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SPECIAL ISSUE

Opinion Papers by SIF & Farmindustria

THE VALUE OF THE PARTNERSHIP BETWEEN THE PHARMACEUTICAL INDUSTRY AND THE ITALIAN SOCIETY OF PHARMACOLOGY FOR INNOVATION AND SUSTAINABILITY

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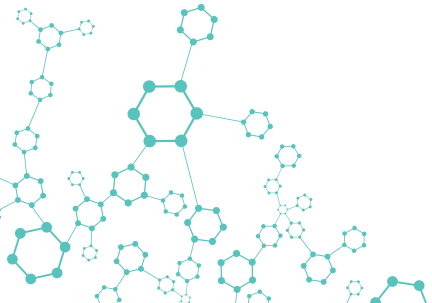

This Special Issue is the result of a translation from "Quaderni della SIF" (ISSN 2039-9561), volume 1 – February 2022, titled: *"Il valore della partnership tra industria farmaceutica e Società Italiana di Farmacologia per l'innovazione e la sostenibilità"*.

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PREFACE

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This document, structured around the contributions of different working groups, stems from the observations that emerged during the regular SIF-Farmindustria table meetings held during 2020-2021, as well as from the 40th National Congress of the Italian Society of Pharmacology (March 9-13, 2021).
The document was edited by the Editorial Committee consisting of:
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INTRODUCTION

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In the development of innovative drugs, new technologies and healthcare processes in modern medicine, the need and importance of integrating pharmacological research (PIL) with the pharmaceutical industry's R&D processes is unanimously recognised, through partnership procedures, the strategic value of which was also clearly confirmed during the pandemic period.
Efficient collaboration between public and private research organisations, start-ups, science parks, non-profit organisations and businesses can spread new knowledge, skills and good practices, fostering a shared culture on the new frontiers of science and technology.
Partnership without which it would be impossible to excel at all stages of the research process, from clinical trials to access to treatment for patients. And that makes the pharmaceutical industry one of the most advanced examples of Open Innovation.
The healthcare crisis has made clear the need to further strengthen public-private collaboration to accelerate the innovation processes already under way and to improve the health and life expectancy of citizens. And to attract new resources and talent for the economic and social development of the country.
That's why we need tools and clear rules to encourage basic research, preclinical and clinical studies, registration and protection of patents, technology transfer and digital information. This is the only way to make the Italian innovation ecosystem stronger. For the benefit of today's and tomorrow's patients.
However, the partnership between public and private structures often risks becoming a rhetorical evocation or remaining tied to an institutional conception of conflicts of interest and conflicts between science and the market.
This SIF publication, overcoming all prejudices, addresses the key points and most challenging issues of new drug development and healthcare

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strategies, reporting the results and concrete contributions of an active partnership between the pharmacological community (SIF) and the R&D processes of the pharmaceutical industry (Farmindustria).
The document stems from the observations that emerged during the regular SIF-Farmindustria table meetings held during 2020-2021, as well as from the 40th National Congress of the Italian Society of Pharmacology (March 9-13, 2021).
In particular, the SIF-Farmindustria issue is structured in 6 parts and contributions:

1. the new research methods;
2. data quality;
3. the patient and their treatment needs;
4. breakthrough innovation and PDTAs;
5. digital innovation in medicine;
6. the role of science communication.

The collection provides an overview of the most relevant and significant issues for the changes that pharmacological research and the pharmaceutical industry are facing, with particular attention given to their innovative nature and sustainability for the health system as a whole.
Each contribution is structured in such a way as to outline the current context from which proposals and areas for future development can be made. These form the *core* of each individual contribution and provide extremely important points for discussion and reflection for all those involved in various ways in the world of drug research and new treatment processes.
It starts with new clinical research methods, which are driving the increase in research pipelines, not only quantitatively, but especially qualitatively. In fact, they are more focused on identifying "*first in class*" therapies, biotechnology products, advanced and digital therapies. In order to achieve these objectives, it is essential to develop new study designs and to define paths that can accelerate access to drugs while reducing development costs, and to adopt a regulatory framework capable of regulating and making the new methods of research and access to drugs more efficient.
Subsequently, the role and quality of scientific data in conducting research at all stages of a drug's life is addressed: from preclinical to the study of its use in current clinical practice. In fact, the data is the real fuel for research and, therefore, it is of the utmost importance to have reliable sources, adequate infrastructures and the skills to manage and analyse them. This transition is becoming more and more imminent, especially considering the challenge posed by the *big data* that we generate on a daily basis on our state of health and which represent the real-world scope of wide-ranging research.
A central part of the collection is devoted to the theme of "innovation", approached from different angles: as incremental patient-centred inno-

vation, radical (*breakthrough*) innovation, and, finally, as innovation related to digital medicine.
Incremental innovation, *i.e.* innovation aimed at developing an optimised version of a product already on the market, should increasingly be patient-centred, given the social changes we are experiencing. In this context, research should be aimed at identifying new strategies to promote appropriateness, foster adherence, simplify treatment, and reduce barriers to patient access to treatment. This type of innovation, however, needs greater recognition within the health system; consequently, it becomes essential to devise strategies capable of quantifying and defining it adequately, according to precise algorithms.
On the other hand, when the innovation helps us to treat a never-before treated disease or profoundly modifies its clinical history, it can be defined as radical (*breakthrough*), *e.g.* CAR-T (Chimeric Antigen Receptor T cell therapies) or the agnostic therapies underlying mutational oncology. Thanks to the speed and quality of research and development processes achieved in recent years, this type of innovation is becoming more and more present and it is therefore strategic to study its organisational implications, as well as its technical, regulatory and economic requirements. In fact, only by combining this innovation with new organisational models will it be possible to allow rapid and equitable access to the most innovative treatments within the framework of the costs of care (PDTA). These new models can benefit from forms of public-private partnership, from the ability to assess the whole process and not just a single variable, and from the tools made available by digital medicine and artificial intelligence applied to health.
A separate contribution in the collection is devoted to digital medicine and its revolution in healthcare. In fact, digital therapies, whose efficacy must be evidence-based like other therapies, can be used independently or in combination with drugs, in order to optimise patient treatment and to enable the achievement of desired health outcomes. However, given the paradigm shift associated with these new therapies, it is essential to design an appropriate regulatory pathway that focuses on their efficacy, the integrity and quality of the data collected, and their impact on the organisational model. Only in this way will it be possible to properly value these therapies, taking into account the overall benefits they bring to the process as a whole, as well as the individual, health, social and professional consequences.
The collection closes with a contribution on the important aspect of scientific communication, which, as the pandemic has taught us, represents a crucial point for consolidating public trust in the pharmaceutical sector, as well as for renewing the alliance between health *stakeholders* for the benefit of patients. While it is important to ensure transparent and complete publication of data, whether positive or negative, it is also essential to ensure that scientific communication is appropriate for the target audience in terms of content and language. This is especially true

when addressing the public and patients, who need as clear and understandable communication as possible.
By following the common thread linking the collection's various contributions, it is possible to understand where drug research is heading and where drug companies have demonstrated, and continue to demonstrate every day, their ability to innovate and network by combining science and technology, human skills and artificial intelligence, and public and private excellence.
In order to understand the complex, multidisciplinary and global processes of Life Sciences, a structural confrontation between public and private stakeholders is needed to network all competences. The word 'partnership' is not merely a slogan, it is a strategic competitive factor, indispensable when it comes to finding innovative and shared solutions to the country's real needs.
For the pharmaceutical sector, increasing synergy between the public and private sectors means increasing research, generating added value through economic, social and environmental sustainability, improving patients' access to treatment, increasing employment and expertise, and investing even more in the green transition.
Therefore, it is possible to consider this collection as a possible map for the future (not so far away, considering the speed at which innovation processes currently travel) that may be useful to the world of pharmacological research and to the world of R&D investments by pharmaceutical companies.

OPINION PAPER

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NEW CLINICAL RESEARCH METHODS TO ENSURE PATIENTS' RAPID ACCESS TO TREATMENTS

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HIGHLIGHTS

- Clinical research has undergone a profound transformation, both to facilitate a more efficient and rapid development of New Therapeutic Entities and to enable a more rapid transfer of scientific innovation to clinical practice. Complex adaptive designs, the use of surrogate endpoints and phase I/II studies with registration purposes (instead of randomised controlled phase III studies) are increasingly used, especially in the case of rare diseases or when a molecular target is available (agnostic drugs and precision medicine).
- The use of new and complex methodologies in clinical research programmes, shortened development times in the case of fast-moving life-threatening diseases and the lack of an adequate standard of care make it more difficult to evaluate and accept the evidence that is generated in this way. Close and early collaboration with regulatory bodies is essential in order to verify the validity and acceptability of the results obtained, as well as their reproducibility in clinical practice. Increasingly relevant is the use of Real Word Data to guide or supplement registration research, particularly in the case of an accelerated authorisation process.
- Research innovation is not only methodological but also organisational in nature. The use of digital technology and the use of decentralised study models, for example, facilitate the implementation of studies, offer the opportunity to enrich the wealth of data that can be collected, and facilitate patient access to study programmes. For this reason, the computerisation of research centres, and more generally of places of care, is essential, as is the development of new skills in the professional figures dedicated to research itself.
- The first opportunity for patients to access therapeutic innovation is through clinical trials. It is therefore essential to create a regulatory and infrastructural framework of excellence in Italy, with qualified experimental centres and dedicated staff, and rapid and simplified procedures to make our country more attractive for investments in research.

SUMMARY

The radical evolution of the R&D model of pharmaceutical companies, fuelled by significant advances in scientific knowledge and the adoption of new open innovation methods, has led to strong growth in research pipelines after years of progressive depletion.

This growth is not only quantitative - there are currently 17,737 New Therapeutic Entities (NTEs) - but more importantly, it is qualitative, with a strong presence of potentially "first in class" therapies, an increase in biotechnology products, particularly advanced and digital therapies. The need, in addition to selecting

the most promising NTEs, is to reduce development costs and speed up patient access to treatments, especially in the face of major treatment needs without adequate standards of care. This has led to new and complex study designs that often do not meet traditional gold standards with accelerated development and registration processes. These pathways require the generation of integrative evidence to define the efficacy and safety of new drugs and make the valuation of how innovative they are for the "health system" more complex.
Innovation in clinical research is not only linked to the research structure but also to the execution of protocols, which is progressively influenced by the emergence of digital technology and the need to make research more responsive to patient requirements.
Given the importance and opportunities that research offers, it is essential to ensure a favourable structural regulatory framework at the national level, and it is therefore urgent to implement the new European Directive through the provision of rapid implementation decrees that allow our country to be competitive on the international market.

BACKGROUND AND OBJECTIVES

One of the fundamental values of clinical research is to bring patients an initial opportunity to access therapeutic breakthroughs that are all the more important as the need for treatment is unmet. The crucial role of research in becoming the only opportunity for treatment in the absence of adequate standards of care has never been appreciated more than during the dramatic experience of the SARS CoV2 pandemic.
Ensuring excellence in clinical research is crucial both to enable early and broad participation in plans to develop a new treatment and to ensure that a safe and effective treatment is introduced into clinical practice for all those who await its benefits, bringing value not only to the individual but to the whole health system.
Research and access first to experimental treatment and then to registered drugs are essential to ensure the transfer of scientific innovation to people awaiting treatment.
Research cannot be considered valuable unless it becomes a means of treatment and becomes available to patients. The increasing use of complex and accelerated research designs as a means of developing innovative New Therapeutic Entities (NTEs) more efficiently leads to the need for a progressive adjustment in the ways in which new drug development plans are assessed and executed in research centres, how quickly the innovative treatment can be transferred to treatment sites, how its risk-benefit profile can be investigated in real life and, ultimately, how appropriately it is prescribed.
The objective of the document is to stimulate an open and articulate dialogue between the various stakeholders and to identify concrete actions that can promote innovative research and rapid access to treatment.

THE CURRENT CONTEXT

We live in a time of great, incredible scientific progress. The growing understanding of the biological mechanisms responsible for the emergence of diseases and their evolution, the development of omics sciences, the combination of science and technology, with the incredible progress made by bioinformatics and bioengineering, and the development of 'digital medicine' have all contributed to a major breakthrough in the search for new treatments.
The rapid advancement of scientific knowledge has undoubtedly stimulated a radical change in the traditional Research and Development (R&D) model within pharmaceutical companies. This model has become progressively inefficient and incapable of responding to the emergence of new health requirements, to patients' expectations, to the transition towards precision medicine where treatments are personalised on the basis of individual clinical and biological characteris-

tics, and to the emergence of the concept of 'Value-based Healthcare', where the efficacy and safety of a drug must be combined with a new concept of efficiency in improving the treatment process.

We have thus witnessed the progressive adoption of new organisational models within companies with openness to external innovation, the replacement of "closed innovation" models with "open innovation" ones with increasing opportunities for collaboration and partnership between companies and external centres of excellence.

This transformation has led to a strong recovery in the productivity of the biopharmaceutical industry, with several signs of increased productivity and efficiency, with more innovative R&D in terms of mechanisms of action and indications being developed (1).

Looking at the picture of NTEs in development before the disruptive advent of COVID-19, the overall size of the pipeline is 17,737 NTEs, with a growth rate of 9.62% in the 2020 report (2) (**figure 1**).

This is nearly double-digit growth, much higher than the 5.99% reported in the 2019 report and 2.66% in the 2018 report.

The updated picture for 2021 shows NTEs rising to 18,582 with 798 new COVID-specific drugs, including vaccines (2). It is important to note that this growth is not only quantitative but also, and more importantly, qualitative in nature.

The opportunities for transformative medicine are growing with biotechnology drugs, up 13.2%, with gene and cell therapies showing the highest increase (**figure 2**).

A confirmation of these innovative treatment opportunities comes from the picture of what has been approved by the regulators. In the Food And Drug Administration's (FDA) 2020 Report (3) 40 percent of licensed drugs were "first in class." The relevance of innovation in addressing unmet treatment needs is also confirmed by the widespread adoption of facilitated approval processes: 23% accelerated approval, 32% fast track, 57% priority review, 42% breaktrough designation.

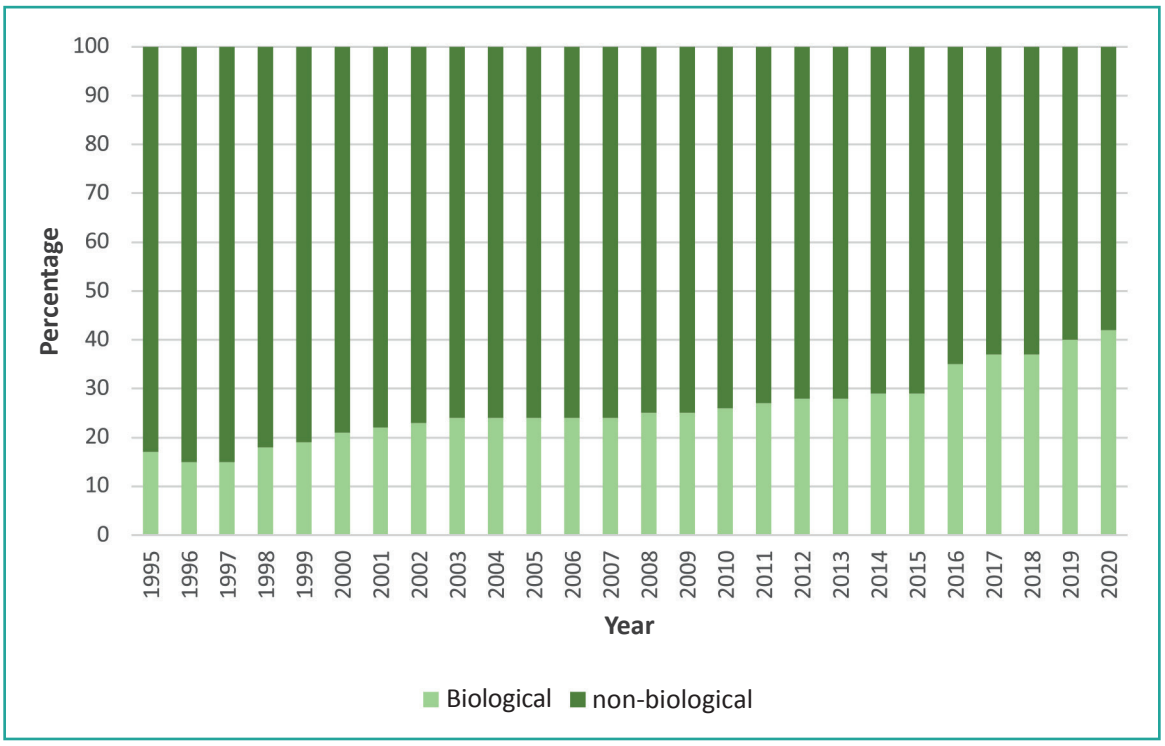

Figure 1. 2001-2020 increase in the number of pipelines (taken from (2)).

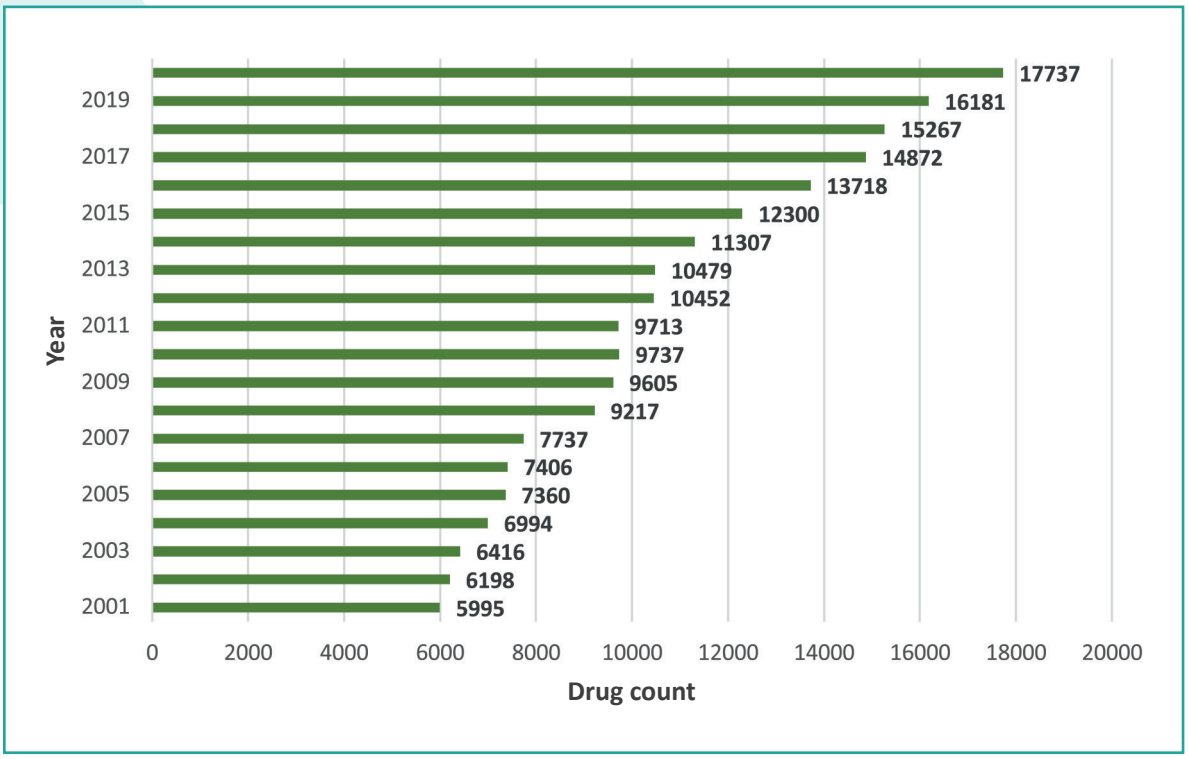

Figure 2. Share of biologic drugs vs. non-biologic drugs from 1995 to 2020 (taken from (2)).

The EMA's Priority Medicine (PRIME) programme - the plan defined within existing European regulatory models designed to accelerate access to medicines for patients with unmet medical requirements - was also applied to 20 NTEs in 2020, the highest number since the Prime programme was launched in 2016 (4).

Randomized controlled trials (RCTs) and sequential completion of the three phases of clinical development have traditionally been considered an undisputed paradigm for pre-registration research for decades.

Although RCTs have historically played and are still playing a decisive role in evaluating the efficacy and safety of an NTE prior to marketing authorisation, significant advances in knowledge of disease biology and clinical pharmacology, the need to improve the speed and efficiency of NTE development, and ultimately the need to bring a new treatment to patients more quickly, have led to the development of new ways of designing and managing clinical trials.

In particular, the concept of adaptive research studies and programmes has been progressively extended and articulated.

Adaptive studies make clinical trials more flexible by using the data generated within the study itself while it is being conducted to decide how to modify certain aspects of it without undermining its validity and integrity. In order to preserve this objective it is necessary that changes are always predefined within the research plan. Adaptive studies are not a solution for inadequate planning, but are intended to improve trial efficiency.

These new designs allow for better use of resources such as time and money and, in addition, limit the exposure of patients to therapies or dosage regimes that were identified early on as being ineffective or unsafe. The FDA, in its guidance document on adaptive studies, had already indicated their advantages and critical issues, fully recognising their value (FDA 2010 Adaptive Studies) (5).

The pre-planned changes that an adaptive design can allow are many. They may concern

the size of the sample to be recruited, the ratio of allocation of patients to treatment arms, the addition or deletion of treatments or doses, the variation of statistical assumptions (*e.g.* non-inferiority or superiority), the discontinuation of the entire trial at an early stage due to the success or lack of efficacy of the tested treatment.

"Seamless study designs" are examples of adaptive studies where successive stages of development are combined within a single protocol. This saves a great deal of time, especially in terms of reducing the time needed to approve the protocol and activate the centres, as well as speeding up the translation of scientific discoveries into innovative medicine. One example is the development of immune checkpoint inhibitors (*e.g.*, pembrolizumab) and agents that target rare and specific molecular alterations (*e.g.*, crizotinib). Both of these agents took only 3-4 years from first study in humans to regulatory approval, an unprecedented timeline for solid tumours (6).

A strong impetus for the evolution of these new study designs has come from the development of therapies with a defined biomolecular target, designed and developed for increasingly precise medicine. Assessing targeted therapies in target populations identified on the basis of putative predictive biomarkers creates challenges in recruiting patients whose eligibility for study is assessed by criteria other than those that traditionally define disease status. This, together with the need to answer more questions more efficiently and in less time, has led to the creation of structured master protocols to evaluate, concurrently, the activity of different therapies in a given disease (umbrella study) or a single targeted therapy in multiple diseases or disease subtypes (basket study) (7).

This methodological innovation, which is now consolidated and widespread, is a significant example of how study design can lead to overturning the traditional way of thinking about patient care and access to treatment, which is no longer decided on the basis of the anatomical location of the disease but on its genetic characterisation.

Thus, the first agnostic therapies in oncology were born, a great challenge first for regulatory assessment and then for use in clinical practice.

There are, however, a number of critical elements. Firstly, basket studies typically lack a control group. It would actually be unethical to have one of these because the patients involved are often those with no other treatment options and are destined to die quickly without intervention.

These studies also focus on how the tumour responds to a drug, rather than survival. For example, larotrectinib was approved based on 3 studies involving a total of 54 adults and achieved an overall response rate of 57%. But the frequency and magnitude of the response do not necessarily correlate with survival (8).

