to identify patients, assess outcome and provide safety assurance. The work of IMI GetREAL which will finish in October 2016, aims to show how robust new methods of RWE collection and synthesis could be developed and considered for adoption earlier in pharmaceutical R&D and the healthcare decision making process; this work should allow better exploitation of the platform provided by EHR4CR as well as similar resources. Equally EMIF (European Medical Information Framework) aims to create an environment that enables the consistent re-use and exploitation of currently available patient-level data. To support novel research the platform intends to provide the means to "browse" data on around 40 million European patients across 7 member states via advanced search, analysis and visualisation functionalities and navigations interfaces. Pragmatically the work will focus on two research questions initially, metabolic disease and Alzheimer's disease, as a proof of concept that will help guide a wider information framework in the future.

Capacity-building work from the EU Regulatory Network (in addition to the registries initiative)

Recognising the importance of RWE, the EU Regulatory Network, is already involved in building capacity in this area. ENCePP established in 2008 facilitates the conduct of high quality multi-centre, independent post authorisation studies by developing and maintaining methodological standards and governance principles and by providing a platform for collaboration (http://www.encepp.eu/). The methods work has included specific consideration of challenges and opportunities for studies to deliver results for HTA as well as for regulatory needs. ENCePP also provides a freely accessible online database of resources in RWE comprising networks, data sources and centres of excellence.

In January 2015, the EMA Pharmacovigilance Risk Assessment Committee (PRAC) adopted a strategy for measuring the impact of pharmacovigilance measures that relies heavily on using RWE (http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/01/WC500199756.pdf). Proof of concept studies are underway to use a common protocol at EMA, in the UK and in Spain to study the impact of risk minimisation measures for the medicine codeine used in children, by using RWE to study drug use over time, including compliance with indications and contra-indications. Lessons-learnt from this study and potential rollout to other real-world scenarios, are foreseen in the 2016 EMA work-plan.

Annex 3 provides some examples of how RWE has been used to support drug safety work at the PRAC over recent years.

Realising the full potential of RWE for STAMP

RWE is already routinely used in aspects of regulatory monitoring and post-authorisation decision-making. The initiatives described above highlight that RWE will play an increasingly important role in health care decision making and illustrate the substantial amount of existing investment. While registries can potentially be established in any healthcare market, secondary use of EHRs or insurance data requires that such data exist and for it to be accessible and analysable.

There are challenges to realising the full potential based on EU-wide, rapid access to robust data:

- Not all Member States have widespread use of EHRs. In some Member States the insurance market is fragmented, and data may be commercially owned and either not shared or only sold at a high price. This results in an incomplete longitudinal follow-up of individuals and of duplication of individuals' records in different systems that may not be reconcilable if the records are anonymised as soon as they leave the healthcare system (e.g. the GP practice, the laboratory, the hospital);
- Some Member States healthcare data cannot be shared across borders and new data protection regulations in the EU will need to be assessed for their impact on secondary use of RWE;
- Electronic recording of healthcare data at patient level is relatively limited in hospital care and this presents a gap for specialist use products (underlining the critical role for registries for such products);
- Data quality is variable and data structure and choice of terminologies and languages differs between Member States and between databases within Member States. This means that combining data or running studies across datasets may require mapping or data conversion which can be expensive and time consuming;
- While methods for drug safety studies and drug utilisation are now very well established, use of RWE for efficacy studies and for health outcomes for HTA are less well developed, and further methods development and validation are needed;

- Delays in starting studies are found and while the reasons are multiple, key include: a lack of proactivity by industry (very few scientific advice requests for post-authorisation RWE studies); limited expertise within small companies; and, regulatory complexity (PASS vs PAES, EU vs national, imposed vs voluntary, one MS vs multiple MS, etc);
- Real world data are generated for clinical management of the patient, not for the purposes of research or medicines regulation. As a result, a thorough understanding of the healthcare system that underlies the data generation is crucial for the design, analysis and interpretation of studies using the data;
- Fragmentation of initiatives to support development and use of RWE;
- Lack of sustainable funding to allow routine data processing and analysis, and therefore support fast conduct of studies as, without sustained funding, data processing needs to be re-initiated for each of them.

While these challenges exist, it should be remembered that RWE studies already support routine medicines regulation and decision-making every month at the EMA committees. The challenges listed are challenges to realising the full potential of RWE and with collaboration and focus they can be addressed.

