ORIGINAL ARTICLE

Open Access

Expert opinion on Real-World Evidence (RWE) in drug development and usage

N. Martini¹, G. Trifirò², A. Capuano^{3,4}, G. Corrao⁵, A. Pierini⁶, G. Racagni⁷, L. Pani^{8,9,10}

¹ ReS, Research and Health Foundation, Rome, Italy

² Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy

³ Department of Experimental Medicine, University of Campania Luigi Vanvitelli, Naples, Italy

⁴ Regional Center of Pharmacovigilance, Campania, Italy

⁵ Department of Statistics and Quantitative Methods, Section of Biostatistics, Epidemiology and Public Health, University of Milan Bicocca, Milan, Italy

⁶ Integrated Access Roche, Monza, Italy

⁷ Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy

⁸ Department of Biomedical Sciences, Metabolic and Neuroscience, University of Modena and Reggio Emilia, Modena, Italy

⁹ Department of Psychiatry and Behavioral Sciences, University of Miami, Miami, FL, USA

¹⁰ VeraSci, Durham, NC, USA

E-mail: nello.martini@libero.it; luca.pani@unimore.it

Summary

Real-World Data (RWD) refers to data on patients' health status and the provision of health services that are routinely collected from various sources during routine clinical practice. The scientific evidence on the potential benefits and risks of a drug derived from the analysis of RWD, and, therefore, related to the use of drugs in the Real-World setting, is called Real-World Evidence (RWE) (1). Randomized clinical trials (RCTs) are the gold standard of clinical research to assess the efficacy and safety of a drug treatment, but they have a number of important limitations that make their results difficult to generalize to the entire populations of patients treated in everyday clinical practice: this is why RWE is becoming increasingly valuable in clinical and regulatory practice (2). RWD are useful in the pre-marketing phases of drug development, providing information on disease burden and unmet clinical needs, as well as in the post-marketing phases, where scientific evidence can be generated on drug uptake, prescriptive appropriateness, comparative effectiveness research, short- and long-term drug safety and implementation and impact of risk minimisation measures (3). The marketing of new drugs and innovative therapies, such as advanced therapy medicinal products, mutation-driven cancer drugs and digital therapeutics, requires both innovative pricing and reimbursement processes and a post-marketing re-evaluation of the benefit-risk profile of these drugs/therapeutic options through RWE generation (4). On the other hand, the increase in health expenditure linked to the ageing population, together with the limited availability of economic re-sources, requires an integrated assessment of health care costs, especially in the setting of chronicity, for which the development and monitoring of outcome and process indicators through RWD analysis is essential (5). The Italian Society of Pharmacology has developed the present expert opinion document on RWE as a technical-scientific reference framework for institutions (Italian Medicines Agency, Regions and State-Regions Conference), scientific community, health care professionals, and pharmaceutical companies, with the aim of examining the role that RWE can play in five thematic areas: A. Chronicity and Multimorbidity management; B. Regulatory; C. Governance of care processes (overcoming silos budget); D. Population studies; E. Health emergencies.

Background

Global health systems are increasingly at risk of becoming unsustainable and the trend will continue in the absence of policy and regulatory interventions based on sound scientific and technical evidence. To address this issue, the Italian Society of Pharmacology (Società Italiana di Farmacologia, SIF) has convened a first working group to design a preliminary roadmap and to identify the usefulness of Real-World Evidence (RWE). A wider group of multi-stakeholders, including payers, patients, academics and regulators, will then evaluate the proposals of this working group, in the form of pilot projects, publications and presentations at conference.

Points of discussion worthy of further investigation and modelling could be, *inter alia*, the following:

- growing awareness that health systems are increasingly vulnerable from a socio-economic point of view; in Italy, this is worsened by regional stratification and fragmentation;
- lack of correspondence between the ageing population and increased burden on the health and social system, resulting in misalignment between the demands for health care provision (especially for chronic diseases) and the resources allocated and planned;
- on the other hand, refinancing of welfare systems, especially in conditions of crisis or stagnation of the economy, will never be able to adjust and cross-reference the demand for health that results from the increase in life expectancy and older patients with multimorbidity;
- alongside refinancing models, there is a need for care pathway reorganisation models to “transfer” the management of chronic diseases from the hospital to the community by taking care of chronic patients in the catchment area of interest; this phase of transformation of the national health service (NHS) is based on the reorganisation of the primary, secondary and tertiary care settings;

recognition, that can no longer be put off, that far-reaching changes are needed to ensure sustainable access to high-quality healthcare for patients in the future;