Similar problems are also observed in the development of drugs for rare diseases where the scarcity of those affected by the disease and the need for patients to have rapid access to treatment lead to the design of studies without a comparison arm and using non-validated or surrogate endpoints.

Lastly, one must consider the challenge that comes from the development of digital therapies in which the traditional active ingredient is associated with software or an application/medical device or, even, in some cases, is a therapeutic solution without a pharmacological active ingredient (*e.g.*, ReSET approved by the FDA in 2017 for the treatment of Substance Abuse Disorders) (9).

Translating methodological innovations applied to research plans into approved therapeutic interventions that are accessible to patients requires very close and early collaboration with regulatory bodies to verify the applicability and acceptability of the results obtained.

In 2020, the Food and Drug Administration (FDA) finalised a guideline on the use of complex innovative designs ("Complex Innovative Trial Designs") for trials (10) useful for advanc-

ing and modernising drug development. The guideline emphasises that there is no fixed definition of what constitutes a complex innovative study design, what is considered innovative or novel today may change over time, and study designs may vary by therapeutic area.
In the process of guiding the ongoing dialogue between regulatory agencies, several thematic areas are addressed:
The EMA (European Medicine Agency) addresses the issue of innovation in clinical trials in its document "EMA Regulatory Science to 2025 Strategic reflection" (11).
Innovation should be supported by promoting and facilitating the conduction of complex clinical trials and other innovative research projects, by adopting new pathways to facilitate the authorisation of a study, and by providing regular bodies and Health Technology Assessment (HTA) agencies with the necessary information so that patients can gain earlier access to treatments.
The document then focuses attention on the unmet needs of paediatric and rare disease populations, stimulates the increasing integration of new digital tools in drug development, emphasises the need to integrate clinical information collected in registration studies with that related to real-life health care, critically evaluates the clinical value of new and emerging endpoints and their role in facilitating patient access to new medicines, and promotes the inclusion of neglected populations such as pregnant women, the elderly and those of different ethnicities in clinical trials.
Clinical trials, whether set up in a traditional way or with new, less conventional designs, are often the first means of access to innovative medicines.
Clinical research implements irreplaceable processes for the advancement of scientific knowledge and for the improvement of clinical practice itself, also finding legitimacy in Italian Constitutional values, such as the promotion of scientific research and the protection of health as a fundamental right of the individual and interest of the community: "The Republic promotes the development of culture and scientific and technical research (art.9)... protects health as a fundamental right of the individual and the interest of the community" (art.32).
Clinical research, in addition to being an important opportunity for cultural growth, represents a driving force for the development and economic growth of a country (12). The increase in trials is directly related to the greater availability of therapeutic alternatives, access to innovative drugs, and greater prescriptive appropriateness. "Early*Access* Programs" also play a positive role in terms of both the treatment options offered to patients and the economic value to the SSN (13).
For these reasons, it is important that the value of clinical research is adequately perceived by institutions and citizens, and that it is supported through an up-to-date regulatory framework, fast authorisation processes, the availability of dedicated and trained staff, and adequate infrastructures. On 30 December 2020, the Italian Drug Agency published the 19th National Report on Clinical Trials of Medicinal Products in Italy, with data for 2019 (14).
It can be seen from this report that the number of clinical trials has remained at adequate levels, having already recovered as of 2018 in terms of total number, despite the fact that there has been a steady and general contraction of trials conducted in Europe. This has led to a further increase in the percentage of trials authorised in Italy compared to the rest of Europe (equal to 22%) (**table I**).
The distribution of trials by therapeutic area is in line with previous years, with about half in oncology and haemato-oncology.
The upward trend of trials in rare diseases continues significantly, accounting for 32.1% of the total. In 38.1% of trials, a biological/biotechnological active ingredient is studied and in 3.6%, an ATMP is studied.
In Italy, multi-centre and multi-national trials prevail over national ones. This finding, as reported in the same report, makes it increasingly urgent to bring the Italian system into line

Table I. Experimentation by year: comparison between the European Union and Italy.

Year	CT in UE*	CT presented in Italy**	% Italy/UE	CT authorized in Italy***	% Italy/UE
2015	3.918	744	19,0	672	17,2
2016	3.255	767	23,6	660	20,3
2017	3.125	669	21,4	564	18,0
2018	3.256	716	22,0	666	20,5
2019	3.048	722	23,7	672	22,0

CT: Clinical Trials.
*Number of studies uploaded to the European system.
**Number of clinical trials presented in Italy in 2019 is taken from table V, while for the other years it is taken from previous editions of this National Report.
***The number of clinical trials authorised in Italy is taken from **table II**.

with the requirements of Regulation 536/2014, with the indispensable adjustments of a more significant organisational nature for trials evaluated in a coordinated manner with other Member States.
The SARS-CoV2 pandemic has not only brought to the forefront the importance of clinical research as a tool for treatment, knowledge and growth, but it has also demonstrated the need for good organisation to enable clinical trials to be launched quickly and conducted optimally.
The Guidelines published by AIFA for the Management of Clinical Trials in Italy during the emergence of COVID-19 (in version 1 of March 12, 2020 and the subsequent version 2 of April 7, 2020) have shown that this is feasible.
Under emergency conditions, simplified and accelerated ways of approving, initiating and conducting clinical research were applied while maintaining high levels of quality. These methods, with less bureaucracy and more digitalisation, could enable studies to be conducted more easily, even under normal conditions, as called for in the policy document drawn up by leading scientific societies. (15)
To this end, it is considered useful that the following be quickly implemented:
AIFA approval and a single Ethics Committee opinion for each protocol.
The submission of applications for authorization exclusively by electronic means, through the Observatory (OsSC).
The adoption of measures aimed at facilitating the employment of a sufficient number of professional figures such as Study Coordinators/Data Managers with adequate preparation, also envisaging the possibility of including a quota for the financial funding of research support figures in contracts between Sponsors and the Hospital Administration.
The use of measures and technologies to make participation less of a burden for patients.
The definition of guidelines to facilitate remote monitoring of the study by the monitor and the adoption and implementation of validated electronic medical records that can also be consulted remotely by authorised personnel is considered essential.
The implementation of these indications is essential to ensure that Italy is seen as an attractive candidate for international investment in clinical research and, ultimately, to enable scientific innovation to be transferred more rapidly to patients, because it is a well-established fact that where research is carried out, there are better opportunities for treatment.

FUTURE PROSPECTS

Innovation in research represents an important opportunity for the entire health system sup-

ply chain and, ultimately, for the end user of this innovation, the patient.
The scientific excellence of our researchers, which is widely recognised and undisputed, is a fundamental element although it is not in itself sufficient to guarantee the transfer of knowledge to treatment, firstly experimental and then clinical practice based on appropriate prescribing.
In research centres, it is essential to have adequately trained staff available, able to accommodate methodological innovation and ensure the process excellence required by modern clinical research.
The training of dedicated research staff is an issue that is often left to the initiative of individuals, to the vision of certain universities or scientific associations, to the collaboration between institutions and the business world without ever having been addressed in a structured and programmatic way. The preparation of dedicated research staff should be incorporated into the curricular training of these individuals. In particular, it would be useful for the medical degree curriculum to include a specific course of preparation for research, capable of making people understand not only its value but also the importance of possessing the necessary tools to become not only good clinicians but also good researchers. The boundary between research and clinical practice should be seen more and more as a regulatory and normative boundary but not characterised by different levels of attention to quality and rigour required for data production and evidence generation in the two areas.
The issue of training is one that should be applied to all professionals who collaborate with the clinician, as researcher, in the management of the patient in a study protocol. Figures such as data managers and research nurses, in addition to being officially recognised and legitimised within a regulatory framework and professional registers, should be able to count on training and continuous development courses dedicated to them. They could be joined by a clinical engineer and an expert in artificial intelligence for all matters relating to the development of digital therapies.
Finally, clinical research training should also be carried out outside the research centre. It should be available to patients and citizens, the protagonists of clinical trials, who are able to express their opinion on whether the entire NME/NTE development process is appropriate to their needs. Not only is it important to foster the growth of expert patients such as in the EUPATI (European Patients' Academy on Therapeutic Innovation (16)) project, but it is also important to help all patients and carers develop the basic knowledge to enable them to make informed choices, to ensure responsible participation in a study and to avoid using false or misleading sources of information.
Clinical research should also be accessible to all patients. The creation or otherwise strengthening of centres of excellence for research is not sufficient to enable its widespread distribution in Italy. It is important to stimulate and encourage the creation of territorial networks, real networks that allow patients to be referred to specialised centres so as to allow a wider population to gain access to clinical trials. This approach is essential to ensure access to experimental treatments, especially for patients suffering from rare illnesses who would otherwise run the risk of not being referred to sites where a study dedicated to them is active. It also increases the speed and efficiency of completing a clinical trial, a development programme that can be completed more quickly to the benefit of all patients waiting for a new treatment.
Networking is increasingly becoming a strategic choice, not only for rare illnesses or diseases that require a study using particularly sophisticated equipment, but it is also important to facilitate the continuity of participation in a study in chronic diseases, in protocols that require a long follow-up, where there is a higher risk that patients will discontinue their participation, potentially jeopardising the validity of the study itself.

Looking ahead, the strategic component of this approach is also underpinned by the implementation of increasingly collaborative research, as envisaged by the new European Regulation 536 of 2014, which also provides an opportunity to strengthen an important and early synergy with the pharmaceutical industry by facilitating the creation of shared development paths.

Innovation in clinical research is also expressed through new ways of managing studies.

The advent of digital technology, the increasing focus on patients, the need to make the management of a study more efficient and to have the results available quickly, all favour the development of increasingly decentralised models of clinical research.

Remote Decentralised Clinical Trials (RDCTs) (17) are one way to make studies more accessible. The use of technology can enable people to take part in clinical trials in their own homes without the need to travel to attend visits and having to be away from work or family. RDCTs have the ability to make participation in a clinical trial simple and convenient.

This approach also reduces drop-out rates, increases the efficacy of studies, and allows innovative drugs to be brought to market more quickly, with significant savings in development costs.

Implementing RDCTs does not mean conducting trials in the absence of health care providers. Nor does it mean, in most cases, completely eliminating the need for any physical contact with the patient. Instead, it is a question of examining areas where technology and other innovative solutions can enable a hybrid approach to clinical trial design, for example with health workers making home visits or apps facilitating data collection without patients having to travel, thus providing an alternative to an inflexible, single-centre anchored system that can facilitate a high drop-out rate from patients.

In order to facilitate the adoption of RDCT, it is very important that regulatory agencies are willing to validate these new ways of managing clinical trials.

It is also essential to find new technology providers, a courier system capable of delivering drugs and other medical supplies and equipment in a safe and legally acceptable way, to be prepared to handle a higher volume of patient data received via apps and wearable devices, to be able to count on properly trained staff and to limit as much as possible the risk of technological failure resulting in loss of patient data.

Beyond the challenges, there are many opportunities presented by RDCTs and their increasingly widespread adoption can be expected.

RDCTs represent another frontier of digital evolution that can facilitate the collection and analysis of Real Life data. They are part of a digital ecosystem that needs to evolve and that becomes even more important when innovation reaches the patient quickly, with accelerated approval processes and the need for confirmation of its risk-benefit profile.

Real World Data, which is already important in the development phase of a drug, is becoming more and more relevant when used for general Real World Evidence to ensure the future: 1) fast and sustainable access to innovation for patients, 2) high quality health care, 3) verification of the risk/benefit ratio of a drug and its actual value in a real life context, 4) precise definition of the most efficient and cost-effective diagnostic and therapeutic pathways.

CONCLUSIONS

As the pace of scientific innovation accelerates, the drugs in development become increasingly complex and have the potential to bring important innovation to unmet treatment needs. This innovation occurs throughout the entire life cycle of any given treatment, from screening and characterisation of candidates to pharmacovigilance and re-use with new indications.

Patients' first access to new treatment opportunities is through clinical research. Clinical research is a fundamental tool for guaranteeing a quality care process for patients and

for bringing about real innovation, without neglecting the enormous potential it holds for Italy both in terms of employment and the economy.
For this reason, it is extremely important to create a favourable environment for its development at national level by fostering a network to facilitate the conduction of clinical studies and a regulatory and access approach favourable to the incorporation of methodological innovation and new experimental designs.
The rapid issuing of the implementing decrees necessary to transpose the new European Directive is a priority and indispensable element to ensure that Italy continues to be one of the leading countries in the sector and, above all, to allow our patients fundamental access to innovative therapies that are often essential for their treatment and recovery.
It is also possible to speed up and increase the efficiency of the process of authorising studies and setting up centres in Italy. The methods used in emergencies during the pandemic are a clear demonstration of this, and should represent an important lesson to be learned when reviewing the regulatory and organisational framework needed to support clinical research in Italy.
It is also essential to recognise the profound transformation that the clinical development of new therapies has undergone in recent decades, starting with the systematic involvement of the patient, who is increasingly a key player in research, and who not only participates in a study but also helps to define its methods and objectives.
The advent of digital technology has facilitated an increasingly large and systematic collection of patient clinical data. This technology has also enabled the implementation of decentralised clinical research methods, with increased use of telemedicine and home care tools, which will gradually become a new standard for conducting studies.
Effective research requires the existence of a digital ecosystem that includes the computerisation of medical records with the adoption of national standards and the increasingly widespread adoption of the necessary IT equipment with adequately trained staff.
The gradual digitisation of clinical data is also of great importance to ensure the availability of Real World Data, which is essential in the development phase of a drug to obtain information on the epidemiology and natural evolution of a pathology, as well as to obtain Real World Evidence which is indispensable in assessing the efficiency of a new treatment in clinical practice.
This last point becomes particularly relevant in the light of a new drug development process that increasingly adopts innovative, adaptive designs, new endpoints and which, when it concerns therapies that can overturn the prognosis of rapidly fatal diseases without a standard of care, may lead to accelerated registrations based on data that does not meet the traditionally required quality standard.
It is important to adopt collaborative approaches to evolving evidence generation and drug development. In the European context, this collaborative approach can be combined with greater integration with downstream decision-makers, such as health technology assessment (HTA) bodies and payers, to accelerate patient-centred access to innovative treatment.
An early dialogue between institutions and those involved in pharmacological innovation is essential to ensure the timely transfer of scientific discoveries to patients, respecting their needs but also the sustainability of the system, with an increasingly important and concrete orientation towards Value Based Healthcare without which there can be no health and economic growth.

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OPINION PAPER

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QUALITY OF SCIENTIFIC DATA IN PRE AND POST-AUTHORISATION CLINICAL DRUG TRIALS

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HIGHLIGHTS

- Data quality is an increasingly important aspect in the generation of both experimental and observational evidence and is an essential requirement for the reliability of the results on the basis of which regulatory and clinical decisions are made.
- Reliable data sources, adequate infrastructure, staff expertise, and management tools and procedures are key elements in the implementation of quality studies and for this reason should be described in detail and clearly in *peer-reviewed* publications.
- Over the years, there has been a significant increase in the focus on the use of "*real world*" data to integrate experimental evidence on drugs and vaccines in the authorisation processes, both in the pre and post-marketing setting. However, a set of data quality indicators widely recognised by the scientific community and regulatory agencies has not yet been defined.
- A challenge for the future will be the management of patient data from wearable medical devices and their scientific evaluation. The *real world data* generated by these devices, suitably processed through AI analytical techniques, will be a useful addition to the results of the experimental studies and, therefore, data quality aspects will be relevant in this context as well.

SUMMARY

In the last decade, it has been recognised that a crucial aspect of clinical trials, whether experimental or observational and therefore based on *real-world data* (RWD) analysis, is data quality. Poor data quality can lead to erroneous conclusions and recommendations in terms of both clinical and regulatory decisions. Data quality is essential for the reliability of the results generated in both experimental and observational clinical trials. Ensuring that data is managed effectively requires reliable sources, adequate infrastructure, staff expertise, management support, and resources. The use of data quality indicators, recognised and formally validated by the scientific community, could support the development and reinforcement of a cul-

ture of data quality in both experimental and RWD-based studies.
Some scientific societies have developed guidelines for assessing data adequacy and especially *fitness-for-purpose*. Looking ahead, it is also necessary for the scientific community to consciously address the issue of data quality, also in relation to the challenge of *big data* collected through *apps* and wearable devices, which will increasingly occupy a predominant role as a source of *real world* data in the era of *digital health*.

BACKGROUND AND OBJECTIVES

Clinical trials are an important research method for improving medical knowledge and patient care. According to the *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice* (ICH-GCP), clinical trials must protect the rights and safety of all patients and ensure that results are legible and valid. Ensuring that data is managed effectively requires adequate infrastructure, competent staff, management support, and adequate financial resources.
In general, there are two main types of clinical studies designed to evaluate the efficacy (*effectiveness)* and safety of drugs: experimental (or interventional) studies and observational studies. In experimental studies, subjects are randomly assigned to one of the experimental groups. The most common type of experimental study is the randomised controlled clinical *trial* (RCT), which is conducted on patients enrolled according to predefined eligibility criteria, in order to evaluate the efficacy and/or safety of specific drug treatments in a given population. Experimental studies are essential for the production of the documentation required for the marketing authorisation of new drugs or for the extension of the indications for use of drugs already on the market.
A crucial issue in conducting clinical trials is data quality. Poor data quality can lead to erroneous conclusions and recommendations and, therefore, it is essential to pursue the highest data quality to ensure the reliability of the results. Since poor data quality can result from errors in data handling within the study, preventing these errors is as important as the development, design, and collection of the data itself (1).
Data integrity is defined as the extent to which all data (electronic or paper) is complete, consistent, accurate, and reliable throughout its life cycle, from creation to archived state and eventual destruction. Regulatory agencies, as well as the bio-pharmaceutical industry, rely on data to ensure both the rights and safety of patients and the scientific value of clinical trials (2). The ICH E6(R2) *addendum* reinforces the principles of data integrity and the role that monitoring can and should play in verifying data integrity during a study (E6(R2) GCP: *Integrated Addendum to ICH E6* (R1) *Guidance for industry* 2018) (3).
In contrast to experimental clinical trials, observational studies examine the natural course of clinical practice. Changes or differences in one or more variables (*e.g.*, risk of developing a particular *outcome*) are studied in relation to changes or differences in other variables (*e.g.*, drug exposure) without the intervention of the researcher, who merely observes the trend of the phenomena. These studies can be designed with the aim of mimicking a trial in all cases where ethical or practical reasons make it difficult to conduct a randomised clinical trial (*e.g.* inclusion of patients not usually enrolled in clinical trials such as pregnant women, children and the elderly; long follow-up). The main objective of these studies is to generate evidence on the safety and use of drugs in *real world settings*. Observational studies can be classified into cross-sectional (or prevalence studies) and longitudinal (cohort studies, case-control studies, and *nested*case-control studies), based on the type of *outcome* and exposure measurement. Cross-sectional studies involve observation over a specific period of time, whereas longitudinal studies involve observation over an extended period of time.

The aim of this document is to review the state-of-the-art in data quality assessment of experimental and observational studies in the regulatory environment and in the scientific community in general.

THE CURRENT CONTEXT

Multiple international and national guidelines establish the necessary quality and accuracy standards for clinical data even though these guidelines are relatively methodologically non-specific (1). This topic has been gaining particular prominence in recent years, so much so that a few months prior to the release of the updated version of ICH GCP E6 (R2), three draft guidance documents on the topic of "Data Integrity" and an explanatory Q&A document were published by the U.S. *Food and Drug Administration* (FDA) (4), the Medicines & Healthcare products Regulatory Agency (MHRA) in the United Kingdom (5), the Convention on the Pharmaceutical Inspection Co-operation Scheme (PIC/S) (6) and the *European* Medicines Agency (EMA), respectively (7). They all emphasise that a clinical trial must have a sound scientific design, accurate and timely data collection, complete and accurate reporting of results, and that the results must be reproducible. In fact, accurate, complete and reliable data protect and respect the rights, safety and well-being of subjects, and maintaining data integrity throughout the clinical development process is both a regulatory (legal) requirement and an ethical obligation towards all subjects involved in the clinical trial.

These guidance documents represent the thought processes of regulatory agencies on critical compliance issues with general applicability and can provide guidance and/or practical advice on GxP (Generic Good Practice) challenges, which may also be useful for clinical trials. The first of the guidance documents to be finalised and the first with GxP scope was the MHRA guidance, published in March 2018 (*Data Integrity Guidance and Definitions* - Revision 1.6) (8). "This guidance aims to promote a risk-based approach to data management." An important element emphasised in the guide, which should always be the *driver* for researchers, is that "the organisation needs to take responsibility for the systems used and the data they generate. The organisational culture should ensure data is complete, consistent and accurate in all its forms, *i.e.* paper and electronic." In addition, "The impact of organisational culture, the behaviour driven by performance indicators, objectives and senior management behaviour on the success of data governance measures should not be underestimated." All this underlines how important the organisational culture of the clinical trial sponsor and trial managers is from a legal perspective. The emphasis placed by the principal investigator on the importance of data quality and data monitoring systems is fundamental to the proper management of the data and the conduction of the study by all staff involved in the trial.

According to the above guidelines and question/answer document, the principles of data integrity can be summarised in four main pillars (2):

ALCOA +

Data must be Attributable; Legible; Contemporaneous; Original; Accurate (ALCOA) (**figure 1**). These are the core attributes of data quality and good documentation practices (GDocP). Recently, four more attributes were added: complete, consistent, durable and available (ALCOA +). This emphasises that data should also be complete (*i.e.* include relevant metadata), consistent (*e.g.* date and time of activities should be in the right sequence), durable throughout its life cycle and readily available for review or inspection. These attributes apply to both paper and electronic data and are the foundation of data integrity.

Computer system validation

It is essential that adequate resources are devoted to the validation of the IT systems used before starting a clinical trial.

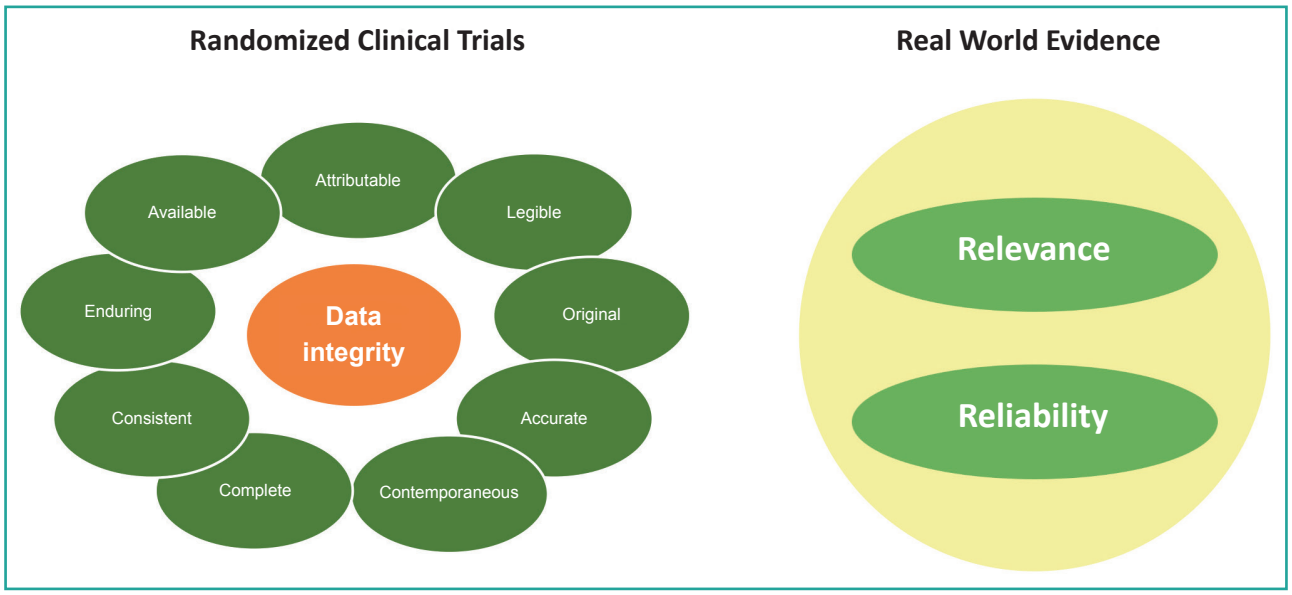

Figure 1. The principles of data integrity.