Longer-term

While a common data model has been possible in the U.S. (the 'Sentinel' System) and in the EU in a number of IMI or FP7 funded studies, a common system in the EU cannot solely rely on this approach. The long-term goal for RWE in the EU should include connecting and making best use of the diversity of healthcare systems and data available. Whereas common data models may be beyond what can be obtained in some data sources, minimum data requirements, common data fields, agreed mappings between terminologies, common protocols run in different data bases and much greater access to data underpinned by robust governance should be obtainable with sufficient effort and collaborative, cross-stakeholder support.

A further opportunity for the future will be the systematic integration of genomic and potentially other 'omic' data into EHRs. Given the known influence of genomic variation on both drug efficacy and safety and the increasing use of genetic testing for commonly used medications such as warfarin, genomic information has the potential to stratify benefit-risk much more accurately. Some initiatives are already combining genomic information with clinical information. For example the UK Biobank holds genetic and biochemical data on 500,000 carefully phenotyped people who have agreed to have their health followed long term via electronic health records; all data is made available for research on an open access basis. Similar data exist in other European countries, notably Denmark where the Danish National Biobank which links electronic data about all residents in Denmark with access to over 16 million biological samples. EU wide initiatives exist aiming to establish a pan-European distributed research infrastructure of biobanks and bimolecular resources which currently includes 16 Member States and one international organisation which may provide relevant models for other datasets.

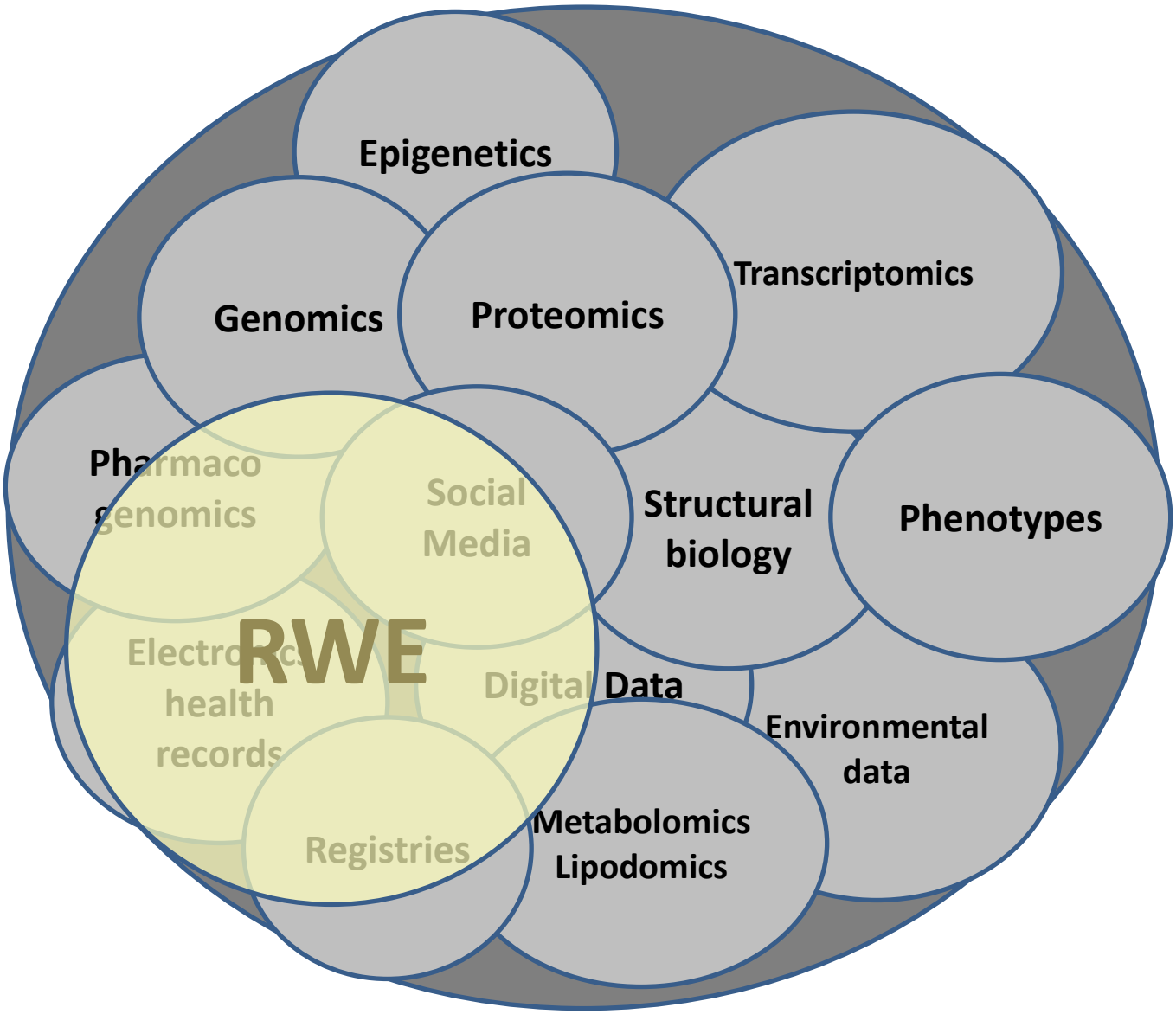
Lastly, although a long way from current utility in regulatory decision-making, there is a growing interest in how online activity and behaviour data, in addition to data from wearable technologies and mobile devices, can be integrated with the more structured, traditional datasets to inform our assessment of the disease process and its progression (disease phenotype) and treatment efficacy, safety, use and compliance. Obvious examples of current applications are the use of online health data to monitor outbreaks of infectious disease and the use of large scale analysis of web search queries to identify adverse drug reactions (currently being evaluated through the IMI-funded WEB-