- health care systems should shift the focus to patient-centred outcomes, using existing resources more effectively and efficiently;
- need to optimize the overall care pathway from the diagnostic to the therapeutic approach, (DTP), overcoming the governance of individual “silos budget” variables; the management of the entire healthcare process should be addressed through so-called “Cross Stakeholder” models and be employing mostly digital platforms (i.e. patient-driven RWE);
- need for regulatory bodies to understand, based on the previous points, how and when to authorise accelerated patient access to innovative technologies, considering the greater uncertainty in the long-term outcomes (regulatory certified RWE);
- opportunity to discuss alternative sources of funding (complementary and non-replaceable) to alleviate the burden on the publicly funded system.

Objectives of the document

The main objective of the present document is to design future models for the negotiation of agreements on innovative therapies in conditions of uncertainty at the time of the decision. In particular, to explore and propose new solutions to optimise conditions for future therapies (e.g., unconventional, advanced, genetic, agnostic, and for orphan diseases) using new payment strategies, unifying some of the market entry agreements (risk and cost sharing and payment by/at results) managed in an advanced way, linking pharmaceutical reimbursement to results and prices based on the real measurable value in terms of avoided costs certified by RWE. This project will have to address the issue of proposing new payment models on innovative thera-

pies, and even more so when such therapies are approved under conditions of uncertainty, mainly but not exclusively, about their long-term effectiveness (i.e., the duration of the response) at the time of their first registration. The working group should be intended as a multi-stakeholder initiative involving patients and patient representatives, healthcare professionals, industry, and the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA). Further objectives are:

- to identify points of interest and different value elements among the different stakeholder groups (e.g., alleviating symptoms for patients and obtaining savings for payers) to allow the alignment between the resources invested and the results obtained through the different interventions;
- to analyse existing data collection tools and infrastructures, recommending improvements and designing future models for the creation of appropriate systems to enable the optimisation of data analysis.

The change in research and development and the concept of value

a) Over the next 3-5 years, a new wave of pharmaceutical products will come to the market in a progressive and somewhat disruptive way that differs from those traditionally marketed in the last decade (based on chemical synthesis or biotechnology), and that comprises Advanced Therapy Medicinal Products (ATMP), including Gene Therapies (GT), mutation-driven cancer drugs (Mutational Oncology-OM) and even digital therapies (DTx).

b) Mean time to market access will decrease to about 6-7 years due to the “pressure” on regulators to register many of these potentially life-saving GT, ATMP, OM and DTx. More and more “conditional approval” or “under exceptional circumstances” type registrations will be used without providing enough evidence of efficacy over the duration of clinical response.

c) Regulatory decisions will need to be made on limited data (Phases I-II studies) and uncertainty will need to be incorporated into the reimbursement processes, transforming RWE generation as an essential approach for producing relevant knowledge and value for newly marketed innovative technologies.

d) The above points will produce a necessary metamorphosis in conventional health technology assessments (HTA) in order to adapt and weigh, unlike before, the classical criteria and efficiency measures (which here - for reasons of simplicity - are understood as the relationship between effectiveness and safety in real-life situations and outside the clinical trial phases) at the time of the first approval.

In other words, as we will see below, comparative efficacy and the resulting economic impact when a potentially life-saving product is approved could change substantially after, for example, 5 years from the first marketing date of the product.

As a result, cost-effectiveness analyses (based on quality-adjusted life years - QALY - measurement) or any other traditional method based on classical modelling will lose their meaning.

Instead increasing importance will be given to Management Entry Agreements (MEAs) based on pre-defined cost/value agreements that are dynamically modifiable over time and rely on results from individually populated and certified real-life databases.

e) Regardless of the agreement model used, such databases using digital phenotyping and extensive use of Electronic Patient-Reported Outcomes (e-PROs) will need to collect information from real world setting to demonstrate, at a more “granular” level, the ability of the new product to produce not only the expected effectiveness, but also significant cost savings (otherwise unavoidable) associated with the best existing standards of care.

In this case, local variants at national and loco-regional level could be applied to the same type of MEAs to take into account heterogeneity across different settings in various Italian regions.