ICH E6 (R2) in Section 5.5.3 emphasises that information systems should be validated based on a risk assessment. Validation should take into account "the intended use of the system and the system's potential to influence the protection of the subject and the reliability of the trial results".

The MHRA guidance points out that "risks to data may be increased by complex, inconsistent processes with open-ended and subjective outcomes, compared to simple tasks that are undertaken consistently, are well defined and have a clear objective." Other factors that should be considered include the degree of automation versus human intervention and the ability to alter or delete data.

Access Control

Limiting the ability to record, edit, and delete data is a fundamental requirement for ensuring data integrity. Roles and types of data access must be defined and assigned, clearly indicating who can do what within the system and process.

Potential conflicts of interest must also be considered to ensure that individuals cannot perform steps that affect data integrity. Roles should be carefully defined and assigned in order to limit access to only those who need it to perform the tasks for which they are responsible. Similarly, a user's access should be removed in a timely manner once it is no longer needed. Routine review of user access should also take place to ensure that roles are correctly assigned, that there are no conflicts of interest and that access is limited only to those strictly necessary.

Metadata and audit trail

Metadata is the information that must be included in a computer document in order for it to be properly formed, managed and preserved over time. The electronic document has no material component in the form of paper and is stored in systems containing many digital objects; in order to be preserved, made accessible over time, and to be correctly placed in its context, it must be placed in relation to a set of information describing it at various levels. The most basic metadata are the format and name of the *file*; technical specifications about the *software* version *and hardware*; dates of creation, access and last modification; and the author. The most complex data are description, subject matter, terms of release, access and use, *etc.*

Metadata is an integral part of the original recorded data, and without metadata, the data has no meaning. Consequently, metadata should be maintained and controlled in the same way as the original data it belongs to.
Audit trail reviews should be performed by users of the computer system as part of the normal management process and should be based on an adequate understanding of the process supported by the computer system, applicable GCP requirements, risk to the protection of trial subjects, and the reliability of trial results. The *audit trail* can help identify missing data, inconsistent data, anomalous data, unexpected lack of variability and protocol deviations, systematic or significant errors in data collection and reporting at a site or between sites, and other data integrity issues.
The draft data integrity guidance documents, the EMA Q&A document, and the final MHRA *guidance* document offer very useful information regarding regulators' expectations for data integrity. These expectations must be met by both commercial sponsors and independent research centres during the implementation and conduction of a clinical trial.
In summary, all testing centres should review their processes to ensure that they meet the data integrity expectations documented in ICH E6 (R2).
Lack of or inadequate data quality control can have very significant effects, up to and including the withdrawal of publications reporting the analysis of clinical trial data. Evidence of this phenomenon is reported in the online blog Retraction *Watch*, which specialises in publication retractions. In 2017 alone, this website listed 562 publications that had to be withdrawn due to incorrect data/analysis. At the root of these withdrawals appears to be a lack of knowledge of systematic methods and procedures for assessing data quality in clinical trials. (1). The effect of these retractions on the reputation of research centres and science in general is evident.
To ensure data integrity in clinical research, it is imperative to introduce a "recognised methodology" that ensures that published manuscripts explicitly reference the methods used to ensure data validity. It may be time for the quality assurance and quality control tools and procedures implemented in clinical trials to be mentioned in a dedicated section in all publications (1).
It is evident that there is a need to develop a set of common data quality indicators to meet future data management challenges. The use of performance indicators or measures is a well-established methodology for assessing the quality of health care, and many articles have been written dealing conceptually with this topic. Based on a literature review, 34 useful indicators were identified to enhance data quality in 31 publications. It is now clear that the indicators could be systematically organised for selection on the basis of specific use cases, allowing a more standardised approach to data quality (9). It is more necessary than ever that a set of indicators be defined, recognised and formally validated by the scientific community. Their application becomes automatic and recognised, providing clear support for researchers to ensure the application of data integrity principles in clinical trials.
In addition to the importance of quality indicators, other measures that can be taken to minimise quality/integrity problems or detect them when they occur during RCTs should not be underestimated. These include understanding the systems and processes for collecting, recording, reviewing, reporting and archiving data; assessing risks; applying appropriate controls, including "real time" actions and independent reviews; reviewing/monitoring/auditing from a data integrity perspective; validating all IT/software systems that collect, record, archive and/or report data; knowing what is in the audit trails before a problem occurs; monitoring access to systems, data and records.
The "behavioural" approach in research organisations may also be important, for example: establishing clear policies on the importance of data integrity; establishing serious

consequences for deliberate misconduct; providing "safe" means for employees to report data integrity issues without fear of retaliation; providing education and training in good documentation practices; and training operations managers, quality assurance (QA) personnel, trainers and internal auditors to effectively verify data integrity and include it in routine audit planning.

Simply put, everyone involved in clinical trials must always act in a way that protects and respects the rights, safety, and well-being of study subjects and ensures data integrity.

This last statement applies not only to randomised clinical trials but also to observational studies. Digitisation of healthcare data, generated and collected daily (*real world data, RWD*), has increased dramatically over the past decade. A substantial amount of health data is currently collected in electronic format from a variety of sources (*e.g.*, administrative databases, *electronic medical* records, and registries), providing important clinical information on hundreds of millions of patients. Today, the ability to access and integrate this data allows meaningful evidence to be generated in a timely manner. These RWDs have been used for many years, in addition to administrative or clinical routine management reasons, to conduct observational studies in the *post-marketing* phase. Their use is now increasingly proposed to generate complementary evidence to support decision making during the drug life cycle (10).

Regulatory agencies are showing increasing attention to the use of RWD to support authorisation processes, especially in specific target populations. Specifically, the EMA and the FDA have accepted the use of RWD to support drug approval, mainly in oncology and rare diseases, areas in which the conduct of RCTs presents several critical issues (10, 11).

However, several aspects need to be carefully considered in order to encourage the use of RWDs in the regulatory environment. The main concerns relate to their internal validity, lack of standardisation, often limited data accuracy and robustness, lack of some values, and variability in dataset content and quality (12). Several studies have shown that the choice of data sources and study design can have a major impact on the evidence that is derived in the *real world setting* (13, 14). In order to be able to use RWD sources to generate evidence to support regulatory decision making, it is therefore critical to understand how much regulatory agencies can rely on these data. The ability to characterise the quality of RWD is therefore a strategic goal for regulatory agencies. Although the *a priori* definition of RWD quality is challenging because the need to use certain data sources often depends on the research question, some general principles can be defined. One possible approach to this problem is to establish guidelines for assessing data adequacy, also known as *fitness for purpose*, which is the degree to which the chosen data source aligns with the ability to accurately and reliably address the research question.

The *International Society of Pharmacoepidemiology* (ISPE) has developed guidelines to support the selection and use of data sources for observational research, highlighting the potential limitations of current healthcare databases used in pharmacoepidemiology and recommending that quality control be conducted (15). These guidelines also provide a *checklist* related to six areas:

1. database selection: reference population, availability of variables needed to answer the clinical question, regular updating of the database, specific dataset.
2. Use of multiple data sources: possibility of *linkage*, comparability of data sources in terms of coding systems, terminology and data access *policies.*
3. Data extraction and analysis for the study group: specify how the study group is selected and what the variables of interest are.
4. Privacy and Security: adherence to privacy and security policies, limited use of sensitive information, secure data storage and transfer.

5. Quality and validation procedures: quality control of the data contained in the dataset, specific analysis on the extraction processes, combination of data, variables under study, *etc.*
6. Documentation: document extraction specifications, output, quality testing, combination of multiple data sources, privacy responsibility and programming code used for data extraction and final analysis.

In 2017, the *International Society for Pharmacoeconomics and Outcomes Research* (ISPOR) and ISPE created a *task force* to make recommendations on *good procedural practices* that could improve the reliability of evidence from RWD studies for regulatory agencies (16). These recommendations include:

1. the *a priori* definition of the hypothesis under study in the protocol rationale;
2. the registration of the study protocol and analytical plan on a public site (*e.g.*, *EU Post-Authorisation Study Register* or clinicaltrials.gov);
3. the publication of studies with a statement of compliance and/or changes to the original analytical plan;
4. the ability to replicate the study;
5. conducting the study using different data sources and different study groups to confirm the significant evidence emerging from the exploratory analyses;
6. a commitment by the authors to publicly address the critical methodological issues related to their study once published;
7. the inclusion of key *stakeholders* (*e.g.*, patients, physicians and other health care providers, and regulators) in the design, conduct, and dissemination of the study.

As part of the *Sentinel Initiative*, funded by the FDA to build a network of distributed healthcare databases to rapidly generate evidence derived from RWD analyses to support drug regulatory decisions, the final report on the *Data Quality Metrics System* was released in September 2020. This project aims to provide a standardised approach to the classification of data from multiple sources to enable researchers to better understand the various data sources and determine their suitability to answer a specific clinical question before using them for research purposes (17). This system contains a set of metadata standards and metrics that describe the quality and characteristics of data sources and their suitability for use. These standards have been used to create a set of *web-based* tools to explore, describe and visualise the quality, completeness, and reliability of data sources.
Validation studies designed to assess the accuracy of the algorithms developed to identify *outcome*, exposure, and covariates of interest are an essential element in demonstrating the validity and applicability of using RWD for research purposes. The term identification algorithm refers to the combination of variables that enable the identification of cases of a specific disease or a specific category of patients in different health databases. These may become obsolete due to possible changes, over time, in coding systems within health and administrative databases or changes in the way health services are delivered. To ensure the validity of the study, the algorithms should be validated against a *gold* standard. Validation studies allow epidemiologists to assess the extent of potential mis-classifications (*e.g.*, misclassifying a patient as (not) exposed to a particular study drug or (not) affected by a particular study *outcome*) and estimate their impact on study outcomes (18-20)
The availability of quality standards to ensure the reliability of evidence generated by *real-world* studies is more necessary than ever in health emergencies such as the COVID-19 pandemic (21). To date, approximately 40 studies of SARS-CoV-2/COVID-19 have been withdrawn, and 18 of these were observational studies (22). Some of these studies were initially published in prestigious journals such as *The Lancet* and *New England Journal of Medicine* and later withdrawn due to critical issues related to data access (23, 24).

FUTURE PROSPECTS

The greatest scientific knowledge and, consequently, the greatest benefits to medical science and patients are obtained when subjects are enrolled in appropriately designed randomised clinical trials. These studies not only ensure that every patient is adequately protected from side effects and other potential hazards associated with the drug, but they represent the universal *gold standard* for producing efficacy data against which medical and regulatory decisions can be made.

Expanded access and compassionate use programmes have been of great importance in recent years as ways to facilitate early treatment of patients without therapeutic alternatives. In a recent paper, Rozenberg and Greenbaum reported that a pragmatic compassionate access/use programme might be of greater use to society if it were designed to produce data that could eventually be used for inclusion in authorisation processes. However, this requires both practical changes in how the data are collected and regulatory advances to allow this new data collection to be best included in regulatory processes (25).

The use of RWD within studies, while still limited, is expanding in many jurisdictions and has even been incorporated into some of the *New Drug Applications* (NDAs) in the United States. The United Kingdom, under the *Early Access to Medicines Sche*me, was the first to officially consider RWD from an early access programme as part of the data to be used in the regulatory submission dossier for the molecule (26).

In a recent paper, Polak et al. (27) reported that for 39 approvals by the FDA and EMA, data from expanded access (EA) programmes, including compassionate uses, were used to provide information on clinical efficacy. In 13 cases, these programs were the primary evidence for approval. Almost all (12/13) of the approvals were granted with "orphan" designations. In 8/13, there were differences in the status of approval and assessment of evidence between the regulatory authorities. Surprisingly, 4 treatments were granted approval based solely on efficacy in EAs.

Under the *Twenty-First Century Cures Act* of 2016, the FDA is required to seek alternatives to the RCT paradigm as the sole source of evidence on the benefit-risk profile of drugs in the *pre-marketing setting*. RCTs are considered to be expensive, limited and inflexible; one of the suggested efforts is to establish a regulatory framework to include *real world evidence* (RWE) for the drug approval process (28). However, RWE, understood as evidence generated by accurate analysis of RWD, still lacks a unified system of quality assessment and comparison, and studies focusing on the production of RWE are therefore still far from replacing the randomised clinical trial. Although experimental studies remain the *gold standard* for drug evaluation in the *pre-marketing setting*, RWD studies will increasingly be able to complement experimental studies, especially in patient categories (*e.g.*, patients with rare diseases) in which it is difficult to conduct clinical trials.

EA/compassionate use programmes that collect RWD have several critical methodological issues regarding the collection of usable data for drug approval, including lack of standardised *reporting*, and bias in various aspects of patient recruitment and subsequent data analysis. However, some of these concerns may be mitigated through the grouping of patients into cohorts, the establishment of patient registries, and increased collaboration with regulatory authority in programme implementation. We hope that all stakeholders will work together to enable the standardisation of data collection, to make the RWE more reliable and usable, and to incorporate innovative technologies into data collection to ensure earlier access for patients who need treatment and have no treatment alternatives.

Another aspect to consider in the immediate future, regarding the challenges and opportunities related to RWE, concerns the possibility of using digital tools such as *apps* and *wearable* devices as sources of RWD. The ongo-

ing digital revolution is bringing about radical transformations in all sectors of society and more recently in healthcare too. Two fundamental factors are responsible for this real revolution: 1) the amount of health data generated by each individual patient; 2) the computational capacity, both in terms of storage and analysis. *Apps* or *Web Apps* support users in changing their lifestyles and pursuing wellness goals by generating health data that can contribute to research and clinical practice. These are mainly personalised *Apps*, aimed at promoting adherence to pharmacological therapies, facilitating communication between patient and doctor, offering tools for monitoring the disease and, more generally, promoting the involvement of patients in their daily healthcare. The use of these devices may increasingly generate evidence in the future to be integrated with the results of RCTs, especially in the field of chronic diseases (29).

However, one of the main critical issues associated with the use of these technologies, and specifically *wearable devices*, is the management and sharing of patient data. Although the digitisation of healthcare is progressing slowly, the amount of individual patient data has increased exponentially over the past decade, making it necessary to ensure patient *privacy* (30). In the European Union, the new provisions of the General Data Protection Regulation (GDPR) do not distinguish between different digital devices, but cover all data generated by wearable devices or health and wellness *apps*. In addition, the EU requires clearly defined purposes for data use, patient consent for data reuse and sharing, and allows patients to withdraw their consent at any time. The above discussion on data quality and integrity in RCTs and RWE-based studies may support the implementation of a data *governance* law in the EU. On November 25, 2020, the European Commission published draft legislation outlining policy measures and investments designed to give the EU a competitive advantage and enable it to capitalise on its vast amount of data (31). The act aims to create a framework that encourages greater data reuse, increasing trust in data providers and strengthening sharing mechanisms across the EU. The act will play a central role in driving the creation of common and interoperable data spaces at EU level in strategic areas, such as health, also with the aim of benefiting citizens through better personalised medicine.

CONCLUSIONS

Data quality is playing an increasingly important role in the management of clinical studies, whether experimental or observational and therefore based on RWE analysis. Poor data quality can lead to erroneous conclusions and recommendations in terms of both clinical and regulatory decisions. Therefore, as reported in documents published by the relevant regulatory agencies such as EMA, FDA, and MHRA, data quality is an essential requirement for the reliability of the results generated in both experimental and observational clinical trials. Reliable sources, adequate infrastructure, staff expertise, management support, and resources are the key elements in implementing quality studies. The quality assurance and quality control tools and procedures implemented in clinical trial management should be reported in dedicated sections of *peer-reviewed* publications, as is the case for materials and methods. It would also be appropriate for a set of data quality indicators to be defined, recognised and formally validated by the scientific community. These indicators should be applied automatically in all studies, experimental or RWD-based (**figure 2**).

In recent years, regulatory agencies have shown increasing attention to the use of RWD to support authorisation processes, especially in specific target populations. The choice of data sources and study design can have a major impact on the evidence that is derived in the *real-world setting*. ISPOR and ISPE have developed guidelines for assessing data adequacy and especially *fitness for purpose*, or the degree to which the chosen data source

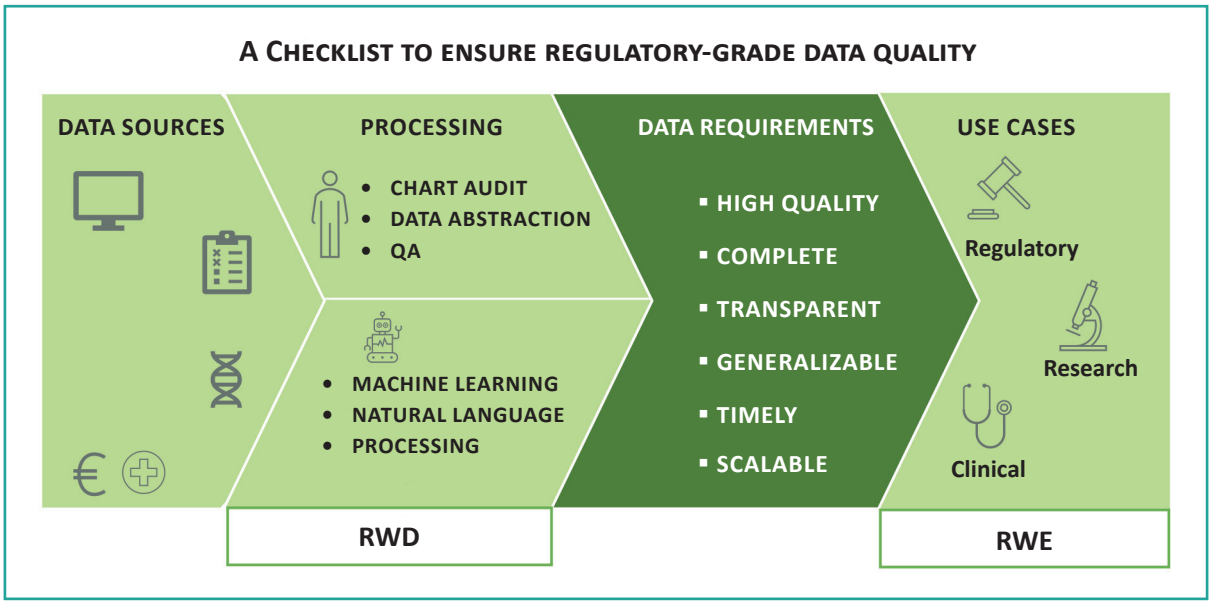

Figure 2. The path from data to evidence (taken from (32)).

aligns with the ability to accurately and reliably address the research question.

A challenge for the future in the regulatory environment will be the management of data derived from wearable medical devices. The ability of these devices to generate RWD, combined with analytical *machine learning* methodologies, may offer useful insights into the benefit-risk profile of drugs. The use of these devices will be able to complement the results of RCTs with a long-term approach, especially in the field of chronic diseases.

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OPINION PAPER

pharmadvances

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THE PATIENT AND THEIR TREATMENT NEEDS

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Nothing exists until or unless it is observed.
William Burroughs

HIGHLIGHTS

- *Patient-centricity* is the set of strategies and tools capable of responding to the health needs of the patient, designed according to the characteristics of the patient and the stage of the disease, reducing the barriers that hinder patient access to more appropriate care.
- From a pharmacological/pharmaceutical perspective, patient-centricity is achieved through radical or incremental innovation pathways that identify the drug that can be taken by the patient most efficiently, safely and completely.
- Patient-Centred Incremental Innovation optimises treatments, promotes appropriateness, fosters adherence, simplifies care, contemplates inter- and intra-patient differences, and makes therapies more efficient and safe. Reducing the impact and complexity of treatments fosters greater adherence resulting in improved efficacy, and promotes a sense of individual well-being, confidence and satisfaction.
- Unfortunately, health systems, regulators, and *payers* exclude from their evaluation *patient-centered* benefits that cannot be "costed" with current health economics methodologies.
- It is important to open an in-depth discussion among the different stakeholders in order to identify the best *road-map* to combine the importance of patient-centricity and the value of pharmacological and healthcare strategies that solve the individual and social complexities of diseases with the current regulatory and healthcare difficulties. Operational strategies starting from the territory and ending with *real-world* analyses must be implemented for the quantification of the benefit and sustainability of incremental *patient-centricity* innovation based on the best pharmacological evidence.

SUMMARY

Patient-centricity is the set of strategies and tools capable of responding to the health needs of the patient, designed according to the characteristics of the patient and the stage of the disease, overturning the barriers that hinder patient assumption of the most appropriate care. From a pharmacological/pharmaceutical perspective, patient-centricity is achieved by endowing the drug with properties, making the drug more efficient, safe and complete for the patient.

Any action to enhance patient-centricity is considered a clinical and health innovation. Innovation is radical (break-through) when it treats diseases that have never been treated before or profoundly improves the clinical history of a disease. In the pharmaceutical con-

text, innovation is radical when an entirely new active substance is typically the first representative of a new class of drugs. Innovation is incremental when it leads to the development of an optimised/better version of an already marketed product. Incremental innovations in pharmaceuticals are typically based on drug analogues or variants or new pharmaceutical formulations that, *e.g.*, exhibit improved pharmacokinetic or pharmacodynamic properties, enable more efficient delivery and uptake of treatments, optimise or simplify care, *etc.*

Patient-Centred Incremental Innovation optimises treatments, promotes appropriateness, fosters adherence, simplifies care, contemplates inter- and intra-patient differences, and makes therapies more efficient and safe. Reducing the impact and complexity of treatments fosters greater adherence resulting in improved efficacy, and promotes a sense of individual well-being, confidence and satisfaction. But unfortunately, health systems, regulators, and payers exclude from their evaluation patient-centred benefits that cannot be "costed" with current health economics methodologies.

It is important to open an in-depth discussion among different stakeholders about the importance of the centrality of the patient in their human, clinical, and social uniqueness, about their right to effective and safe care, and about the value of pharmacological and healthcare strategies that resolve the individual, human, and social complexities of disease. It is necessary to identify operational strategies and new models that take into account the best pharmacological evidence, in terms of translational research, clinical, regulatory and post-marketing studies, to design the best road-map towards the enhancement of incremental patient-centred innovation.

BACKGROUND AND OBJECTIVES

In recent years, diagnostic advances and advances in "omics" methodologies have reinforced the importance of the patient, in their uniqueness as an individual, as the central subject of the therapeutic pathway, making personalised medicine possible, with a rationalisation of sustainable access and an objective improvement in the efficacy/safety ratio. The progress achieved in some areas, such as oncology, in being able to sub-classify patients in relation to specific diagnostic and therapeutic bio-markers related to the presence of mutations and polymorphisms is a clear example of how it is now possible to move from a concept of universal therapy (one-fits-all) to that of personalised medicine, allowing for the optimisation of the efficacy/safety ratio of drugs both in development and especially in clinical practice (1-6).