RADR project). New approaches will be required to capture and better utilise the various digital modalities in a routine way to inform both clinical and regulatory decision making in the future.

Conclusions

RWE is in routine use today for certain aspects of drug monitoring and decision-making. This is most established in drug safety and drug utilisation but holds promise also for efficacy monitoring and rapid cycle evaluations of drugs. There are multiple opportunities for RWE to support STAMP both in drug development, to supplement RCTs and once a medicine is on the market and this is reflected in multiple EU and national initiates on registries and EHRs / insurance data. Challenges remain before the full potential of RWE will be realised but these can be surmounted with focussed, cross-stakeholder collaboration.

Annex 1: Graphic to explain that RWE is a subset of big data relevant to healthcare



Annex 2: Synopsis of EMA initiative on registries

Patient Registry Initiative

In September 2015 the European Medicines Agency launched an initiative on patient registries following the recognition that regulators increasingly requested the use of registries to measure the safety or efficacy of individual products in routine practice but that predominantly companies chose to establish new registries rather than use existing disease registries. This potentially results in a duplication of effort, a slower resolution of the initial concern and multiple relatively inflexible registries which have limited applicability beyond the initial specific product. The aim of the Registry Initiative is to facilitate interactions at an early stage in the authorisation procedure between industry and registry owners to increase use of existing registries. Where no suitable disease registry exists the initiative would support the MAH to create a new registry based on standard methodological approaches created by the PARENT JA initiative, including the application of standard core data elements and standardised protocols to ensure that the new registry has wider applicability. Through this process the initiative will highlight the challenges faced by industry in establishing new registries or interacting with existing registries allowing the EMA to put measures in place to better facilitate the process.

In order to determine if this strategy better supports MAAs/MAHs to meet regulators (or other stakeholders) needs, a pilot phase has been initiated. To support the launch of the pilot phase a task force was appointed composed of representatives of EMA scientific committees and working parties, the European Commission, experts from National competent authorities and EMA staff.

To date the initiative has received 10 expressions of interest from both registry owners and MAHs. Four case studies have been identified from discussions which together represent the need to either establish a new registry, use an existing disease registry or the need to use a combination of both approaches. The products include two gene therapy products, a treatment for metabolic disease and a T-cell receptor therapy. A workshop is envisaged for later in the year incorporating key stakeholders to discuss the identification of standard methods and processes for patient registries.

Ultimately through this pilot the initiative aims to:

- Understand the challenges faced by registries and industry alike in collaborating;
- Understand how regulators can better facilitate relations to avoid duplication of effort;
- Identify and evaluate existing data tools;
- Build a toolkit of methodological guidelines building on those created by PARENT JA;
- Establish privacy and governance models;
- Map coordination between ongoing initiatives at national and international levels.