Figure 1 below illustrates the ongoing transformation, which shifts value determination of a new technology from traditional clinical trials (*efficacy*) to post-marketing observational studies (*effectiveness*) using RWD.

More recently, a document of the European Commission's Expert Panel on effective ways of investing in Health (EXPH) has been published. In this document "value" is defined based on 4 dimensions (Personal - Technical - Allocative – Societal), as shown in **figure 2**.

Figure 1. Framework of health technology value definition.

Figure 2. The dimensions of value in healthcare proposed by the Expert Panel on effective ways of investing in Health of the European Commission.

RWE: applications, fields, methodology and rules

Considering the changes defined above, in the following paragraphs we illustrate the applications, fields, methodology and rules through which RWE can offer essential tools for the management of processes integrated and complementary to clinical trials.

1st field: chronic diseases and multimorbidity management

The majority of patients affected with a chronic disease is affected by at least another one additional chronic disease. In Italy, a large amount of patients are suffering from at least two of the following chronic diseases: renal, rheumatic, gastro-intestinal, cardiovascular, respiratory, neurodegenerative or endocrine. The management of this multimorbidity, which affects about 25% of the general population in Italy, accounts for more than 70% of the resources of the National Health Fund (Fondo Sanitario Nazionale, FSN).

In other words, out of € 116.4 billion (FSN 2020), more than € 81.5 billion are used for the health care services provided to patients with chronic diseases. Multimorbidity, which is common in elderly population, is an extremely significant problem when one considers that this condition is related to reduced quality of life, increased mortality, polypharmacotherapy and adverse drug reactions.

In order to achieve an effective management of chronicity and stratify the population through models that take into account health and socio-economic needs, the scientific community agrees on the need to have data on a general classification of patients with multimorbidity, in epidemiological terms, specifically on the main criticality of care as well as on the definition of expected results and indicators for monitoring. Finally, considering that the objective of the development of a new drug is to respond to an unmet medical need, to identify the therapeutic need of patients with chronic conditions, it would

be appropriate to collect data on the burden of disease, which includes the estimate of the disability-adjusted life years and the clinical efficacy and safety profile of the already available therapeutic interventions. Using the RWD in the available NHS administrative databases (e.g. pharmacy claims, hospital discharge records, and requests for specialists visits and diagnostic tests) it is possible to define the following parameters:

- algorithms for the extraction and calculation of the prevalence and incidence of patients with certain chronic disease(s) at the loco-regional level in the DTP pathways;
- process and outcome indicators to quantify the appropriateness of the care process and the impact of DTPs on morbidity, access to the emergency room (ER), hospital admissions and mortality;
- risk stratification in patients with comorbidity on the basis of the level of risk derived from the inclusion of patients in prevention activities, access to specialist and residential facilities and quality of care in outpatient setting;
- identification and certification of models demonstrating avoidable costs in overall expenditure and not based on siloed management of the healthcare chain processes.

Regarding multimorbidity, RWE is essential for health planning and governance at local and regional level.

2nd field: role of RWE at the regulatory level

a) Target population of new drugs: eligible patients

One of the main critical issues in the price and reimbursement regulatory processes is the identification (prevalence, incidence and burden of disease) of the populations eligible for new treatments and the RWE impact of new technologies on the care process. In fact:

- some new drugs are designed and developed for subpopulations of patients with an unmet clinical need or with genomic or molecular mutations, but this “drug-dependent” epidemiology is not reflected in the typical data of clinical epidemiology and cannot be defined through advisory boards that express hypothetical epidemiology estimates which may not be robust;
- in most cases, eligible populations can be identified and defined with high accuracy using integrated patient data from the hospital discharge records, pharmacy claims, and from laboratory and instrumental examinations and outpatient care data;
- there are documented examples in the literature that have shown that through the RWE data above it is possible to identify target populations for new treatments such as proprotein convertase subtilisin/kexin 9 inhibitors, Chimeric Antigen Receptor T-cell therapies, GTs and many cancer treatments (H+/HER2- or triple negative).