This evidence provides an opportunity to refocus on aspects which, beyond holistic considerations or those rather closely linked to diagnostic and therapeutic pathways, underline the need for health systems to pay constant attention to the centrality of the patient. Every patient has the right to be considered first and foremost as a "person", with their biology and illness, according to criteria that also take into account human, social, family and ethical aspects. The health professional caring for the patient-person must always be aware that they are dealing with a person who is also a patient, *i.e.* a human being in whom these two natures coexist and live together with the hope of becoming just a "person" again, *i.e.* of recovering from the illness. (2, 7-10).

In the management of care, in its delivery, but also, ab initio, in its conception, our attention must therefore shift from the figure of the "passive patient" to that of an active person, by virtue of their uniqueness and ability to interact in decision-making processes. The centrality of the person-patient must be the subject of a continuous, progressive, dynamic process in which all structures and actions revolve around the person and their decisions, needs and priorities (1, 3, 8, 11, 12).

Health policy experts often complain that patients are not sufficiently involved in the design and planning of health plans. Although

there are still few indications in the scientific literature that provide significant paths that allow the person-patient to consciously assume their role in the decision-making process, it is important to emphasise the gradual increase in recent years, the result of a growing awareness and partnership with public and private stakeholders aimed at implementing patient-centred strategies. In this context, EUPATI is a strategic and applicative model in the different areas of "patient engagement" in the R&D process, and beyond (3, 8, 11, 13-15).
Patients have an increasing importance in defining and changing standards of care. Patient advocates are increasingly speaking out through new media (blogs, advocacy groups, social media). Knowing these tools helps to better understand the needs of patients and to establish a modern but scientifically sound dialogue with them, with the aim of increasing their knowledge and maximising the benefit/risk profile of treatments (8, 16-18).
Person-patient centred benefits occur not only in relation to the individual, but also in the perspective of the health care system. Solutions that place the person-patient at the centre of the treatment process and the choice/ranking of therapeutic solutions achieve cost savings due to individual health benefits, increased price competition, better understanding of the different components of drug classes by healthcare professionals, and simplified monitoring by the physician, *e.g.*, for products with higher therapeutic index (1, 9, 14, 15, 17, 19, 20).

THE CURRENT CONTEXT

We can define "patient-centricity" as the set of strategies and tools that can respond to the health needs of the patient:

- designed based on the characteristics of the patient and on the stage of the disease and
- reducing barriers to patient access to the most appropriate care.

From the pharmacological/pharmaceutical point of view, the centrality of the patient, which starts primarily from the specific clinical need in its complexity, is achieved by endowing the drug with properties which improve its efficacy, safety and adherence.
The concept of "assumption" of the drug by the patient is important since patient-centricity is not limited to getting the drug close to the patient (*e.g.* in the pharmacy or at home), but aims to ensure that the drug is effectively and appropriately taken by the patient or administered to the patient by the caregiver, when needed. "Patient-centricity" implies the possibility of profoundly transforming the decision-making pathway to meet the need for health and health care, and should therefore influence the health choices of the relevant authorities. Any action to enhance patient-centricity is considered a clinical and health innovation.
Pharmaceutical innovation represents the moment of fundamental synthesis between technical-scientific progress and the possibility of responding to unmet clinical needs. Pharmaceutical companies are constantly looking for new and/or improved drugs, as pharmaceutical innovations are intended to address a health need while providing a return on investment.
Innovation is radical (break-through) when it treats diseases that have never been treated before or profoundly improves the clinical history of a disease. In the pharmaceutical context, innovation is radical when an entirely new active substance is typically the first representative of a new class of drugs.
Incremental innovation, on the other hand, leads to the development of an optimised/better version of an already marketed product. Existing drugs are often used and redefined during the development phase. Analogues are derived from chemical variations of the original drug and may have different pharmacological properties than the original compound (**figures 1** and **2**). Incremental innovations in the pharmaceutical field are typically based on pharmacological or pharmaceutical analogues or variants of an already known drug or therapeutic strategy. They feature improved properties, for example, in their pharmacokinetic or pharmacodynamic profile, enabling more efficient de-

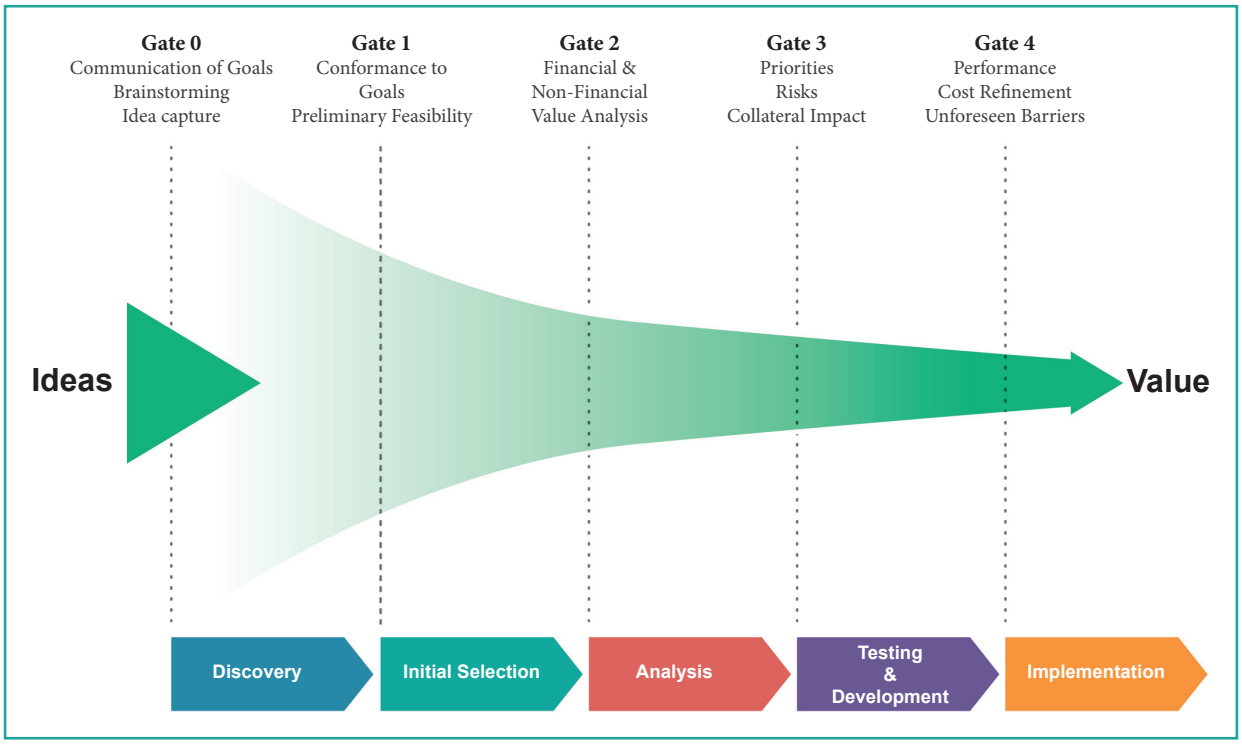

Figure 1. The Innovation Funnel (taken from (23)).

livery and uptake of treatments, optimising or simplifying care, *etc.*, and differ from analogues that show no improvement over existing drugs, also known as "me-too" products (9, 21-23).
"Follow-on" drugs, pre-established associations of multiple drugs, drug reformulations, repositioning to other uses/indications, drugs associated with digital applications or medical devices - these forms represent a significant percentage of incremental medical innovations and have long been recognised as an integral part of the innovation journey. They provide benefits to stakeholders throughout the health care system: patients, caregivers, physicians, and payers. They can also benefit the health care system through increased price competition resulting in cost savings.
These innovations are all characterised by being "person-centred therapeutic innovations," in that they are the result of efforts to improve the use of the drug and supplement the drug's properties with strategies that optimise, expand, or enhance its value in relation to the specific patient (9, 11, 21, 23-26).

What are the main "person-patient centred" benefits? The process of patient-centred care depends closely on the health system model, the degree to which it reserves access to primary care, and the advancement of care based on outcomes and policy choices. The approach also broadens in relation to incremental innovation, which can then take into account numerous aspects. A non-exhaustive list includes:

- refinement of therapeutic diagnostic pathways to include pharmacokinetic and pharmacodynamic variables;
- higher efficacy (a new drug in the class may show greater efficacy than the first-in-class product);
- new modes of use, new formulations, new posologies;
- treatments best suited to specific patients;
- dosage optimisation;
- improved safety/tolerability (fewer adverse events);
- improved adherence;
- greater convenience/ease of use;

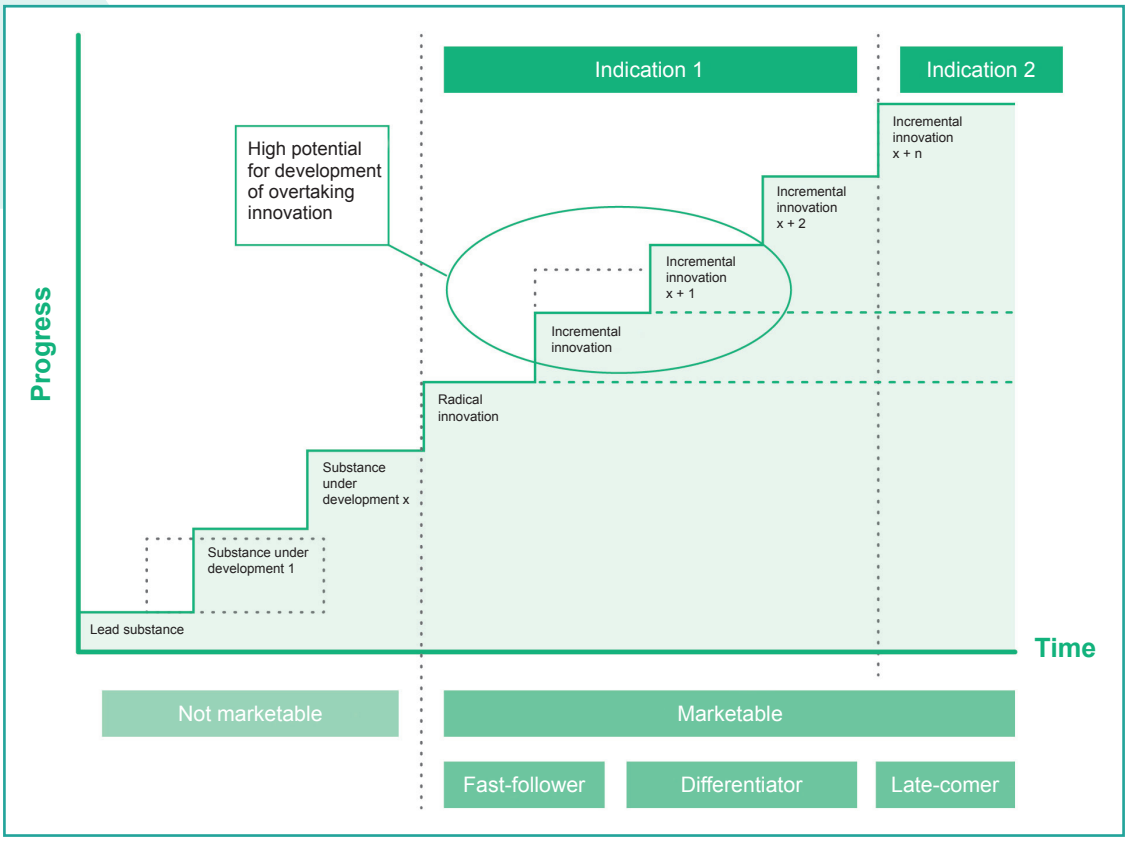

Figure 2. Overview and relationships of different terminologies of "innovation". The most successful components of a drug class are usually derived from early incremental innovations. Post first-in-class products can also be used for completely different clinical indications (taken from (21)).

- less complexity (*e.g.*, by moving from in-hospital to at-home administration or through medications that require less efficacy or tolerability testing);
- psychological and QoL benefits;
- greater confidence in treatment and the health care system;
- better interaction with the physician;
- lower burden on the caregiver.

Each of these benefits meets specific needs of the person-patient.
Unfortunately, most of these benefits are not documented or valued by the methodologies that health systems and regulators apply to measure the value of drugs. Needs/benefits such as reducing the number of doses, taking a more convenient pharmaceutical form or with a simpler dosage, better interaction with the physician, the opportunity to receive treatment at home instead of in the hospital, the possibility of optimising laboratory measurements of efficacy or tolerability, and greater confidence in the efficacy and safety of treatments (patient and caregiver satisfaction) are of crucial importance to the person-patient and are reflected in better treatment outcomes for the individual and subsequent savings for society. However, none of these aspects are actually taken into account when evaluating a drug's innovation, nor are they considered an important key factor in health policies (4, 15, 18, 25, 26).
This discrepancy is all the more significant when one considers that those variables deemed important by the person-patient and that intercept their needs for care are equally determinant in the therapist's perspective.
There is a mismatch between the perception of the value of care by "users", whether they are the patients who receive it, the caregivers who provide it or the physicians who prescribe

it, and by health systems and payers, who share the "population" perspective adopted by regulatory authorities and tend to exclude from the evaluation perimeter the variables that are not "costable", at least on the basis of current health economics methodologies.

Addressing these issues and the related challenge of assessing how innovative and sustainable they are requires collaboration, sharing and communication at national and local levels, and a clear understanding of the specific issues and needs of the individual and the community.

In the pharmacologist's perspective, pharmacological/pharmaceutical innovation coincides with therapeutic innovation, whether radical or incremental. In its various forms, and on the basis of what has been said above, innovation starts with unmet clinical needs and is based on precision medicine, on the personalisation of therapies including by virtue of a refinement of diagnostic and therapeutic pathways, on pharmacogenetics and pharmacogenomics, as well as on new paradigms of translational research and real-world data investigation and analysis strategies.

Advances in methodological investigation (such as "omics" approaches) are also strategic in this context, allowing, in addition to the recognition of the molecular causes of disease, the identification of new bio-markers (diagnostic and therapeutic) and disease modifiers, fundamental for understanding the phenotype and, for chronic diseases, the course of the disease.

Understanding the needs of the person-patient and responding to their needs is also a question of the credibility of the healthcare system: a health system that doesn't know how to provide personalised responses, in addition to losing the opportunity to maximise the benefit of treatments and therefore their efficiency in terms of health economics, will lose contact with the individuals who make up the "population of the sick" and will leave room for communicators who, outside of "evidence-based medicine", will be better able to intercept the needs of the individual by "speaking" the patient's language, the language of their suffering and their hopes for recovery.

Rare diseases represent an important area of innovation. We are talking about diseases with low incidence on the total population (5 cases per 10,000 people in the EU classification), mostly of genetic origin and affecting the paediatric population in more than 50% of cases. In their complexity, rare diseases are chronic, disabling, and at high risk of mortality. Despite the low incidence, there are thousands of rare diseases. Many of them go undiagnosed, collectively affecting hundreds of millions of patients worldwide. Only 5% of them have treatment. In this context, the centrality of the patient is therefore fundamental both because of the high clinical need and because of the need for caregivers to manage complex patients, with the consequent clinical, human, ethical, social and economic implications. Therapeutic innovation in rare diseases, from the identification of orphan drugs through to advanced therapies (ATMP), faces uncertainty linked to the different stages of R&D and the risk of missed returns on investment, both linked to the very nature of the rare disease. However, the incentives put in place by the FDA and EMA and, subsequently, by other regulatory agencies in favour of companies developing orphan drugs, represent an important boost to research by bio-tech and big pharma in this area and strengthen the technology transfer of innovation from academic laboratories to companies and vice versa, in virtuous collaborations between public and private. The involvement of various stakeholders (patients, companies, researchers, decision makers) in the entire process is vital; international consortia and networks such as the International Rare Diseases Research Consortium (IRDiRC) represent a shared path of efforts and an open dialogue on the centrality of the patient and their needs (6, 13, 27, 28).

The approaches pursued for the development of orphan drugs are broad and are based on different levels of potential benefit and thus of relative innovation.

In recent years, we have seen important advances in therapies aimed at bypassing the genetic defects (*e.g.*, enzyme-replacement thera-

pies) or correcting them by gene therapy (*e.g.*, antisense oligonucleotides or splicing and gene editing modulators). The achievements in spinal muscular atrophy are exciting examples of the possibility of innovative approaches that can effectively modify the course of the disease.
Similarly, important goals can be pursued with molecules, both chemically synthesised and bio-technologically engineered, that can alleviate symptoms or modulate signalling pathways directly altered by the genetic defect. In the latter case, drug repositioning can also be an important incremental innovation strategy, as it improves patients' quality of life and opens up other pharmacokinetic and pharmacodynamic innovations. In addition, drug repositioning, thanks to the knowledge already gained about the pharmacodynamic and toxicological profile, offers the opportunity for rapid bench-to-bedside transfer and timely expansion of treatment strategies for otherwise incurable patients.

One example among many is that of glucocorticoids, which have been used for years off-label in Duchenne Muscular Dystrophy (DMD) on the basis of benefits on specific clinical outcomes and improvement of the disease course (**figure 3**). In this area, several efforts have been made in incremental innovation, *e.g.*, in the choice of the steroid to be used, dosages and treatment regimens, identification of bio-markers of drug sensitivity and mechanism of action, *etc.*, in order to optimise therapeutic benefits and reduce the heavy side effects typical of long-term steroid therapy in children with DMD. This led to the registration of deflazacort for the specific indication (not without controversy for the very high costs at which the drug was introduced in the USA) and paved the way for the identification of new drugs with dissociated actions, such as vamorolone, now undergoing registration studies in DMD (6, 18, 29, 30).

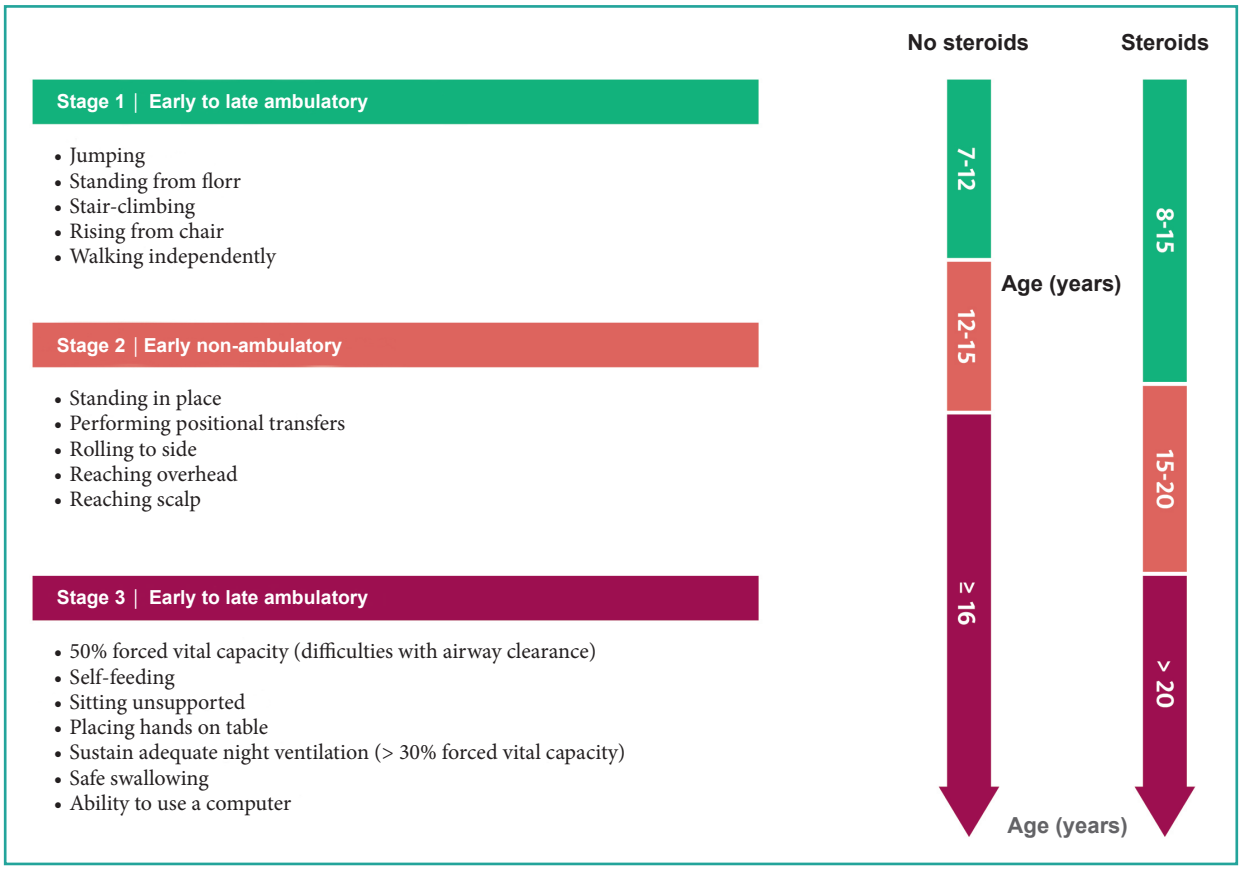

Figure 3. Example of steroid benefit in DMD: from off-label use to repositioning (taken from (18)).

The fundamental issue brought to light by the deflazacort case is how to define the economic value of incremental innovation in the case of a rare disease and how ethical it is to set an exorbitant price for an important but non-curative benefit, which can be obtained with the same drug or other analogues that are "cheap" when used off-label. Thus, in the rare disease setting, incremental innovation, both with first-in-class follow-on drugs, but especially with repositioned drugs, opens up many questions. *E.g.* it is worth asking how to consider the company's real investment in assessing the risk/benefit ratio in the population in question through registered clinical trials or in optimising the pharmaceutical formulation (*e.g.* in rare paediatric patients with swallowing problems), in relation to the patient's clinical benefit compared with off-label and therefore unauthorised use (6).

On the other hand, the efforts of pharmaceutical companies to adapt formulations of known drugs to the specific needs of the rare patient (*e.g.*, difficulty in taking or administering the drug; delivery of the drug at home instead of in the hospital) deserve to be carefully evaluated and appreciated precisely from the perspective of the patient-centred effort, also in light of bio-equivalence studies and/or investments in the identification and development of new materials and new technologies.

Non-communicable diseases (NCDs) represent one of the greatest challenges to global health. Morbidity and mortality data, as well as costs and harms to quality of life and productivity, show that conditions such as cardiovascular disease, diabetes, obesity, cancer, lung disease, and depression, along with risk factors such as smoking, diet, and physical activity, should be the focus of interest for every health care system.

NCDs account for more than half of all diseases. Among them, cardiovascular disease accounts for about half of all deaths. For a long time, NCDs were dismissed as "rich country problems" and not worthy of global attention, but today we know that they are, in fact, a global problem. They are the price we pay for economic development, prosperity, and major achievements in health care, leading to longer, less arduous, but perhaps more stressful lives. The coexistence of multiple pathological conditions in the same individual exponentially complicates the clinical picture and irreparably compromises the autonomy. One in three adults has two or more NCDs. This transformation in the clinical picture of the population has profound implications for health systems and the sustainability of care. Treating a patient with four NCDs is 16 times more expensive than treating a patient with only one NCD. During ageing, numerous biological deficits accumulate that alter the body's homoeostatic balance. The term "frailty" identifies the susceptibility of biologically older people to develop pathological conditions and experience rapid changes in health status.