Annex 3: Some examples of the use of RWE to support decision-making at the PRAC

Table 1: Studies initiated by EU regulators to support decision-making

Topic	Year	EU PAS Register ID
A/H1N1 pandemic vaccines and pregnancy outcomes	2010	5304
Impact of risk minimisation in patients treated with rosiglitazone-containing products	2010	2236
Isotretinoin and the effectiveness of the Pregnancy Prevention Programme in Europe	2011	4654
Patterns and determinants of use of oral contraceptives in the EU	2011	3520
Monitoring the effectiveness of risk minimisation in patients treated with pioglitazone-containing products	2011	3221
Risk of cardiac valve disorders associated with the use of biophosphonates	2011	7967
Association between anxiolytic or hypnotic drugs and total mortality	2012	1062
Metformin use in renal impairment	2013	7492

Table 2: Analysis of e-health data initiated by EU regulators to strengthen drug safety signals (examples)

Topic	Year	EU PAS Register ID
Self-controlled case series study in THIN on fluoroquinolones and retinal detachment.	2014	6708
Prescription patterns of combined hormonal contraceptives with 3rd or 4th versus 2nd generation progestogens in France, Germany and the UK during 2002- 2011: A retrospective analysis of the IMS Disease Analyser databases	2013	3712
EMA drug utilisation study of cyproterone-ethinylestradiol products	2013	3718
Trends in co-prescribing of renin-angiotensin system (RAS)-acting agents in France, Germany and the UK during 2001 - 2012.	2013	4389
Prescribing of zolpidem in the primary care setting in France, Germany and the UK during 2012.	2013	5106
Prescribing of testosterone in the primary care setting	2014	6827
Initial drug utilisation analysis of statin use in Germany, France and UK	2014	n/a

Table 3: Requests to ENCePP for real world data in the context of PRAC reviews and information received.

Topic	Information received
Combined hormonal contraceptive and risk of venous thromboembolism + medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 mcg and risk of venous and arterial thromboembolic events	Data from IMS on the dispensing of CHC in 5 EU countries
Flupirtine-containing medicines and concerns over liver problems associated with their use for short- and long-term pain relief	None
Strontium ranelate in the treatment of osteoporosis	* 1 centre provided a review of 51 publications and EU guidelines * 2 centres provided 1 published article * 1 centre provided a review of status of strontium ranelate in its country * 1 centre provided a paper and final report of a prescription event monitoring study and review of cardiovascular events identified * 1 centre provided information from HTA body in its country
Oral bromocriptine-containing medicines indicated in suppression of lactation post-partum	* 1 centre: review of spontaneous ADR reports * 1 centre: nb. of users and prescriptions in the country * 1 centre: research paper
Valproate and use in pregnant women	* 3 centres: set of publications related to previous studies
Oral methadone containing also povidone	None
Ambroxol- and bromhexine- containing medicines and allergic reactions	* 1 centre: review of spontaneous ADR reports * 1 centre: results of data analysis on mucolytics
Codeine-containing medicines < 18 years and risk of morphine toxicity	* 1 centre: review of spontaneous ADR reports * 1 centre: report on codeine use, misuse and dependence
Hydroxyzine-containing medicines and pro-arrythmogenic potential	* 1 centre: review of spontaneous ADR reports * 1 centre: review of cases series of 22 patients hospitalised in emergency department

Table 4: FP7-funded drug safety studies based on real-world data to support EMA benefit-risk evaluations (2007-2013)

Study	Topic
SOS	Cardiovascular and gastrointestinal safety of NSAIDs
ARITMO	Arrhythmogenic potential of drugs
ADDUCE	Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects
EUROmediCAT	Safety of Medication use in Pregnancy in Relation to Risk of Congenital Malformations
PHARMACHILD	Long-term Pharmacovigilance for Adverse effects in childhood arthritis
STOP	Suicidality: Treatment Occurring in Paediatrics
CARING	Cancer risk and insulin analogues
SAFEGUARD	Safety of anti-diabetes drugs (cardio/cerebrovascular and pancreatitis/pancreatic cancer)
Astro-Lab	Assessment of safety of LABAS in asthma in routine care by combining healthcare databases and direct patient follow-up
EpoCan	Risk of thromboembolic events and tumour growth progression in cancer patients, and cardiovascular and cancer risk in chronic kidney disease
Prediction-ADR	Genetic factors predisposing patients to adverse reactions (ADRs) from cardio-vascular disease drugs.