It is necessary to give further methodological foundation to this use of RWE so that it can be accepted by companies and regulatory agencies as an integral and strategic part of the access and reimbursement processes.

b) New AIFA Registers

AIFA monitoring registers and MEAs are a “typically Italian” experience, founded in March 2006, to ensure prescription appropriateness and economic sustainability based on treatment prices and costs conditional to the clinical outcome: economic risk sharing (cost sharing) or outcome-based (payment by result) MEAs. A great advantage of the registries and MEAs procedures is that different extensions of indications with a different final treatment cost can be managed even if they are related to the same active ingredient, and the evaluation of the outcome and, therefore, of the value is defined for each the individual patient in normal clinical prac-

tice. In this sense, registries and MEAs are innovative and strategic applications in the field of pharmaceutical governance, which are gradually being extended to other European countries and at the international level. The limitations of this experience in Italy derive from the fact that the large amount of the data collected by the registries has not been (if not only initially) adequately analysed and shared with the regions and health structures. These registries therefore ended up having a predominantly bureaucratic function. In addition, there was no planned and organic closure of the individual registers, resulting in a data compilation burden that was difficult to reconcile with the care activities of hospital wards. Finally, the non-availability of an online IT management has made the quantification of the possible savings due to a lack of closure of the end of treatment form difficult and, in the case of payback after years, the economic amount has hardly returned within the pharmaceutical budget from which it had originated.

However, there exist the conditions and solutions to return to the original spirit of the registries in a context of efficiency by eliminating or containing payback procedures as much as possible. The recent application of the Payment at Result (PaR) procedure within the CAR-T registries is the most advanced and strategic procedure in Europe, because in many European countries adequate pricing and reimbursement procedures have not yet been structured. However, PaR allows for payment by instalments and follow-up payment only for patients in complete remission, and, consequently, the cost of treatment is linked to and reflects a health gain in the individual patient, based on decisive endpoints such as complete remission or survival. PaR is also the methodology by which the procedures for access and reimbursement of gene therapies and other "one shot" therapies can be defined. Also from this perspective, a new governance can be defined for drugs with "agnostic procedure" and for oncological therapies based on genomic profiling (next generation sequencing, NGS) accompanied by the establishment of the Molecular Tumor Board and genomic

platforms (modern expression of registries in the era of mutational oncology). In conclusion, it is quite clear that registries and MEAs, including PaR (CAR-T and GTs) and mutation-driven oncology mutation platforms, are perhaps the most advanced and strategic regulatory RWE application.

c) Post-marketing RWE studies

After the drug marketing, RWE can:

- confirm the therapeutic value of a drug in clinical practice: this includes the personal value - the availability of adequate care to achieve specific outcomes in the individual patient; the technical value the achievement of the best possible results with available resources; the allocative value - the fair distribution of resources among all patient groups; the societal value - the contribution of healthcare to participation and social connection. This is of fundamental importance especially for those drugs for which there is little information, wide regional differences, fears about prescription independence and therapeutic continuity, as in the case of biosimilars and generics. For these drugs, in fact, the collection of data from the real world that confirm their full overlap with the respective originators could increase patient and clinician confidence and implement their use;
- compare the effectiveness and tolerability profile of drugs belonging to the same homogeneous therapeutic class (classe terapeutica omogenea, CTO, i.e., drugs that share the same mechanism of action as well as a substantially overlapping effectiveness and safety profile). In this regard, if, on the one hand, the advantage of identifying CTO may bring on expenditure rationalization, on the other hand there is a clear lack of head-to-head studies among the drugs belonging to the above classes; the overlap is based, in fact, on indirect comparisons, characterized by a series of methodological limitations. The issue of therapeutic equivalence between medicines containing different active ingredients is, therefore, a current issue for health

policy and public health, especially if we consider the imperfect identity of different active ingredients even when declared therapeutically equivalent. It is considered, therefore, that, even in this context, RWD may represent a valid instrument for directly confirming the therapeutic equivalence or for overlapping of drugs belonging to the same CTO.

To assess the application of post-marketing RWE studies, reference should be made to the scientific literature mentioning highly qualified experiences that have enabled the RWE methodology to define comparative efficacy and safety of generics and biosimilars, in addition to the comparative exercise adopted by the European Medicines Agency (EMA) for the registration of biosimilars, and in the face of unjustified resistance by clinicians or market interests.