The increase and ageing of the elderly population will be accompanied by an increased prevalence of chronic diseases and medical conditions that are predictors of health care (**figure 4**). In the absence of changes in care models, demand for outpatient and speciality care will increase at the same rate as the population carrying the chronic conditions treated by each speciality. The same will be true for A&E access and inpatient stays, in terms of number and duration (**figure 5**) (14, 18, 31, 32).

NCD and frailty require the use of many drugs in the same subject, with complex implications such as drug interactions, the impact of clinical risk conditions (age, reduced excretory functions, *etc.*), the burden of adverse events, *etc.* Adherence to treatment decreases progressively as the number of drugs taken per day increases.

The "therapeutic need" of these patients is, therefore, particularly complex, because their care must be personalised by definition, designed on the individual and situational characteristics of the individual patient, whose clinical conditions are not constant, but vary and can complicate, even suddenly. Incremental innovation allows them to improve, simplify and facilitate the management of their care,

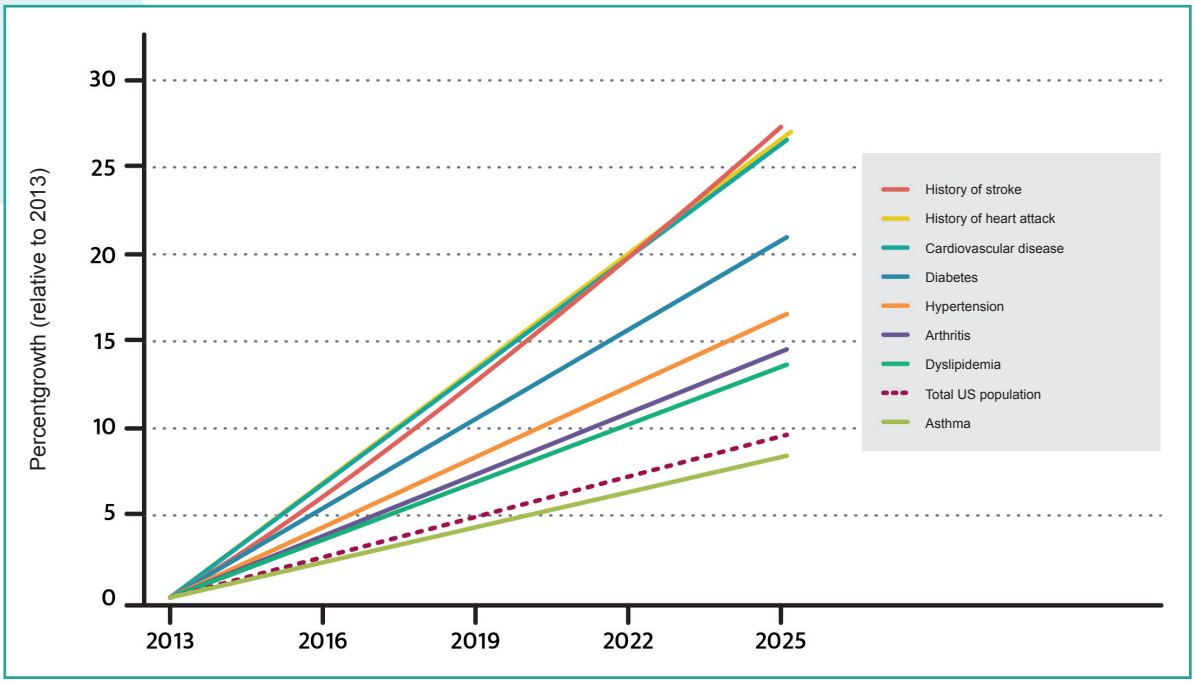

Figure 4. Projected growth of population with chronic conditions, 2013-25 (taken from (31)).

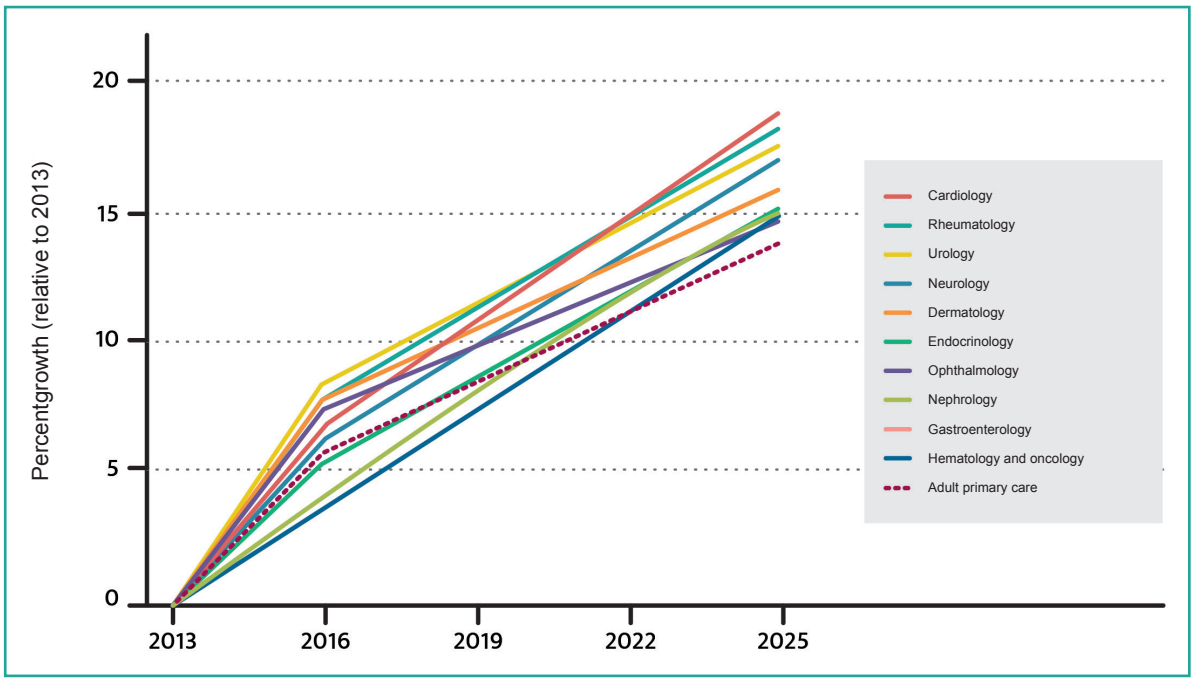

Figure 5. Projected growth in specialist visits, 2013-25 (31).

enabling more practical, safe and customisable treatments. Classic examples of this are pre-constituted combinations or once-daily formulations, but equally important are pharmaceutical innovations that allow, for example, to more easily administer a drug in liquid form to patients with dysphagia or in need of enteral feeding. Personalisation of care can also be achieved through formulations that allow dosages that can be adapted over time

to the needs of individual patients. Examples of this type are liquid formulations of psychotropic drugs that allow progressive adaptation of dosage and posology, with better therapeutic results achieved in less time and with fewer side effects, especially at the beginning of treatment.
Extraordinarily innovative, even if incremental, is any innovation that succeeds in bringing a treatment to the home of the frail or comorbid patient which would otherwise administered only in a hospital setting.
Any solution that simplifies treatment, its preparation or delivery, while maintaining a consistent benefit/risk profile, is an important contribution to clinical management, centred on the needs and characteristics of these patients, as well as offering economic benefits to health systems.
Telemedicine and digital health developments offer additional solutions that intertwine the needs of the individual with cutting-edge technology. These technologies also allow us to innovate the way we monitor adherence to therapies as well as disease progression and control, *e.g.*, through systems with which patients can track their health status in a simple and interconnected way.

FUTURE PROSPECTS

A closer look at the data regarding pharmaceutical, pharmacodynamic, and pharmacokinetic properties suggests that the most successful incremental innovations offer important benefits from several perspectives. Patient-centred incremental drug/pharmaceutical innovation optimises treatments, promotes appropriateness, fosters adherence, simplifies care, contemplates inter- and intra-patient differences, and makes therapies more efficient and safe. Reducing the impact and complexity of treatments fosters greater adherence resulting in improved efficacy, and promotes a sense of individual well-being, confidence and satisfaction.

But unfortunately, health systems, regulators, and payers exclude patient-centred benefits from their evaluation because they are difficult to "cost" using current health economics methodologies (1, 3, 8, 10, 15, 16, 19, 23).
How the value added by these innovations is measured? Is this added value currently intercepted by the economic estimates that determine the value of a drug and its sustainability? Below are some possible areas of implementation.
We are used to using clinical measures of outcomes converted into saved costs and consequent economic efficiency for health systems. Many of these measures are based on recognised, well-documented, and established methodologies.
Compared with these traditional outcome measures, person-patient-centred outcome measures include the pathway and process by which an individual, with their characteristics, preferences, and expectations, achieves drug benefits.
"Patient-centred" benefits have value in and of themselves and may not always or solely translate (directly or indirectly) into outcome benefits. *E.g.*, reducing the impact or complexity of treatments on the individual can lead not only to improved adherence, resulting in better efficacy and outcomes, but also to improved quality of life because of the gratification of the patient exposed to a therapy that better fits their needs, and to a simplification and optimisation of caregiver activities.
While traditional outcome benefits are easily identifiable and measurable, evaluation of the user experience and evaluation of individual variables require a deeper understanding of how patients and caregivers experience their condition and their relationship to treatment. This requires integrated analytical approaches, including ad hoc assessments of real world data, active monitoring programmes, or through digital health tools. They can cross-reference outcome data with patient-dependent variables (genomics, interactions, lifestyles, expectations, care, *etc.*) and support the real

areas of incremental innovation with objective data, overcoming oversimplifications or, on the other hand, pure holistic speculation. In this context, analytical tools that have limited correlation with objective clinical outcomes, such as the Quality of Life Scale (QoLS) used for chronic diseases and many rare diseases with a high degree of disability, should also be carefully reconsidered and implemented.

These tools, if properly integrated, can offer an active role to patients and caregivers in the therapeutic assessment process, with the possibility of measuring across the board the experience of use and the quality of life among groups of patients who may differ widely in terms of clinical, social and cultural phenotype. They also measure the satisfaction and reduction of stress, related to the disease and treatment, for the patient and the caregiver, a very useful parameter in the perspective of the shift of health care towards the territory.

Other proposals include those related to the new challenges generated by the so-called "new chronicities", which concern the complex management of patients receiving innovative breakthrough treatments. These treatments do not lead to recovery, but instead lead to chronicity of the disease, which may include incremental innovation processes for adjuvant and supportive therapies.

Registries and real world analysis can be useful in documenting the value of incremental innovation, although one must consider the limitations of "observational" research tools, which are not always able to differentially and objectively capture the favourable effects achieved by treatments in individuals.

The pandemic has highlighted the importance of territorial care, the optimisation of which is also among the objectives of the NRP. Incremental innovation that enables, facilitates or simplifies the territorialisation of treatment that would otherwise only be possible in a hospital environment, for example, is in itself worthy of appreciation without requiring specific determination: even if the efficacy and safety are equal, treatment that can be territorialised should be rewarded by health systems. In these scientific and common-sense assessments, the pharmacologist's perspective should be central.

Educating physicians at all levels, pharmacists, decision-makers and patients and caregivers themselves to understand the benefits and opportunities of incremental patient-centred innovation is another important goal for the evolution of our healthcare system, in which Pharmacology (meaning the scientific society SIF and academic pharmacologists involved in pre- and post-graduate training) should play a crucial role.

CONCLUSIONS

Managed and leveraged effectively, patient-centred drug/pharmaceutical innovation means fewer tests and fewer physician visits, fewer hospitalisations, and shorter stays. Complex and fragile patients will have to interact with fewer health professionals, while having a designated professional to take care of their overall well-being. This will help millions of patients regain a sense of control and a better quality of life for themselves and their caregivers.

It is therefore important to open an in-depth discussion among the various stakeholders on the importance of the centrality of the patient regarding their human, clinical and social uniqueness, their right to effective and safe treatment, and which analysis strategies should be implemented to ensure the correct processes of advancement of scientific knowledge and pharmaceutical innovation, whether radical or incremental, considering the complexity of diseases and the difficulty in designing clinical trials in specific populations.

Virtuous collaboration between pharmaceutical companies interested in pursuing innovation as a driver of health, economics, and sustainability, and academic pharmacologists, thanks to the latter's well-rounded expertise in translational research, clinical, regulatory, and post-marketing studies, as well as training, can represent a

broad strategy to design the best road-map toward the introduction and proper exploitation of incremental patient-centred innovation.

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OPINION PAPER

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BREAKTHROUGH INNOVATION, DIAGNOSTIC, THERAPEUTIC AND TREATMENT PROCESSES AND IMPACT ON CHRONICITY

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HIGHLIGHTS

- It will be increasingly important to design research and development processes taking into account the organisational implications, technical, regulatory and economic requirements that the most innovative treatments will have to meet at the same time, in order to ensure rapid and equitable adoption within national and local healthcare settings.
- Given the contrasting roles and sensitivities of the stakeholders involved in the innovation process, knowledge exchange and partnership at all stages of the process is crucial.
- Along with the need to ensure equitable access to innovation, great importance will also be placed on the possibility of defining forms of public-private partnerships that maximise the application of these technologies to strengthen health systems.
- The complex management of innovation requires the identification of an objective and shared methodology, allowing the patient's entire diagnostic and therapeutic care pathway (PDTA) to be evaluated, including through real-world data.
- In order to foster breakthrough innovation, new organisational models need to be defined to enable the management of the entire process and not just the governance of the drug.
- The advent of digital medicine and the use of artificial intelligence approaches applied to healthcare could be some of the tools used to improve the monitoring and care of patients throughout their treatment or care pathway.

SUMMARY

The potential and value of pharmacological innovation, to be considered as such, require new organisational models to make it usable. Given the current acceleration in pharmaceutical research, this need is increasingly relevant, especially in the presence of *breakthrough* innovations, which require a radical change in the dynamics of patient management along the entire diagnostic, therapeutic and care pathway (PDTA). Examples of *breakthrough* innovations related to CAR-T cell therapies, mutational oncology and Digital Therapeutics are given to better illustrate this transition. In

all these examples, it is clear that the evaluation of innovation must address not only clinical outcomes, but also social, economic, political and environmental ones. To encourage the flow of innovation, it is therefore necessary to assess its impact horizontally, going beyond the silo budget view. To this end, the use of real-world data is strategic. It should not only be used for retrospective analysis, but also from the earliest stages of clinical development, in order to estimate the real impact of innovation on the entire process and to plan tools to govern it without being overwhelmed. In order to assess in advance the overall impact of innovation, a multidisciplinary approach is also essential, with the involvement of all stakeholders, including the patient. Such an approach requires new professional figures and appropriate training, as well as implementation research to accompany breakthrough *innovation,* in order to identify the most suitable models for its entry into the current system by governing the entire care process and not only the drug variable.

BACKGROUND AND OBJECTIVES

Innovation has always been a fundamental requirement in healthcare. The development of innovative therapies, together with the evolution of treatment paradigms, generate a continuous improvement in health outcomes or provide answers to unmet medical needs. However, the potential and value of pharmacological innovation, to be considered as such, requires revision and evolution of the organisational models necessary to ensure its usability. The most obvious example is represented by the new frontiers of innovation and the exemplary case of CAR-T (Chimeric AntigenReceptor T cell therapies), or "therapies based on T cells expressing a Chimeric Receptor for antigen", consisting of complex procedures in which the new type of the "drug" is one of the variables of the entire process involving the pharmaceutical industry, health facilities, professionals, production facilities and regulatory agencies. In this perspective, innovation must be assessed, interpreted and included in the relevant care context, which needs time to adapt to organisational, operational and cultural changes. Some reflections on treatment models are also valid when innovation is not revolutionary (*breakthrough*) but incremental, as is most often the case with therapies for the treatment of chronic diseases.

In this *Opinion Paper* chapter, we started with the enormous strides made by research (both experimental and clinical) to make available therapeutic approaches that can interfere with disease progression and simultaneously improve patient quality of life. We have reflected on how the interaction and exchange of knowledge between the various stakeholders involved in the process of innovation currently takes place, referring to models of excellence for therapies already on the market. We found issues related to an underestimation of the value of innovation and equitable access to innovation, leading us to formulate some proposals to overcome existing barriers in implementing innovation and improving chronic disease management.

THE CURRENT CONTEXT

An exciting phase of drug innovation has opened up in the pharmaceutical industry with exponential acceleration. The factors that have triggered this acceleration are, on the one hand, a deeper knowledge of molecular biology and bio-markers and, on the other, open innovation, *i.e.* the opening up of industrial research to collaboration with university researchers and the *biotech* world. By bringing together, enhancing and pooling their respective knowledge and specialisations, it has been possible to develop new technological platforms that are changing the face of *early stage* research. Moreover, the synergy with ICT (Information & Communication Technology) companies and the advancement of artificial intelligence systems, *i.e.* cognitive systems that exploit enormous computing power,

are enabling the analysis of endless and continuously updated databases that are affected by the integration of different aspects of the large-scale approach (omics) to acquire as much information as possible from experiments (Genomics, Transcriptomics, Proteomics, Lipidomics, Metabolomics). The *drug discovery* phase is increasingly efficient as well as easier to substantiate candidates for *full development*. The promise of new *network innovation* models in research and development is to formulate increasingly effective and safe treatments more quickly.

The introduction of advanced therapies in clinical practice has been a real revolution (*breakthrough* innovation or *disruptive innovation*) and has required the acceleration of a complete revision of the dynamics of patient management along the entire diagnostic, therapeutic and care pathway (PDTA). In fact, the great changes in medicine imply a change in the very concept of innovation and value: in fact, innovation and value are not linked solely or exclusively to the drug, but to the entire care process of which the drug represents only a part. The real innovation is therefore represented by the innovation of the organisational model of the PDTA (1, 2) (**figure 1**).

In the case of CAR-T cell therapy, for example, treatment innovation does not depend on the single variable, but on the entire process that includes admission of the patient to the hospital and conditioning of the cells, followed by transfer of the cell bag to the centres for engineering, re-infusion of the bag with the engineered cells, patient follow-up in the ICU to control the cytokine storm, and clinical monitoring of the patient in the course of treatment. Specifically, for CAR-T cell therapy, highly specialised centres authorised for use must guarantee a complex chain of patient care and high quality standards, in accordance with the requirements defined by the regulatory authorities. Standard requirements include adequate infrastructure and trained medical staff to manage all phases of the patient *journey*, from patient intake to patient *follow-up*. The presence at the centre of healthcare professionals who are adequately trained to answer questions from patients eligible for treatment in a competent manner, and to accompany them in explaining the Informed Consent, is necessary. At the same time, medical personnel must be adequately trained in the collection of biological material (lymphocytes), which must then be transferred to the production centre for the engineered cells. Once ready, the cells will need to be transferred to the patient's bedside and infused into a CAR-T *Unit*. Only in the presence of well-defined work flows and coordination of the various actors operating along the pathway (starting from the patient, informed of the process) is the "chain of identity" of biological material guaranteed. The role of the hospital pharmacist also changes according to this model, remaining by law the authority responsible for receiving and accounting for biological material, but whose work is in synergy with other facilities within the centre for storage (cryo-preservation units) and distribution of the product. In highly specialised centres, new professions have gradually emerged that require intensive training (including abroad) and the upgrading of the skills of various figures, including nurses, in order to adapt to the complexity of processes and clinical frameworks. This model is not only applicable in the context of centres specialising in CAR-T cells, but will become increasingly important in the field of gene therapy, where the technical skills and quality standards of the operator are of particular importance, in addition to the characteristics of the approach used.

A further example of momentous change is the advent of precision medicine and mutational oncology, which is based on genomic mutations that may be susceptible to drugs (*druggable*) and the use of new oncology agents active on the mutations and/or mutational load (*tumour molecular burden*) identified by genomic profiling tests. In order to manage this major innovation, a major organisational change is needed, with the creation

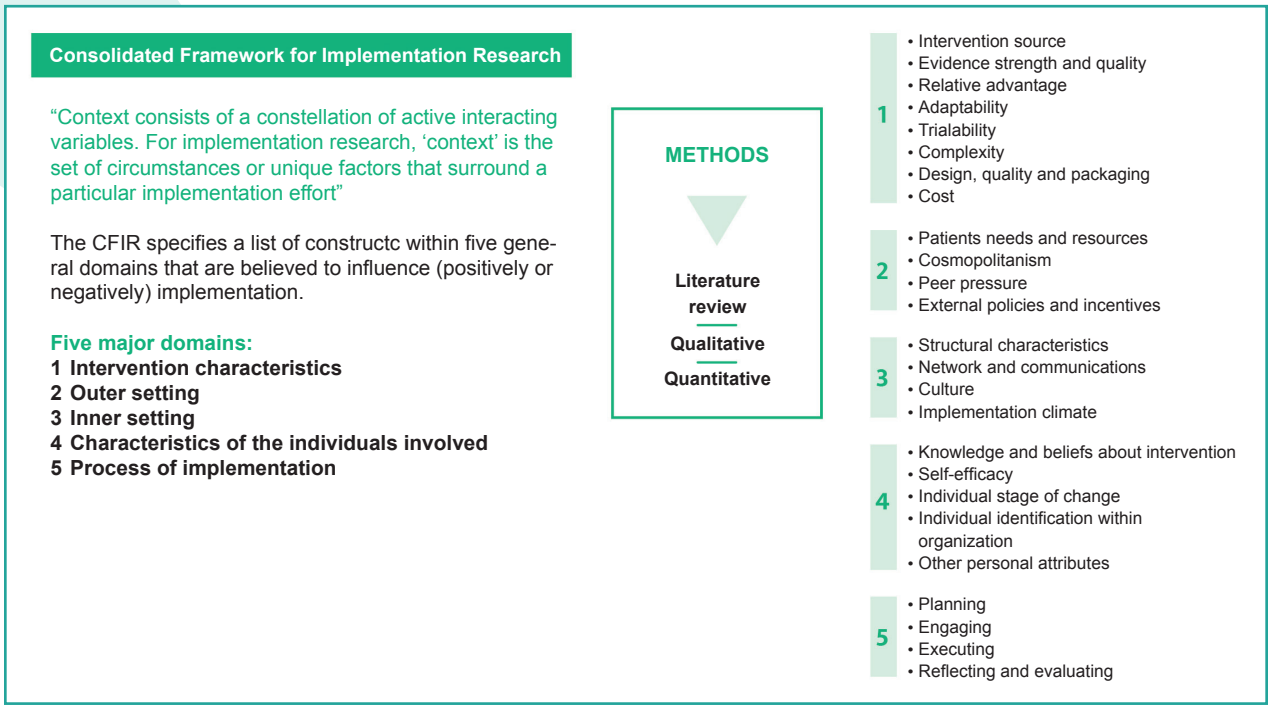

Figure 1. The need to share objectives and methodology in order to achieve the PDTA evaluation (adapted from (24)).

of special inter- and multidisciplinary teams called Molecular Tumor Boards (MTB) (3) and the inclusion of genomic profiling tests within individual PDTAs, as called for by several scientific societies and study and research foundations (4-6). Only by implementing these substantial changes in governance, which involves different institutional levels (*e.g.* Ministry, AIFA, Agenas, Regions), and at the same time designing systems capable of collecting all general information (in a National Genomic Platform) will it be possible to implement and control the development of Personalised Medicine and Mutational Oncology in Italy.