3rd area: governance of care processes - overcoming silos budget

One of the main challenges that the NHS is called to face is the transition from a concept of silos, in which each sector (pharmaceutical, hospitalizations and outpatient specialization) is considered separately, to a cross-sectional concept, in which the entire path of the patient is examined. This, from the clinical care point of view, makes it possible to implement a global assumption of responsibility for the patient and, from the governance and cost assessment point of view, makes it possible to arrive at an overall view of the costs incurred by the NHS.

Also in this area, current routine health care data collection through health administrative databases provide a unique opportunity to implement this change, as they allow a real and comprehensive assessment of patient care path costs (DTPs), overcoming the ceilings linked to the single process variable. In fact, if properly analysed, they allow the selection of persons affected by a specific disease and, therefore, the description of their real use of

health resources within the NHS. The average cost incurred by the NHS for the population with a disease is obtained through the application of the costs incurred by the NHS in the form of reimbursement of drugs, hospitalisation fees and specialist outpatient services (visits and examinations). Once the average cost generated by the individual patient with a given chronic pathology over a defined period (usually 12 months) has been obtained, it is possible to estimate the average annual cost of that condition. From this perspective, the cost of a pharmacological treatment should be considered as a variable of a complex system, and therefore, its potential ability to reduce other items of expenditure (e.g., hospitalizations and related costs) should also be assessed. The methodology illustrated has the advantage of providing the average per capita NHS cost of the population carrying a pathology, considering all the care events related to the period considered, including those due to comorbidities or interventions not related to the condition under examination.

In order to reach also the objective of estimating the average per capita cost of a given pathology, it is possible to isolate as the specific healthcare costs related to a given condition, in order to highlight the disease-specific fraction on the total costs related to the total care burden of that population. The disease-specific average integrated care cost illustrates the current economic weight for the NHS, in the light of the diagnostic-therapeutic tools used at the time of the evaluation, also allowing a forecast of the impact of a new technology (i.e., drug, medical device, diagnostic or interventional technology) on the specific target population.

This vision of healthcare costs, which starts from the single disease, allows the regional healthcare administrator and the healthcare provider to approach the clinic (and vice versa), through a common language, because:

- for the clinic, it is the peculiar point of view, which manages to describe the complexity/specificity of the healthcare service in its different phases (diagnostic-therapeutic care);

- the administrator can understand the “trigger events” and the relevant nodes of the treatment of a disease, placing it in the context of the overall care burden of a given population, stratified by geographical area and, for budget purposes, also for specific groups (as the Italian AFT/UCCP) or individual GP.

In this context, the problem of adherence to therapy and a modern view of pharmacy is particularly relevant. In particular, in patients suffering from chronic diseases, the levels of adherence to treatment do not exceed 50%, leading to increased morbidity, mortality and healthcare costs.

Since one of the main causes of non-adherence is a lack of motivation and health education for patients, it would be appropriate to promote training programmes for patients aimed at increasing the appropriate use of medicines, thus increasing the cost-effectiveness profile of therapies. Finally, another tool for the optimization of therapies and the containment of healthcare costs is the implementation of Pharmaceutical Care, or Service Pharmacy, i.e., the transition from the simple dispensing of the drug to a set of activities that include, together with the delivery of the drug, a series of services provided by the pharmacist to promote continuity of care on the territory, optimize the investment in pharmacological treatments, and increase patient involvement. In this way, it is possible to achieve a reduction in waste and preventable healthcare costs, such as those resulting from complications and therapeutic failures.

In conclusion, if the overcoming of the budget silos and the management of the entire care process constitutes a structural change in the management of the NHS, again RWE and data are the basis of a solid methodology to conduct pilot projects and guide the institutional and regulatory/implementation phase.

4th field: population studies

Fragile populations, such as children, older adults with polypharmacy (i.e., ≥ 5 concomitant drugs) and

pregnant or lactating women, are usually excluded from pivotal clinical trials, which results in a limited availability of data on the efficacy and safety of marketed drugs. In this context, the analysis of RWD and the related generation of RWE is an essential element for the generation of clinically relevant information on the benefit-risk profile of health interventions for subgroups of patients that are generally excluded from clinical trials.