Medicine is also changing profoundly as a result of technological innovation. Alongside a multitude of applications already available on the market for monitoring lifestyles (physical activity, nutrition, sleep, *etc.*), *digital therapeutics* are emerging as an all-round drug therapy, and constitute a radical innovation (for more details see section 5 of the Opinion paper "New technologies and digital therapies at the service of patients"). The regulatory aspect is certainly a limiting factor towards the diffusion of these approaches. The management of aspects related to *privacy* and *data security* and the possible prescription and reimbursement modalities are the main points. The evolving sociocultural context, as well as the regulatory context, can also have a strong impact on the use of this particular type of therapeutic innovation. Collaboration and partnerships with the ICT sector will also be essential in this area. In fact, the development of technologies and networks with easy and user-friendly access can remove the barriers of the "digital divide" caused by limited availability of equipment and user skills in disadvantaged and weak groups such as the elderly (7).

In addition to the above examples of *breakthrough* innovation, it should be noted that the improvement of health outcomes in many therapeutic areas, primarily those related to chronicity, is to a large extent determined by so-called incremental innovation, which stems from a better understanding of the *unmet needs* and the physio-pathological mechanisms of disease to implement the treatment *outcome*.

The case of multiple sclerosis is significant. Until the early 1990s, therapy was based on the use of symptomatic medications. Progressive knowledge of the complexity of the immune system and the development of diagnostic techniques in general and of imaging in particular have formed the basis for the development of increasingly effective, well-tolerated and safe therapies, which have been shown to slow down the progression of motor and cognitive deficits and are therefore classified as *disease modifiers* (8, 9). Today, several therapeutic options are available for the treatment of multiple sclerosis, with different pharmaceutical forms, routes of administration, dosages, and indications. The physician can then choose the therapy that best suits not only the patient's clinical characteristics, but also their preferences. The incremental innovation offered by the different therapeutic options has allowed a significant reduction in the *burden of disease*, *i.e.* the social impact and, consequently, the economic impact of the disease on the system (10).

For the above reasons, the identification of the therapeutic value of a pharmaceutical product must take into account the benefit to the patient and also to society. This suggests a broader evaluation of innovation in the pharmaceutical sector, taking into account not only clinical outcomes but also economic outcomes related to the improvement of the system, and the role of the informed patient (and their family) in parallel with their management by the physician. (11). Such a step is the starting point for implementing the often theorised but poorly carried out elimination of health expenditure planning by budget silos. (12). In fact, there is a consensus that this way of looking at healthcare expenditure no longer meets the needs of the National Health Service (SSN) and patients' demand for health. In order to encourage the introduction of innovation, it is therefore necessary to assess its impact horizontally, throughout the patient's care pathway and taking into account all the cost items for the SSN. in this step, real-world data (13) are strategic.

Italy has the highest number of elderly people in the world. According to ISTAT, in 2023, 27.6% of the Italian population will be represented by individuals over the age of 65. 30.8% of the 65-69 age group have at least one serious chronic illness, a proportion that doubles among the over-80s (59.0%). 37.6% of the 65-69 age group report having at least three chronic conditions (known as co-morbidity or multi-chronicity), compared with 64.0% of those over 80. Although patients with co-morbidities only represent a minority share of the entire population, they account for more than 75% of the total costs paid by the SSN. In this scenario, there is a need to implement the healthcare system's ability to manage chronicity. The SSN in Italy continues to be recognised as one of the most efficient systems in guaranteeing that health is a fundamental right of every citizen. However, the *SARS-COV-2* pandemic has highlighted the limitations of a hospital-centric system and regional plans that make the provision of health care to citizens uneven. Demographic and epidemiological factors call for new models of prevention and territorial care that ensure continuity with hospital care and the possibility of follow-up care at home through the development and implementation of telemedicine and monitoring services. The National Recovery and Resilience Plan (*Mission 6 - Healthcare*) goes precisely in this direction.

Currently, in Italy, more than 3000 randomised clinical trials (RCTs) are underway or in the recruitment phase; a trend that has been growing strongly in the last decade, not only in Italy, but also in the rest of the world.(14). Although it is clear that the methodology used in controlled clinical trials allows reliable estimates of efficacy and safety levels to be obtained, which together with a proper randomisation process minimises the risk of incurring systematic errors, there is often a gap between the levels of efficacy observed in controlled clinical trials and those observed in clinical practice. This needs to be carefully considered when an innovation goes through

the scale-up process, as these differences may be related to a number of variables more pertinent to the implementation process of the innovation itself rather than a real difference in effectiveness (15).

FUTURE PROSPECTS

In order for drug innovation to reach its true potential, new strategies to facilitate the translation of clinical trial results into clinical practice (*real-world evidence*) and thus across the population as a whole have been under consideration for some time, in order to maximise their value in the real life of a patient and the community. The aim is not just to analyse *a posteriori* problems, but to study, from the earliest stages of clinical development, an approach to action that assesses the health system in which the therapeutic innovation will be inserted. For example, one can already anticipate and analyse factors that might hinder or facilitate patient access to therapy, test solutions that reduce barriers to translation into clinical practice, understand and analyse the context to identify strategies and interventions to enable large-scale diffusion and sustainability of innovation. In addition, real-world data makes it possible to identify the target populations for a new therapy in order to study their real size (prevalence - incidence), demographic and clinical characteristics (*e.g.* comorbidity, presence of concomitant drugs, *etc.*), as well as to assess their integrated care costs for the SSN (16). Thanks to the wide availability of health data in Italy, several initiatives have already been implemented in this context, for example for CAR-T (17), for Multiple Sclerosis drugs (18) or for cancer treatments (19). Only through analyses of this kind is it possible to estimate the real impact of innovation on the whole process and to plan measures to govern it without being overwhelmed. Understanding the dynamics that link the efficacy of an intervention, programme, or service, with the relevant organisation, is critical for addressing implementation challenges in healthcare. Taking into account contextual influence is necessary for bridging the "gap" between evidence and clinical practice; it is necessary to describe the context, to identify the main causes hindering the full expression of innovation and to obtain sufficient evidence to develop strategies and interventions aimed at overcoming these obstacles and barriers.

It involves thinking in a multidisciplinary and methodical way, providing for the active participation of all organisations involved in the process itself. From this point of view, the context analysis can be considered as a tool to reach an effective and sustainable solution. This approach could represent the natural evolution of clinical research, as the pharmaceutical company is increasingly involved in collaborating with other stakeholders in the health system, including governmental and non-governmental organisations, private providers, carers and patients themselves from the earliest stages of therapy development. Each with individual goals, but sharing the need to put the individual and the country in the best possible state of health. This cooperation provides the opportunity to assess in advance the social, cultural, economic, political and environmental impact of a more structured intervention based on a therapeutic innovation.

A concrete example is the recent unfinished UK study of an innovative hypolipidemic therapy. Hypercholesterolemia is certainly one of the most important risk factors for cardiovascular disease and the incidence of related deaths is expected to rise at least until 2030 (20, 21). Despite the magnitude of the problem, the uptake of the most effective therapies for reducing cholesterol levels is hampered in clinical practice by major barriers (22). The "hybrid" study underway in the UK, in addition to evaluating its efficacy, includes in its objectives the analysis of the health system in which the drug will be inserted, focusing on an approach supported by a strategy of action that involves a population-wide approach. Such a design, referred to in the industry as a *Hybrid effectiveness-implementa-*

tion study, generates the ability to simultaneously assess clinical and non-clinical outcomes. The objective of obtaining evidence on the level of *real-world effectiveness* is coupled with a multi-disciplinary analysis aimed at framing the characteristics of the context in which the innovation is implemented, identifying its strengths and obstacles or barriers, selecting strategies and interventions to be applied in the reference context and finally testing its success (23).

At the same time, innovative organisational models will have to be considered in order to give digital health a real chance to open up health systems to new ways of delivering services. The Aspen document "Innovative therapies and welfare: a new paradigm", drafted in 2019, proposes the creation of public-private *hubs* for the experimentation of digital technologies in specific areas and specific territorial realities, created also on the basis of the characteristics and problems of a given territory, as a winning move to start the evolution of the system while minimising the risk of resistance. The COVID-19 lockdown has undoubtedly led to increased telemedicine interventions to track chronic disease evolution and therapy adherence. It remains to be understood whether older individuals, who require more frequent monitoring, have the ability and adequate knowledge to interact with the attending physician and/or specialist through telemedicine.

Last but not least, the role of patients in the use of innovative therapies should be mentioned. Patients should be involved rather than being "treated" or "enrolled." In fact, when referring to the role of the citizen and the patient in the SSN, it is often spoken of rhetorically, stating that the patient must be placed in the process, but in reality there are very few concrete examples. Instead, it would be desirable to determine the ways in which the patient can contribute to the monitoring and verification of quality, safety effectiveness and appropriateness of care processes. With regard to therapies that have been expected for years, these can be an answer to patients' needs, but patients must learn about them and must be able to make an informed and shared choice in order not to preclude other possibilities. In the specific case of advanced therapies, the patient, through the signing of the Informed Consent, is made responsible for the procedure that will be implemented (surgical procedure for the administration of a gene therapy, or the process of managing one's biological sample from collection to re-infusion in the case of cell therapy).

In some cases, the patient may receive specific documentation related to the Risk Management Plan in order to be instructed on how to identify risks related to the therapy. Patient Associations have a great responsibility to advocate and justify the role of patients themselves in decision making. The role played in the formulation of Informed Consent for advanced therapies is crucial. Some associations have also already put in place adequate training for their patient communities to better understand the opportunities offered by innovation. The role of Patients' Associations can be decisive in compensating for a press communication often aimed at portraying innovative therapies, especially advanced therapies, as therapies "for everyone", without taking into account the need for them to be initially reserved for selected subjects on the basis of diseases with specific criticalities that initially require management with high quality standards.

CONCLUSIONS

Looking to the future, we hope to contribute to the development of a dynamic healthcare system in which research and clinical practice influence each other in order to promote continuous improvement. A virtuous cycle that involves all stakeholders (**figure 2)** begins with the identification of problems, continues with the design of innovative solutions based on the evidence collected, the verification of their applicability on pilot projects and finally the integration into the health system of an optimised model, a model that can be studied and improved again - in continuous implementation and evolution - to bring continuous and concrete benefits to an informed

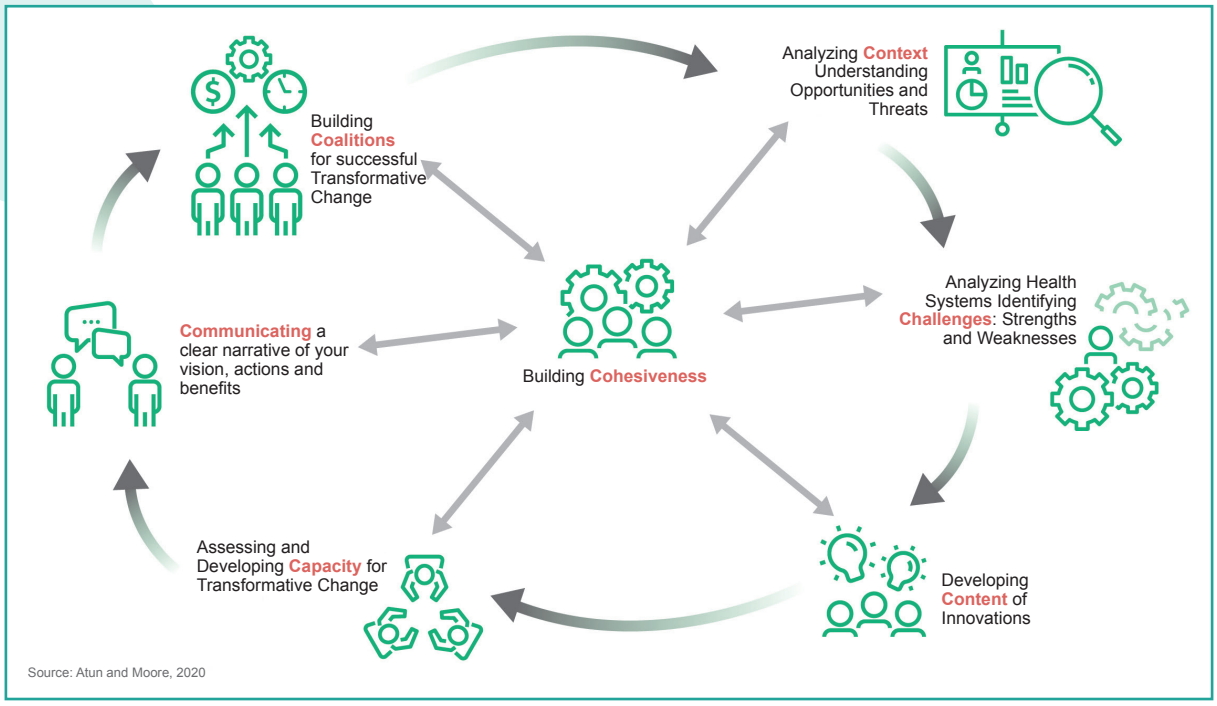

Figure 2. Knowledge exchange and partnership among health system stakeholders as crucial aspects of innovation implementation.

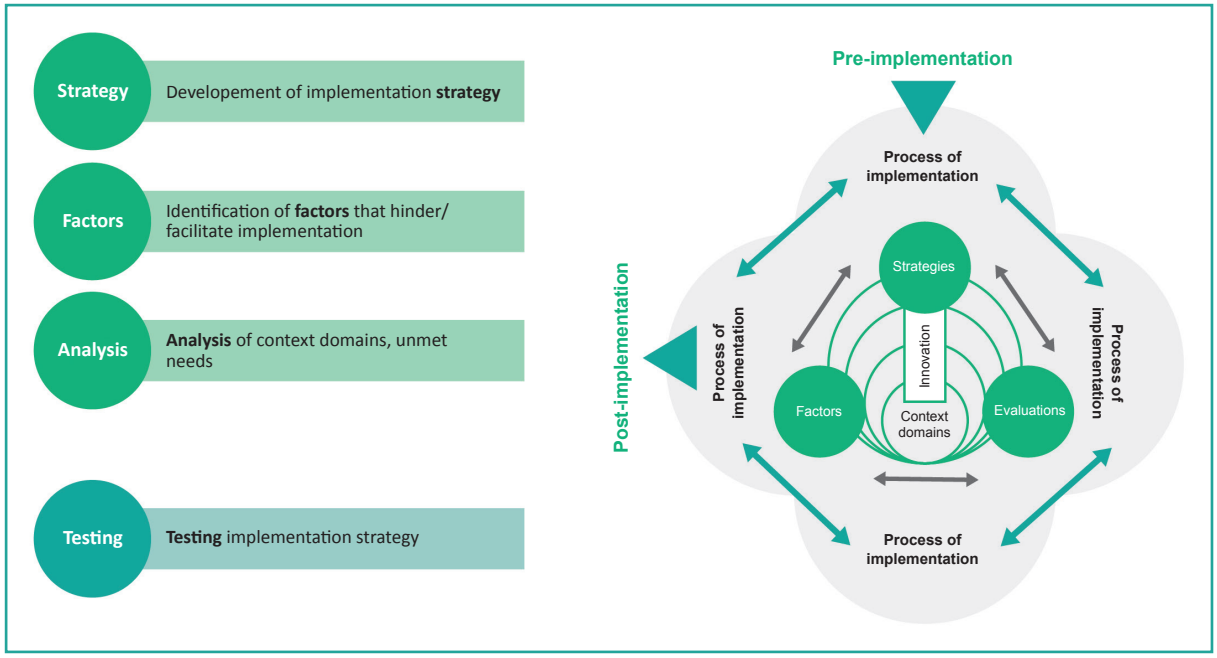

Figure 1. How innovative solutions are incorporated into the Health System by promoting their use and sustainability (adapted from (25)).

and aware population. In this scenario, it is evident that *breakthrough innovation* must always be accompanied by organisational research aimed at identifying the most suitable models for its introduction into the current system, governing the entire care process

and not just the drug variable (**figure 3**). All this will also require the creation of new professional figures, able to understand and integrate the different needs to facilitate the process of introduction of innovative therapies into the health system.

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OPINION PAPER

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DIGITAL INNOVATION IN MEDICINE: FROM *DIGITAL HEALTH* TO *DIGITAL THERAPEUTICS*

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HIGHLIGHTS

- The digital revolution is widely affecting the entire healthcare field: from the organisation of services to the management of the clinic (remote visits and consultations), to treatments (digital therapies).
- DIGITAL THERAPIES (the first, *ReSET*, was cleared by the FDA in 2017) provide *evidence-based* therapeutic solutions using high-quality software to prevent, manage, or treat a disorder or disease. They are used independently or in combination with medications, devices, or other therapies to optimise patient healthcare outcomes.
- The regulatory pathway for DIGITAL THERAPIES should focus on evaluating three main aspects: incremental efficacy on the clinical endpoint, integrity/quality of data collected, and organisational impact.
- It is necessary to orient the evaluation of DIGITAL THERAPIES towards the enhancement of the overall benefits they bring to the entire diagnostic and therapeutic pathway of the patient and to the individual, health and social effects.
- The adoption of DIGITAL THERAPY opens several possibilities for reflection: from the need for training of doctors, nurses and patients to the need to include new professional figures in the SSN such as "data managers", the clinical engineer, as well as the expert in Artificial Intelligence applied to health planning.

SUMMARY

The pandemic has prompted the various entities of the SSN to implement solutions to contain the infection, protect the frail, preserve health categories, and manage patients in Italy. The digital revolution that has been taking place for more than a decade in our society, and that is also widely affecting the health sector, has contributed at this stage to the organisation of the services to be provided and the management of the clinic (remote visits and consultations). In fact, the pandemic has created the conditions for a definitive transformation, turning the Italian healthcare into a DIGITAL healthcare.

On a European level, the world of "Digital Health" is a rapidly expanding area and is the third largest in the health sector after pharmaceuticals and medical devices. DIGITAL THERAPIES (the first, *ReSET,* was cleared by the FDA in 2017) provide *evidence-based* therapeutic solutions using high-quality software to prevent, manage, or treat a disorder or disease. They can be used alone or in combination with medications, devices, or other therapies to optimise patient healthcare outcomes. The potential offered by Digital Therapies must be well regulated both in the evaluation and access process and in the enhancement of the overall benefits they bring to the patient's entire diagnostic and therapeu-

tic pathway and to social-health planning. On the other hand, DIGITAL THERAPIES opens several possibilities for reflection: from the need for training of doctors, nurses and patients to the need to include new professional figures in the SSN such as "data managers", the clinical engineer, as well as the expert in Artificial Intelligence.

BACKGROUND AND OBJECTIVES

The digital revolution, which Eric Topol calls the "creative destruction of medicine," (1) is broadly affecting healthcare as a whole: from the organisation of services (*e.g.*, the creation of health service booking) and the management of the clinic (remote health and consultation) to treatment (digital therapies).

The key factors responsible for this revolution are:

I. the ability of digital systems to generate data (from management programs to individual wearable "devices");
II. the growing ability of digital systems to collect, integrate and analyse data;
III. the ability of digital systems to "learn" as they are used, adapting the choice options subsequently proposed to decision makers.

There are increasing demands at health system level for a change in the organisation and management of health services related to:

a. digitisation and the rise of medical technologies;
b. paradigm shift from a physician-centred to a patient-centred health system;
c. imbalanced distribution of health professionals across the territory and problems with access to care;
d. increased prevalence of chronic diseases linked to an older average population;
e. request for greater patient involvement;
f. economic pressure on the Health System;
g. the use of digital applications in everyday life.

On this basis, health professionals, patients, legislators, and the public expect Digital Health to contribute to:

a. improve the approach and quality of health care services;
b. facilitate the implementation of a personalised medicine process;
c. support the sustainability and efficiency of the health care system.
d. In 2018 in Italy, digital spending in health stood at € 1.39 billion (2).

BOX DEFINITIONS

DIGITAL health: Digital health involves the proper use of technology to improve people's health and well-being at the individual and population level, as well as improving patient care through intelligent processing of clinical and genetic data (3).

DIGITAL Medicine: Digital medicine is a discipline that focuses on the use of technology as a tool for measurement and intervention in the service of human health. Digital medicine products are driven by high-quality hardware and software that support the practice of medicine in general, including treatment, recovery, disease prevention, and health promotion for individuals and among populations.
Unlike "digital health" or "digital wellness" products, digital medicine products are characterised by evidence supporting their quality and efficacy (**figure 1**).

DIGITAL therapies: provide *evidence-based* therapeutic solutions using high-quality software to prevent, manage, or treat a disorder or disease. They are used independently or in combination with medications, devices, or other therapies to optimise patient healthcare outcomes (4, 5).

Since its inception, the SARS-COV2 pandemic has been the accelerator of a phenomenon that was already on the rise over the past decade.

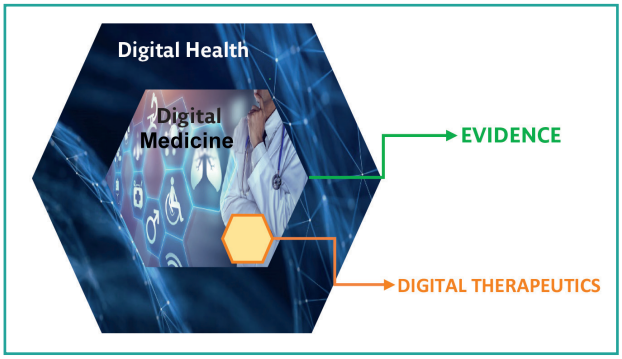

Figure 1. The large family of Digital Health includes that of Digital Medicine and Digital Therapies (taken from (18)).

The 2020 research by The Health Observatory (6) showed how interest in platforms such as Skype and Zoom has grown among physicians, with 38% of GPs (+ 34%) and 47% of Specialists (+ 33%) ready to use them.

Digital tools like Skype, able to connect the patient with their doctor, is part of the Telemedicine solutions (part of Digital Medicine). The "Televisit Manual" launched in March 2020 is an example of how to structure the remote visit pathway, starting from the "traditional" pathway and replacing the presence of the patient in the outpatient clinic with a "virtual" interaction in accordance with the Personal Data Protection regulations. (**figure 2** (7)).

The Health Observatory's 2020 research (6) also showed how the pandemic was an opportunity to implement solutions aimed simultaneously at containing the contagion, protecting the frail and preserving health categories, and managing patients in their territories. In fact, the emergence we have been experiencing since the early 2020s has created the conditions for a "Connected" form of Healthcare.

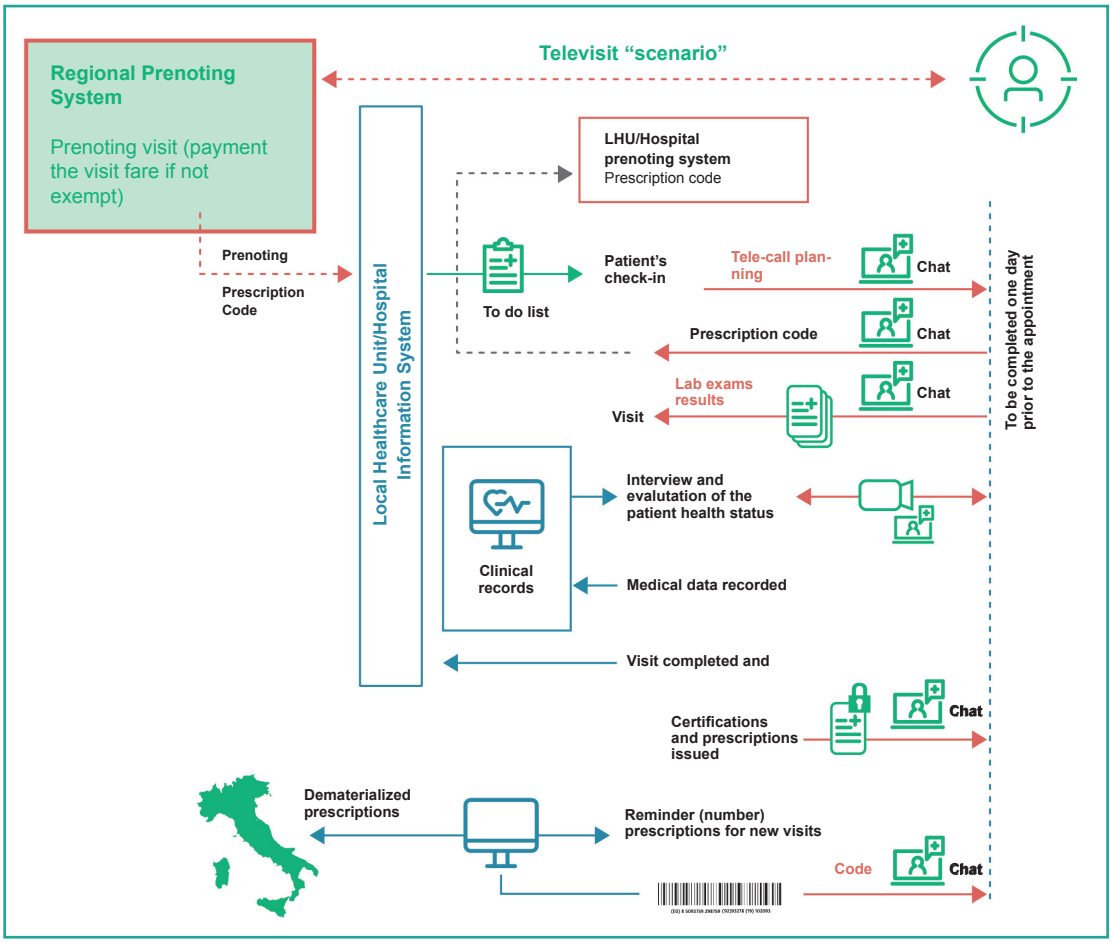

Figure 2. The Televisite flow as outlined in the "Telemedicine Now!" manual (taken from (7)).

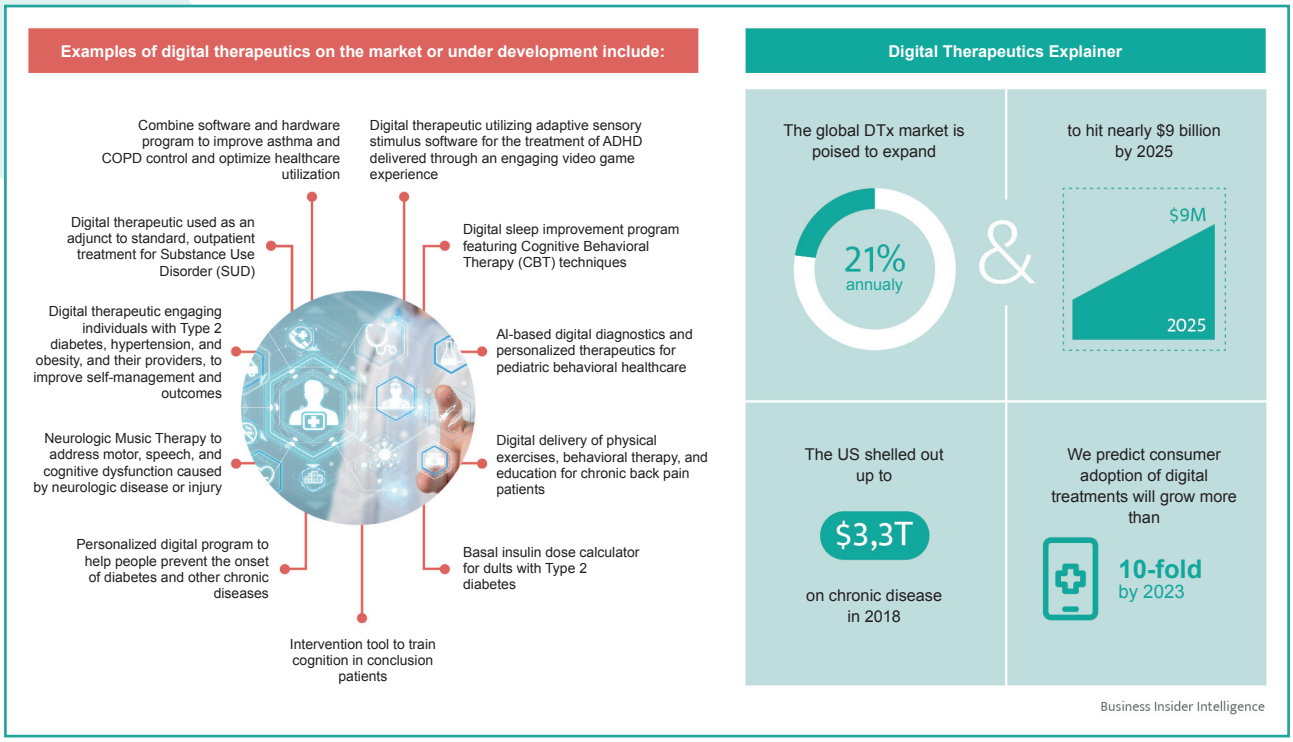

Figure 3. Annual Growth Rates of Digital Therapies DTA_DTx-Definition-and-Core-Principles.pdf (dtxalliance.org).

At the European level, Digital Health represents a rapidly expanding area and is the third largest in the health sector after pharmaceuticals and medical devices (**figure 3**).
In line with this evolution we find, within Digital Therapies, the family of "Connected Therapies". These are solutions that integrate devices, APPs and drugs, and are designed to offer improvements in adherence to therapy, customisation of dosage and constant tele-monitoring by the doctor of indicators, both of efficacy (example: post-prandial blood glucose levels in diabetic patients), and safety (example: continuous glycemic control for the prevention of hypoglycemic episodes, **figure 4**).
The concept of "Digital Therapy" thus covers everything from the actual digital active ingredient to the combination of a "traditional" active ingredient with one (or more) digital "devices", capable of collecting and transmitting data, as well as providing elements to support patient decisions (*e.g.* dose customisation).

"Digital therapies" are growing rapidly, and the *trend* seems to be consolidated especially in some therapeutic areas such as Nervous System, Cardiovascular and Metabolic diseases. They are projected to grow by a factor of "10" by 2023 (**figure 3**). For example, the European Society of Cardiology (ESC) provides a series of apps and other tools to the cardiologist through a dedicated portal aimed at improving integration of patient data and suggesting treatment options in accordance with guidelines (8).

The current regulatory path to support innovation

The development of innovative therapies has, over the years, triggered an evolution of evaluation pathways among regulatory agencies worldwide. The latest European Medicines Agency (EMA) Annual Report shows that in 2019 (9) EMA received:

- 549 requests for scientific advice, representing an 18% increase over 2018 requests;

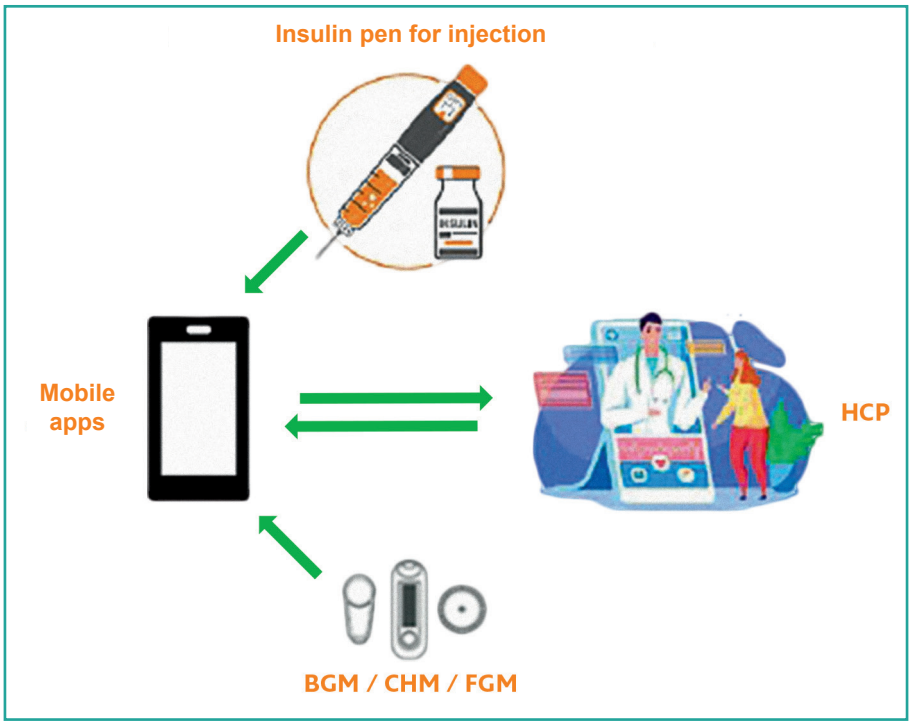

Figure 4. Example of possible "connected therapies" for diabetes care.
CGM = continuous glucose monitoring; BGM = blood glucose monitoring; FGM = fasting glucose monitoring; HCP = Healthcare provider.

- 60 PRIME requests (priority medicines) of which 28% were accepted (in 2018 26% were accepted);
- 70 requests for ATMP (advanced therapies), which is 27% more than 2018 and of which 67 were adopted (56% more than 2018);
- 117 requests for assessments (39% more than in 2018);
- 24 requests for expedited evaluation of which 13 were accepted (11 in 2018).
- In addition, in 2019, 8 drugs received conditional approval (1 drug in 2018).

In the United States, the FDA approved the first digital therapy in 2017. This is ReSET, an app suitable for the treatment of patients with Substance Abuse Disorder (SUD) (10), although the EMA has not yet recommended the authorisation of any digital therapy either as a "digital active substance" or in combination with a drug.
That being said, the EMA has recently finalised, after public consultation, the "*Regulatory science strategy to 2025*" document, which specifically includes *digital* among the areas of interest in which it intends to invest most, so that there is an adequate regulatory response to digital therapies (11).
From the regulatory point of view, digital therapies are currently classified as medical devices according to Directives 93/42/EEC, 98/79/EC and 90/385/EEC.
As noted, Regulation no. 745/2017, whose full application took place on May 26, 2021, replaces these directives, so digital therapies - in their *medical device* component - will, from that date, have to comply with new regulatory requirements, more stringent than the current ones.
In accordance with these principles, medical devices with active software will need to have a quality management system in place, a safety and clinical impact summary, and a post-marketing analysis plan. It would be useful to think of a real "digital surveillance", made possible by the very nature of the devices used, and their ability to connect continuously with servers and databases.

Preliminary guidelines have currently been drafted in relation to the aforementioned Regulation or associated products, including digital therapies (12).

FUTURE PROSPECTS

Assuming that digital therapies are such because they ensure the achievement of a clinical goal through the use of "digital" based technology, the possible development of the regulatory pathway these therapies would face would assess two main aspects: efficacy on the clinical endpoint and integrity/quality of the collected data. Nevertheless, with respect to "traditional" regulatory development and evaluation, it remains to be seen how the "safety" of a "digital therapy" can be measured and evaluated.

Clearly, the focus on these aspects extends to the design of *pivotal* studies, how to "tele-verify" the quality of the recorded clinical data, and the procedural standards to ensure their integrity.

The EMA could extend the evaluation of the dossier to these aspects, as well as to device manufacturing standards related to data recording and transmission and/or storage.

Another innovative element relates to the fact that "digital therapies" already offer the technological solutions for conducting *Real World Evidence* studies to measure efficacy in the post-registration phase. Finally, the possibility of collecting data in the real world makes it possible to generate evidence that provides the clinician with all the information in real time to "adapt" the decision to the patient's dynamic condition.

In a paper published in JAMA in 2019 (13), a *web-based* clinical monitoring approach was compared with traditional monitoring in patients with lung cancer. The Kaplan Mayer curve, in **figure 5**, demonstrates a significant increase in Overall Survival in the group subjected to *web-based* monitoring, suggesting that in this way, even if not referring per se to a digital therapy, all suspicious elements of progression or "safety" signals were recorded and processed earlier than the "traditional" monitoring based on regular visits to dedicated clinics.

Therefore, "digital therapies", despite their novelty, retain the relational cornerstones of medicine that connect the patient with the doctor in a dynamic relationship, always keeping **the patient at the centre** of observation and clinical decision-making.

"Digital therapies" changes two ways of bringing this relationship to life:

- the administration of the drug, which from an "active pharmacological principle" can become a "digital principle" or combine a "traditional active principle" with a *digital device*;
- the collection of data that enables verification of the efficacy and security of the treatment.

From what has been said, it seems that the EMA's evaluation activity, in its necessary renewal to focus not only on an active ingredient but also on processes and technologies that are inseparably integrated with the drug, may in future be renamed the European Therapeutics Agency.

Could "digital therapies" be evaluated by the Italian Drug Agency (AIFA), under current regulations? (14). We believe that, as long as regulations consider the "drug" (or what is assimilated to it as a drug and its *unconnected* device) on the basis of the marketing authorisation issued by the European Commission, "digital therapies" will have difficulty in entering the overall Italian market following the constitutional dictates and, therefore, it will be difficult for them to become solutions accessible to all citizens according to a defined and transparent pathway. In the case of "connected digital therapies", there will always be a duality between the 'pharmacological' component and the "device", with the relevant authorisation processes, which are currently separate and which often, especially in the purchasing processes, see the decisions on the drug regulated by the AIFA diverge from those

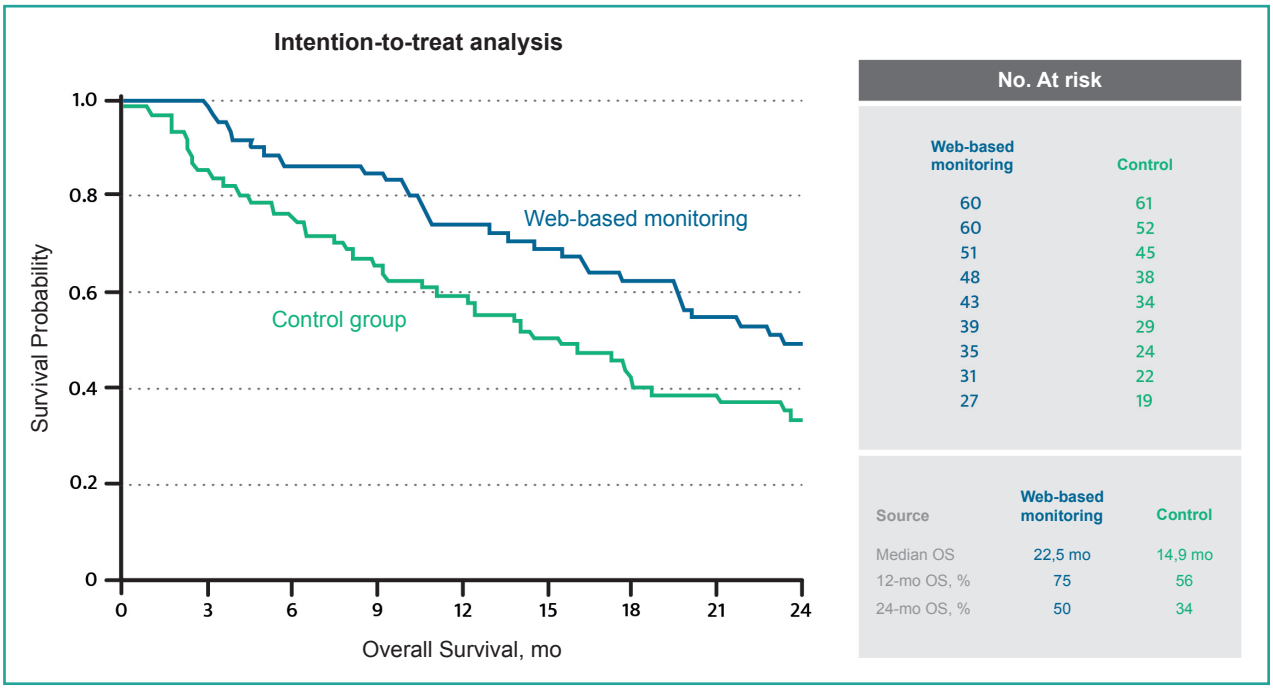

Figure 5. Kaplan Mayer curve of overall survival analysis: Comparison of web monitoring and traditional outpatient monitoring. (taken from (13)).

on devices purchased at regional/local/hospital level. Evaluating "digital therapies" would require an integrated approach to the active ingredient (whether pharmacological or digital), to the technology that carries it and to the benefits offered: from efficacy to adherence, through the organisational impact related to the possibility of tele-monitoring, to the revision and simplification of treatment paths and outpatient care, to the possibility of integrating patient data collected through the technology associated with the "digital therapy" in a single electronic health record.

This scenario would require a revision of the current evaluation procedures, further extending the evaluation of the therapeutic solution (currently essentially based on the comparison of efficacy with the standard of care) towards the evaluation of all the processes involved in the adoption of "digital therapy", from the perspective of *Health Technology Assessment*, currently applied only in part to medical devices (15). It is therefore a matter of integrating everything from the healthcare organisation to its programming (from micro to macro), to the patient, and to society.

The issues raised by "digital therapies"

We briefly addressed the major challenges that "digital therapies" pose to the regulatory world, from clinical development to registration, from national approvals to patient access to care. There are, however, additional areas that must be considered in order for digital therapies to reach their full potential. We identified four:

the first, considering the current different evaluation of the active ingredient and technology components, concerns the possibility of finding a synthesis regarding access and integrated remuneration of care. It would be useful to create a framework of regulations and standards at national level that could be applied systematically to "digital therapies", providing for their inclusion in specific LEAs (Essential Levels of Care) in each therapeutic area, starting with those where the need is greatest, as mentioned above (chronic diseases, metabolic diseases, nervous system, *etc.*). There is a growing awareness of this, certainly accelerated by the current pandemic, and European decision-makers are already discussing this issue ("*A Europe ready for the digital age is one of the Commis-*

sion's 2019-2024 policy priorities. Health is one of the sectors included in the programme, given the benefits that digital services could offer to citizens and businesses in this area") (16).

The second area, partly mentioned earlier, refers to the enhancement of the overall benefits brought by Digital Therapies in terms of impact on the entire diagnostic and therapeutic pathway of the patient and on the individual, health and social consequences of the benefits resulting from its adoption in clinical practice.

The third area concerns the need to train physicians, nurses, and patients in the use of digital therapies. While for the first two categories, the goal of consolidated training may be more easily pursued within the organisational and managerial structure of the SSN, for patients this is certainly more challenging. Their role, in fact, strongly changes with the advent of "digital therapies": they no longer passively "suffer" the treatment but become able to control it, with an increased responsibility on *clinical outcomes* and a greater involvement in the discussion of therapy with their doctor (*patient empowerment*). For these reasons, the need for "education" in the use of these new therapies is stronger.

Finally, given the characteristics of these technologies, we could see new professional figures involved not so much in the "administration" and use of technology, but rather on the side of the management of the immense amount of data constantly generated: It is therefore a question of making the most of the "data manager" for centres that adopt digital therapies for their patients, or of the *clinical engineer* to support the doctor's decision-making processes, *as well as the "health planning expert"* who uses specific algorithms with the support of Artificial Intelligence for increasingly precise planning of the resources to be allocated to health needs.

CONCLUSIONS

Data collected through the use of "digital therapies" increases the level of understanding of the real value of therapy, helping institutions, policy makers, and regulators make better healthcare decisions. The data generated and collected by these therapies can become the basis for a real revolution in healthcare that speeds up decision-making, provides useful information for healthcare planning, helps regulators in defining evaluation paths to enhance the overall benefits offered to the NHS, and puts the patient at the centre of the entire organisational and decision-making process. A very positive signal in this direction comes from the National Recovery and Resilience Plan (17), which allocates **€ 4.05 billion** to the **modernisation of hospital technology and digital assets** and, above all, **€ 1.67 billion** to the strengthening of the Ministry of Health's technological and application infrastructure, for the collection and production of data and the development of advanced analysis tools, including the Electronic Health File.

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OPINION PAPER

pharmadvances

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DYNAMIC SCIENTIFIC COMMUNICATION TO SUPPORT PATIENT CHOICE AND INNOVATION IN MEDICINE

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HIGHLIGHTS

- To ensure that the data being presented are considered truthful, scientific communication must be transparent and comprehensive. A key element in this direction is to ensure that results are published, whether positive or negative.
- To ensure that scientific communication is truly effective, it must be appropriate to the target audience in terms of content and language.
- Both the scientific community and the pharmaceutical world must listen to their stakeholders, in order to understand the real needs in terms of data to be generated and the methods and content of communication.
- The clarity and correctness of the information given must be consistent with the relevant regulations and with the code of conduct to which all pharmaceutical companies adhere.
- Special attention should be paid to communication with the public and patients. This should be clear and understandable, not strictly scientific, but it should also be the expression of a single voice that expresses evidence and not opinion, provides clarity and does not generate doubt.

SUMMARY

The consequences of poor and inadequate communication with respect to the stakeholder can be devastating, particularly in terms of the resulting social and health implications. The pandemic has brought this reality into clear focus, and now more than ever it is essential to ensure the goodness and veracity of the data, guaranteeing transparent and complete scientific communication. The difficulties involved in combating symptomatic forms of COVID-19, particularly the severe ones, show how important and necessary it is to ensure that the results of trials are published, regardless of their success. The publication, supported by method and scientific evidence, demonstrating the failure has allowed for the refinement of treatments and the careful choice of drugs. Researchers and pharmaceutical companies are required to comply with already established and defined publication requirements. To ensure that scientific communication is truly effective, it must be appropriate to the target audience in terms of content and language. Both the scientific community and the pharmaceutical world must listen to their stakeholders, both to ensure that they intercept the real needs for information and to identify the methods and content of communication. Special attention should be paid to communication with the public and pa-

tients. Communication should be clear and understandable, with appropriate and not strictly scientific language, representing the expression of a single voice which reports evidence and not opinions, clarifying the issues without generating doubts.

BACKGROUND AND OBJECTIVES

The ultimate goal of scientific research is to improve people's lives. To ensure that this objective is achieved, it is important that research, whether sponsored by pharmaceutical companies or so-called 'independent' research, is not only of the quality and characteristics described above, but also "communicated" correctly.

Communication plays an important role and is instrumental in providing correct information to the public on the evolution of drugs, their characteristics, their usefulness in the various diseases for which they have been developed and on what basis they have been repositioned in therapy according to their use in the real world.

To ensure proper scientific communication, it is important that it is transparent, balanced, and appropriate for the target audience. In fact, there are two categories to which communication is addressed: i) health professionals, who include all those who, for various reasons, are interested in medicines from research to the clinic; ii) the public who want to use the products of scientific research in an appropriate and, above all, informed manner.

The purpose of this review is therefore to highlight how communication can be made congruent with the above-mentioned characteristics, as well as highlighting some examples that should be focused on in order to go in that direction.

THE CURRENT CONTEXT

The primary elements of science communication are clarity and transparency. The frequency of generation of new data/evidence is much higher than in the past, and therefore to ensure true transparency and clarity, all available data and results must be published.