5th field: health emergencies

The current pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or COVID-19), which follows other pandemics that occurred in recent decades, highlights the need to rapidly generate evidence that can support very quickly the "Informed decision making" process of the Drug Regulatory Agencies. In these scenarios, it is essential to assess rapidly the benefit-risk profile of repurposed drugs and to make appropriate decisions based on sound scientific evidence. Beyond viral pandemics, this can be applied to other health care emergencies requiring timely responses. In addition to the need of rapidly conducting controlled and randomized experimental clinical trials (according to the procedure provided for by art. 17 of the Decree Law - Cura Italia), the role of RWE in the management of health emergencies such as COVID-19 appeared to be of strategic importance. In fact, RWE studies can be carried out with lower costs and especially in a very short time frame, thus confirming or refuting hypotheses on potential beneficial or harmful effects of drugs based on only empirical evidence or in vitro studies. With regard to COVID-19, in addition to the existing databases, data sources based on COVID-19 regional surveillance registers have been used to conduct observational studies. These registries can be linked to current administrative databases and, in this way, in Italy it becomes possible to create a data infrastructure for generating a wealth of information of great value with ultimate goal to produce timely evidence on the mentioned issues above (e.g. potential effects

of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, non-steroidal anti-inflammatory drugs on COVID-19). Finally, in the coming months, these data sources will be a valuable tool to assess the impact of the COVID-19 pandemic on chronic disease management, integrated care costs and associated burden of disease.

Take home messages

The present SIF-RWE document outlines the following points for RWE methodology and application:

- RWE is necessary to integrate the evidence generated in the pre-marketing setting;
- in relation to the change in Research and Development (see advanced therapy medicinal product and digital therapeutics) and the updated concept of "value" of the drug, the generation of RWE in the post-marketing phase is required for the completion and verification of experimental studies and the evaluation of the different "value" dimensions: personal, technical, allocative and societal;
- the main areas of application of RWE are considered to be:
 - 1st area: Chronicity and multimorbidity;
 - 2nd area: Regulatory needs;
 - 3rd area: Governance of care processes;
 - 4th area: Special population studies;
 - 5th area: Health emergencies.

In conclusion, the present SIF-RWE document aims to constitute a technical-scientific initial reference framework on RWE for scientific societies, health professionals, regulators, payers and pharmaceutical companies. Moreover, the document indicating some specific fields of application for RWE studies could be used, where appropriate, to support the Italian Ministry of Health (Ministero della Salute), the Italian Medicines Agency (AIFA), the Regions and the State-Regions Conference.

Reference materials: book and documents

- Corrao G. Real World Evidence - Buone pratiche della ricerca basata sull'osservazione del mondo reale. Il Pensiero Scientifico Editore, Settembre 2019.
- Trifirò G. Real World Evidence e farmaci Razionale, criticità e applicazioni nel contesto italiano. SEED, Novembre 2019.
- Martini N, Pammolli F. White Paper - Le sfide della medicina e la Governance Farmaceutica. Il Pensiero Scientifico Editore, Novembre 2019.
- Documento FADOI, Novembre 2018. Dentro la Ricerca: la Persona prima di tutto – Una proposta in 10 punti.
- Documento SIF, Aprile 2017. Real world data e real world evidence: considerazioni e proposte da un network di società scientifiche.
- European Commission: Defining value in "Value-based Healthcare", Report of ESPH, June 2019.

Acknowledgements

We thank Dr Janet Sultana from University of Messina for contribution in text editing.

Conflict of interests

LP is the Chief Scientific Officer of EDRA-LSWR Publishing Company and of Inpeco SA Total Lab Automation Company and he is the VP for Regulatory Strategy and Market Access Innovation of VeraSci, USA. In the last year he has provided scientific consultation to AbbVie, USA; BCG, Switzerland; Boehringer-Ingelheim, Germany; Compass Pathways, UK; Johnson & Johnson, USA; Takeda, USA; Vifor, Switzerland.

References

1. Chassang S, Mantua V, Snowberg E, Xoxi E, Pani L. Sustainable Reimbursements: Towards a Unified Framework for Pricing Drugs with Significant Uncertainties CESifo Working Paper Series No. 6846 Mar 2018.

2. Goldman DP, Van Nuys K, Cheng WH, Hlávka JP, Pani L, Chassang S, Snowberg E. A New Model for Pricing Drugs of Uncertain Efficacy, *NEJM, The Catalyst* Dec 2018.
3. Pammolli F, Righetto L, Abrignani S, Pani L, Pelicci PG, Rabosio E. The Endless Frontier? The Recent Upsurge of R&D Productivity in Pharmaceuticals, *J Transl Med* 2020 Apr 9;18(1):162.
4. Sultana J, Trotta F, Addis A, Brown JS, Gil M, Menniti-Ippolito F, Milozzi F, Suissa S, Trifirò G, Healthcare Database Networks for Drug Regulatory Policies: International Workshop on the Canadian, US and Spanish Experience and Future Steps for Italy, *Drug Safety* 2020; 43: 1–5.
5. Crisafulli S, Sultana J, Ingrassiotta Y, Addis A, Cananzi P, Cavagna L, Conter V, D'Angelo G, Ferrajolo C, Mantovani L, Pastorello M, Scondotto S, Trifirò G. Role of healthcare databases and registries for surveillance of orphan drugs in the real-world setting: the Italian case study. *Expert Opin Drug Saf* 2019 Jun;18(6):497-509.
6. Ingrassiotta Y, Sultana J, Kirchmayer U, Trifirò G. Challenges in Post-marketing Studies of Biological Drugs in the Era of Biosimilars; A Report of the International Society for Pharmacoeconomics 2019 Mid-Year Meeting in Rome, Italy. *BioDrugs* 2019 Aug;33(4):345-352.
7. Sultana J, Moretti U, Addis A, Caduff P, Capuano A, Kant A, Laporte JR, Lindquist M, Raine J, Sartori D, Trifirò G, Tuccori M, Venegoni M, van Puijenbroek E, Leone R. Workshop on the Italian Pharmacovigilance System in the International Context: Critical Issues and Perspectives. *Drug Saf* 2019 May;42(5):683-687.
8. Trifirò G, Gini R, Barone-Adesi F, Beghi E, Cantarutti A, Capuano A, Carnovale C, Clavenna A, Dellagiovanna M, Ferrajolo C, Franchi M, Ingrassiotta Y, Kirchmayer U, Lapi F, Leone R, Leoni O, Lucenteforte E, Moretti U, Mugelli A, Naldi L, Poluzzi E, Rafaniello C, Rea F, Sultana J, Tettamanti M, Traversa G, Vannacci A, Mantovani L, Corrao G. The Role of European Healthcare Databases for Post-Marketing Drug Effectiveness, Safety and Value Evaluation: Where Does Italy Stand? *Drug Saf* 2019 Mar;42(3):347-363.

Glossary

Advanced Therapy Medicinal Products (ATMP)	Biotechnological medicinal products for human use based on genes, tissues or cells.
Cost sharing	Negotiation agreement that provides a discount on the price of the first cycles of therapy for all patients eligible for treatment, as identified in the Summary of Product Characteristics.
Digital therapeutics (DTx)	Evidence-based therapeutic interventions guided by high-quality software programs to prevent, manage or treat a clinical disorder or disease.
Electronic Patient-Reported Outcomes (e-PROs)	Results reported by patients and collected by electronic methods.
Mutation-driven cancer drugs	Oncological drugs based on genetic mutations.
Gene Therapies (GT)	Therapies that use recombinant genes to achieve a therapeutic, diagnostic or disease prevention effect.
Health Technology Assessment (HTA)	A multidisciplinary process that synthesises information on clinical, economic, social, and ethical issues related to the use of health technology in a systematic, transparent, impartial, and robust manner.
Management Entry Agreements (MEAs)	Conditional market access agreements for innovative and/or high-cost medicines that allow new treatments to be made available to patients, despite the uncertainty of lack of information on therapeutic benefits or actual costs.
Patient-centred	Results relevant to the patient.
Randomized Controlled Trial (RCT)	Randomized and controlled clinical trials.
Quality-Adjusted Life Years (QALY)	Unit of measurement used in cost-utility analyses and takes into account not only the number of years of life gained, but also the quality of life.
Real-World Data (RWD)	Data on the patient's state of health and the provision of health services is routinely collected from various sources during normal clinical practice.
Real-World Evidence (RWE)	The scientific evidence on potential benefits and risks of a drug, derived from the analysis of RWD, and therefore related to the use of drugs in the real world.
Risk sharing	Negotiation agreement that provides a discount on the price of the first cycles of therapy for all patients eligible for treatment, as identified in the Summary of Product Characteristics, and who do not respond to treatment.
Payment by result	Negotiation agreement providing for full reimbursement by the Pharmaceutical Company on all patients who do not respond to treatment.