It is a requirement of both the Clinical Trial Register and Clinicaltrials.gov that within one year of the completion of a clinical trial, the results must be on their respective databases. The reality is that, on the one hand, this obligation is not always respected (1) and, on the other hand, we know that there is a real "publication bias" (2, 3) whereby most scientific publications report positive results, while studies that result in negative results are not published in any form. There are a number of reasons for this discrepancy, including the fact that researchers are not naturally inclined to write a good paper with negative results in relation to the objectives of the study, as well as the psychological factor of proving the failure of one's hypothesis, which is far from irrelevant. Furthermore, journals do not give editorial priority to the publication of negative data, which represent a very small percentage of the number of scientific papers published. In clinical research, this phenomenon, in addition to conflicting with ethical obligations, creates bias with major consequences. It is clear that the absence of available but undisclosed negative clinical data in the literature represents a negative bias as a given research/study could be repeated, resulting in unnecessary expenditure of resources and potential unnecessary risks for enrolled patients. Moreover, in the case of a clinical study, the presence in the literature of only some of the results, mostly positive ones, significantly influences the scientific relevance of the meta-analysis (3).

The second essential element of effective scientific communication is that it is appropriate to the target audience. There is a growing need on the part of different stakeholders (citizens and patients, but also pharmacists, doctors and payers) for adequate and at the same time detailed information. Clearly, the scientific community should be the primary stakeholder reaching out to these stakeholders, joined by pharmaceutical companies when it comes to sponsored research. It is equally clear that the type of information must be within the reach of the specific target audience. In other words, while the concepts and content must be the same, the methodology of communication, in terms of language

and level of detail, must be adapted according to whether it is directed to the public/patient, health professionals or "payers", who represent a third category with specific needs.
In this regard, while communication to physicians is manageable with open debate, when addressing the general population and patients it would be desirable to have a unified voice to ensure better clarity in messages. As an example, perhaps a trivial one but useful for understanding the difference, it can be said that if at a semantic level the sentence "drug X is frequently the cause of an adverse effect" is identical to the sentence "drug X is not infrequent in causing an adverse effect", from a psychological point of view the two sentences are read with a precise distinction: the first sentence is perceived by the reader, without any doubt, as a "certain negative event", the second, although it contains the same concept, expresses it with "the benefit of the doubt". It is also critical that there be uniformity in the communication itself and that the presentation of experimental data be evidence-based and not based on personal opinions/interpretations. With these measures, the communication can be qualitatively high and in line with the target, achieving both the objective of training and information.
For the Italian Society of Pharmacology (SIF), the ongoing pandemic has put considerable pressure on the need for training and information. Separate activities for drug professionals and the public, both of whom are eager to have in their hands adequate data and knowledge to deal with the emergency. The pandemic has thus prompted SIF to set up a crisis unit with the aim of releasing documents and information to drug professionals (both from laboratories and research centres and from hospitals and centres responsible for the care of patients), but also to prepare the same information in a suitable manner for adequate understanding by the public/patient (**figure 1**). Appropriate sites were thus set up on the SIF home page where the pharmacological aspects of COVID-19 therapy

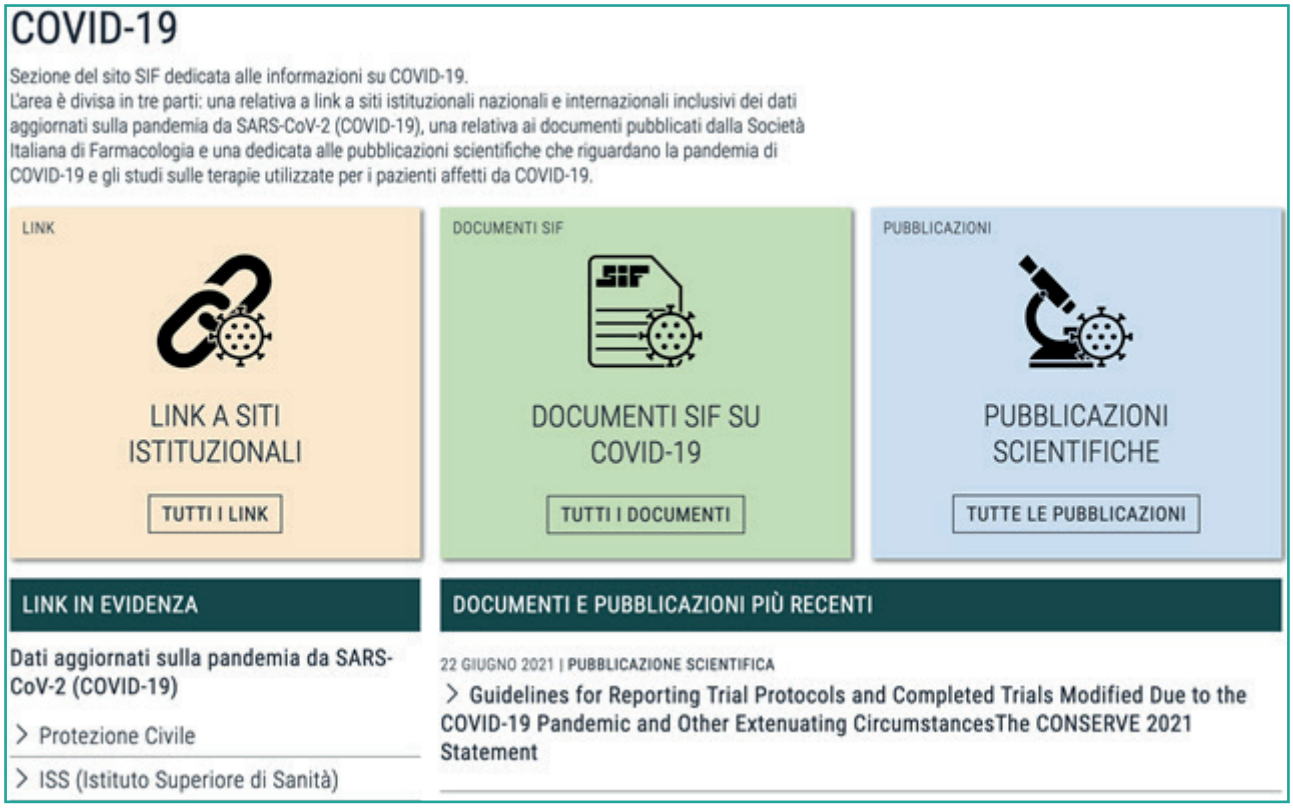

Figure 1. Screenshot of the website dedicated to professionals. The site also has an English version.

were outlined. This has been achieved through a folder dedicated to documents on the various drugs used to counteract the evolution of viral infection, including the control of pathological manifestations, prepared by experts of SIF with the aim of providing, to clinicians involved in therapy, the rational basis of the pharmacological and therapeutic characteristics known of each active ingredient used. All this with timely updates also on the findings of their possible use in COVID-19 patients.

The work of providing information, but also of training, was particularly useful considering that the pandemic had left the pharmaceutical industry unprotected and required the use of drugs that often had been *diverted* from their intended purpose. The positive feedback from this activity confirmed the need for training and information among professionals on the use of drugs in particular pathological situations and highlighted the role that scientific societies can play in disseminating information. An equally important task was to find bibliographic material on the therapies that were applied to combat COVID-19, including vaccines, which was published in international scientific journals and made available on the website, sorted by date, with free access for health professionals. The analysis of accesses showed a large number of them confirming that professionals need to have information sources available.

By way of example, here is the content of an email on this subject:

"From: Brianna Thomas &ltbrianna.thomas@cleverlifetime.com>
Sent: Wednesday, June 23, 2021 12:33 PM
To: sif.pharmacology &ltSif.Farmacologia@segr.it>
Subject: sifweb.herokuapp.com's impact on COVID-19 vaccines knowledge around the world

Hello there, I've been reading about and researching the top Covid 19 Vaccines and I came across your website. I found your article here: https://sifweb.herokuapp.com/en/covid-19/scientific-publications very helpful and would like to thank you for it. Like many people out there, I am extremely worried about the negative publicity most vaccines have received. I'd like to share with you this unique guide I came across, that provides unbiased information on the top 5 vaccines and a bit more.
It really put me at ease and I now have a better understanding of what is available out there.
You can find the guide here: https://www.dnaweekly.com/blog/covid-19-vaccine-ultimate-guide/
I am sure it will help your readers in the same way it helped me.
I suggest you add it to the page I mentioned above.
Best, Brianna."

The next step, for an even greater degree of information and training capacity, will be to share messages between the scientific societies directly concerned according to the pharmacological class and type of pathology impacted by the drugs, a process that will improve the flow of information and its efficacy.

The Italian Society of Pharmacology wanted to pay particular attention to communication to the public, a form of communication that must *bend* the scientific terminology for an audience of non-experts while maintaining the scientific impact and the quality of the data. The Society has had tangible feedback on the information activities put in place, starting with the creation of a shared initiative with pharmacists that led to the creation of a *pharmacological* calendar dedicating each month to reference drugs for a specific pathology. This was definitely important, and further highlighted how information on medication is a hot topic and very much felt not only by ordinary citizens and patients but also by healthcare professionals. The aspect of quality and mode of

communication was instrumental in achieving these results. In fact, before launching the "SIF Magazine" (4) online journal, SIF formed an editorial team of experienced members who attended a course for communication experts. This is to emphasise, once again, how important proper communication methods are.

In the light of what has been discussed so far, it is clear why the SIF website, which before the pandemic had a few thousand visits per year, has reached a total of more than 1,400,000 visits in the last year and a half, almost exclusively related to articles posted on the SIF Magazine, the journal dedicated to information on drugs for the public. Obviously, SIF Magazine's coverage is not limited to drugs and vaccines to counteract the SARS-CoV-2 pandemic but embraces all drug-related issues, as can be seen in **figure 2**.

An important aspect of communication to the public/patient is the continuity of publications containing information. On one hand, it may be considered that the continuity of information output, preferably at a fixed frequency, is trivially a practice of reader retention but, on the other hand, continuity indicates the scientific society's attention to the reader, to whom it continuously provides topics on which to extract knowledge for their attention.

On the part of pharmaceutical companies, a concrete contribution to adequate communication to the general population and patients is the practice of publishing the results of studies in simple, non-scientific 'lay language' through publications dedicated to the participants in the studies themselves. This approach is now in line with the EFPIA-PhRMA principle (5) and will become mandatory when the European Regulation (EU) 536/2014 on "CLINICAL TRIALS ON MEDICINAL PRODUCTS FOR HUMAN USE" comes into force (6).

These publications allow study results to be presented in language understandable to pa-

Figure 2. Screenshot of the pharmacological categories, with an example of the last 4 articles published, which collect the articles, interviews and videos dedicated to information for the public/patient.

tients and care givers and strengthens the partnership between scientific research and patients themselves.
Communication to physicians and payers is done through the dissemination of the results of clinical trials ranging from pre-registration randomised controlled trials to observational or real world studies. These studies may provide different results, having different objectives, but they all contribute to providing more and more evidence that adequately addresses the different needs of different stakeholders. This requires the generation of data on efficacy and effectiveness as well as on handling and tolerability in randomised clinical trials or post-marketing studies. It is also worth collecting pharmacoeconomic data to check the cost-effectiveness ratio in the various treatment settings. Last but not least, it is important to have appropriate interlocutors who are able to speak the right language and use the results in a way that suits the other party.. Undoubtedly, "payers" are interested in data on efficiency, manageability, tolerability and ratio, and cost-effectiveness, the latter preferably presented by experts in pharmacoeconomics.
The third fundamental element for effective communication is that in the construction of the studies, as well as in the definition of the contents of the communication, there is a continuous dialogue with the stakeholders themselves, *i.e.* the "payers", patients and doctors, in order to collect ideas, comments and evaluations.
Finally, in order to ensure the trust of their stakeholders, pharmaceutical companies have an essential responsibility to ensure correct and balanced scientific communication. In this respect, companies are guided by Farmindustra's code of ethics and DL 219, which sets out the following basic principles:

- the content of the information must always be documented or documentable. exaggerated claims, universal and hyperbolic assertions, and unprovable comparisons without an obvious objective basis are not allowed;
- texts, tables and other illustrations taken from medical journals or scientific works must be reproduced fully and faithfully, with exact reference to the source. quotations which, taken out of context, may be partial and/or contradict the author's intentions are not permitted;
- regardless of ministerial authorisation, all-encompassing statements such as "drug of choice", "absolutely harmless" or "perfectly tolerated" and the like are not permitted, and it should not be stated categorically that a product is free of side effects or toxicity risks;
- all information must be accurate, up-to-date, verifiable and sufficiently complete to enable the recipient to be adequately informed of the therapeutic effect and characteristics of the medicinal product;
- the information itself must be in accordance with the documentation submitted for the granting of the marketing authorisation of the medicinal product or its updates.

These aspects, which are taken for granted by pharmaceutical companies, are a guarantee of the quality of scientific information.

FUTURE PROSPECTS

From the perspective of communication to the general public, pharmaceutical companies and the scientific community must: i) produce documents containing scientific data written in comprehensible and simple language; ii) represent a clear voice above the parties, carrying a clear, unambiguous message, not driven by personal opinions but by data.
With regard to this last aspect, the scientific community has a duty to identify the people and communication methods that are in line with the target audience and avoid creating a sense of mistrust towards science due to ineffective communication, thus putting public health at risk.
This is in no way intended to impact on scientists' freedom of thought, which is absolutely guaranteed, but which must be maintained at the level of scientific debate between experts who have the appropriate tools to judge, as in

the case of the following sentences: "drug X is frequently found to cause an adverse effect" and "drug X is not infrequently found to cause an adverse effect". When addressing the population, it is important to ensure the message is clear, aligned with Evidence Based Medicine and as free as possible from personal opinions.

CONCLUSIONS

Pharmaceutical companies and the scientific community are the primary stakeholders that come into play in ensuring both that scientific research is of quality and that the research results are properly communicated.

There is a need for the scientific community and pharmaceutical companies to join forces to ensure transparency in the publication of all scientific data and to provide clear communication, based solely on evidence and not personal opinions, in language that is appropriate to the target audience.

Pharmaceutical companies and the scientific community have an important responsibility and it is important that they represent the main voice, the one that is really listened to, when talking about the results of scientific research, not only to the scientific community itself as a direct and preferential interlocutor, but also to institutions and the general population. Only this will really ensure proper trust in them and put aside the misinformation and non-quality communication carried out by functions that should not be responsible for this.

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EXECUTIVE SUMMARY

This document is not intended solely as a high-profile dissertation on the issues of innovation and sustainability arising from the partnership between the pharmaceutical industry and the Italian Society of Pharmacology (SIF), but rather as a working agenda and a map for the future. In fact, it is a dynamic document that aims to indicate the direction to be taken in all areas addressed in the various chapters and to lead to the emergence of real projects aimed at achieving the objectives set out in the various contributions.
These projects which, for obvious reasons, are transversal to the various areas dealt with in the document, are based on a series of key words and concepts, widely addressed within the various contributions in the "future prospects" sections.
In the following, the key concepts are recalled and the points of observation addressed in the document are reported in order to identify possible developments of the document and to further emphasise the value of the partnership between the pharmaceutical company and SIF.

TRAINING

The topic of training is of fundamental importance both to make the new methods of clinical research effective (***see 1. The new research methods***), as well as to take into account all patient needs (***see 3. The patient and their treatment needs***). In addition, having adequately trained professionals is essential to facilitate the introduction of breakthrough innovation into the health system, as this must be adequately accompanied by organisational research and the implementation of new organisational models in order to see it truly applied (***see 4. Breakthrough innovation and PDTAs***).
To this end, it is necessary to design training courses on objective and shared methodologies to evaluate the patient's entire PDTA in view of the advent of breakthrough innovation. These courses may be implemented both within the framework of university courses, such as Master's degrees or high-level training courses (also organised and sponsored by SIF and Farmindustria), and as training sessions for healthcare personnel (*e.g.* training courses in ASLs or other healthcare institutions), in order to make use of all the experience gained in this field.
The issue of training is also crucial when it comes to the use of health data and the assessment of their quality, as it is only with adequately

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trained expertise that data-based quality studies can be conducted (***see 2. Data quality***)
It is therefore of strategic importance to provide specific preparatory courses for research in all its fields, aimed at all the professionals involved in the process of designing and developing new therapies.
The need to innovate training processes is closely linked to the growing interest in digital therapies, which involves health professionals on the one hand, and patients on the other, whose role changes from being passive to being in control and able to manage these new therapies (***see 5. Digital innovation in medicine***).
Finally, training, together with information, is a key objective of communication processes, which should therefore always be of high quality and in line with the target audience (***see 6. The role of science communication***).

ACCESSIBILITY

Accessibility, understood as the accessibility of clinical research (***see 1. The new modalities of research***),but also as the possibility of optimising local medicine and territorial care (***see 3. The patient and their treatment needs***) is one of the main pillars enabling patients to obtain the best treatment and, at the same time, allowing society to benefit from it.
The issue of access is also crucial in allowing digital therapies to become an integral part of treatments for a clinical condition. In this context, in order to ensure accessibility to treatment, it is essential to overcome the duality between the pharmacological component and the digital therapy that may be associated with it, by making the necessary changes to systems and authorisation apparatus (***see 5. Digital innovation in medicine***).

COLLABORATIVE AND MULTIDISCIPLINARY NETWORKS

Stimulating and encouraging the creation of research networks (***see 1. New research methods***) that also involve patients and decision-makers is an important strategic choice both to make research fast and accessible and to increase its value. Thinking and working in a multidisciplinary way, involving all the stakeholders involved in the health system, would make it possible to understand in advance the social, cultural, economic, political and environmental impact of innovation, whether it be incremental or **(*see 3. The patient and their treatment needs***), breakthrough (***see 4. Breakthrough innovation and PDTAs***).

DATA QUALITY

The quality of data, whether derived from clinical trials or clinical practice (Real World Data) is a fundamental prerequisite for generating evidence (***see 2. Data quality***). In this context, there appears to be an urgent need for a regulatory framework, capable of regulating the generation and use of data, in all phases of drug studies and also for all modes of access to them (including *expanded access* programmes).

The quality of the data collected is also the key to the development of digital therapies in order to assess their safety and efficacy and to meet the required procedural standards (*see 5. Digital innovation in medicine*).
Moreover, data should be the basis for communication processes on scientific advances, whether they are aimed at researchers, health personnel or, above all, citizens (*see 6. The role of science communication*).

REAL WORLD DATA

While it is well established that data produced during Randomised Clinical Trials (RCTs) are the *gold standard* for generating evidence on the benefit-risk profile of drugs, the role of Real World Data (RWD) in supporting drug authorisation processes needs to be better defined (*see 2. Data quality*). These data, when used through integrated analytical approaches, can also allow for the adequate measurement of patient-centred benefits that are difficult to quantify with traditional analytical systems (*see 3. The patient and their treatment needs*). RWD should therefore not only be considered as a product of the later stages of drug development, but represent value from the earliest stages of development, as they can be used to study possible target populations for a new therapy, defining their size, characteristics and costs to the SSN (*see 4. Breakthrough innovation and PDTAs*).
RWD will certainly benefit from digital therapies, which are able to generate information that until now has only been available for specific projects. This information, as well as being used for the evaluation process of digital therapies themselves, will fill the information gaps in Real World Evidence studies, increasing the value of this branch of research (*see 5. Digital innovation in medicine*).

DIGITAL HEALTH

Digital therapies, while maintaining the doctor-patient relationship as the mainstay of care, strongly modify the concept of drug administration, which can go from being an "active pharmacological ingredient" to a "digital ingredient". Moreover, they recognise the "collection of data" as a central element for evaluation and enhancement. This change, however, requires a specific regulatory and evaluative framework that needs to be built as soon as possible, even considering the speed with which these therapies are arriving (*see 5. Digital innovation in medicine*).
In order to give digital health a real chance, it is essential to have innovative organisational models that open up health systems to new ways of delivering services (*see 4. Breakthrough innovation and PDTAs*).
The potential of Digital Health also passes through the generation of specific data through apps and wearable devices that, if appropriately deployed, can certainly enrich the wealth of information about drugs and healthcare in general (*see 2. Data quality*).
In addition, the advent of digital technology has facilitated an increasingly extensive and systematic collection of patient clinical data and has en-

abled the implementation of decentralised clinical research methods, with enhanced use of telemedicine and home care tools, which will progressively become a new standard for conducting studies (*see 1. The new research methods*).

PATIENT-CENTRICITY

It is now well established that the patient should not simply be "enrolled" or "treated" in drug development and access processes, but should be "involved".

The involvement of the patient is of strategic importance from the earliest stages of development and research, as the patient is increasingly becoming a protagonist and is not limited to just taking part in a study but also contributes to defining its implementation and objectives. (*see 1. The new research methods*).

Hence the need to talk about patient-centricity. This concept, often abused or used rhetorically, when combined with the theme of innovation, can be interpreted in different ways: from the evaluation of incremental innovation aimed at simplifying care (*e.g.* by favouring adherence; *cf.3. The patient and his or her treatment needs*), to the definition of breakthrough innovation that takes into account new treatment possibilities, all the way to true organisational innovation (*see 4. Breakthrough innovation and PDTAs*).

The centrality of the patient requires the development of innovative measurement systems that take into account the benefits for the patient, including in terms of improved quality of life, in order to be able to correctly quantify incremental innovation (*see 3. The patient and their treatment needs*). This concept is also crucial when analysing the treatment pathway (*see 4. Breakthrough innovation and PDTAs*).

The patient at the centre should be the cornerstone of innovation related to digital therapies which, despite being based on a new way of approaching treatment, should not change the doctor-patient relationship (*see 5. Digital innovation in medicine*).

Communication processes must also consider the centrality of the patient, seeking to provide clear and comprehensible information, not of a strictly scientific nature, so as to promote clarity and not generate doubts (*see 6. The role of science communication*).

TREATMENT PATHWAY

In order to truly understand the impact of innovation, it is essential to think in terms of the treatment pathway (Diagnostic, Therapeutic and Care Pathway, PDTA), both in analysing and evaluating the innovation itself, and in imagining new organisational solutions to make it applicable and sustainable (*see 4. Breakthrough innovation and PDTAs*).

The evaluation of the pathway will certainly benefit from the analysis of real-world data, including data from wearable medical devices, which represent a challenge for the future (*see 2. Data quality*).

The conception of the entire pathway, and not of the individual variable, will also make it possible to properly value the introduction of digital therapies which will be strategic in simplifying the patient's pathway, fostering new ways of providing and managing care, such as home care (***see 5. Digital innovation in medicine***).

DYNAMIC COMMUNICATION

Communication of innovation should be the primary task of the scientific community. It should be transparent, balanced, and appropriate for the target audience, both health professionals and the public. In a context where communication is increasingly dynamic and crucial, pharmaceutical companies and the scientific community are therefore called upon to collaborate in order to produce documents with a high scientific content, using understandable and simple language. These documents should convey a message that is as clear as possible, data-driven, aligned with Evidence Based Medicine (EBM) and, while guaranteeing the freedom of thought of scientists, should not generate distrust in science (***see 6. The role of science communication***).
In order to achieve communication that not only takes into account the opportunities of innovative therapies for specific patients, but also underlines the importance of the sustainability of the health system, it is of strategic importance to involve patient associations in the communication processes (***see 4. Breakthrough innovation and PDTAs***).
In conclusion, the virtuous collaboration between pharmaceutical companies and the Italian Society of Pharmacology (SIF), guaranteed by the expertise of both parties in the various areas addressed, following the map outlined in this document, can ensure that innovation is a driving force for sustainable health.

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