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Independent Research in Italy

G. Corbellini

Molecular Biology Department, Sapienza University of Rome, Rome, Italy

E-mail: gilberto.corbellini@uniroma1.it

Italy's indicators for research show contradictory performance. Italian governments have been investing significantly less in terms of GDP than other developed countries. Today, Italy is barely above half the European average, which is 2% of GDP. Nonetheless, despite the chronic lack of precious resources, Italian researchers seem to be productive and able to compete with communities that have access to more public and private funding: in particular, they regularly publish the results of clinical and translational studies that leave their mark in the history of traditional and advanced therapies in the most prestigious journals. Italy excels in cutting-edge translational research, having developed Streamvelis and Holoclar®, two of the first and most revolutionary therapies. Streamvelis is a gene therapy for the treatment of patients affected with severe combined immuno-deficiency due to adenosine deaminase deficiency, for whom there is no histocompatible stem donor. It was developed by the San Raffaele Hospital and the Telethon Foundation, through a strategic collaboration with GSK and MolMed. Holoclar® is an advanced therapy, marketed by Chiesi Farmaceutici S.p.A. It is based on autologous stem cells that can restore sight to patients with severe burns of the cornea. It was developed at the laboratories of Holostem Terapie Avanzate srl, hosted at the "Stefano Ferrari" Regenerative Medicine Centre of the University of Modena and Reggio.

Despite the success made possible by the encounter of talented researchers with advanced scientific skills and innovative industrial visions and the fact that Italian researchers are good, private sponsors tend to neglect the Italian clinical research system. Indeed, Italy's reputation is rather lacklustre based on an index that measures a country's appeal as a site for clinical trials. According to this rating, Italy ranks behind Germany, the Netherlands, the United Kingdom, Belgium, France and Spain. Italy barely receives 5% of the budget invested by pharmaceutical companies. The reasons are regulatory and organisational uncertainties, but above all the lack of public investment to consolidate and encourage the construction of infrastructures dedicated to independent clinical research.

There are many reasons why research is not considered an economically advantageous investment in Italy and these are probably linked to a cultural tradition that has been reluctant to use empirical methods to estimate and measure the impact of political decisions.

The international economic and political scenario is worsening the picture, and there has been a general decrease in public investment in clinical trials over the last decade. NIHs too have steadily cut back on clinical research with a 40% reduction in funded clinical trials from 2004 to 2015, making them become smaller and seldom reach phase III. In Italy, the impact of this trend threatens the very survival of non-profit research, which is in a downturn, according to the AIFA Reports on Clinical Trials of Medicinal Products in Italy, resulting in a more than 50% drop in the number of non-profit studies between 2009 and 2017.

The prevailing perception of the value of clinical research, and specifically of research conducted by academic institutions, seems to be impervious even to sensational evidence of economic returns. The performance of clinical research has recently been

calculated by the Association of Australian Medical Research Institutes. The study titled *Economic Impact of Medical Research in Australia* (October 2018) showed that the medical research sector contributes significantly and lastingly to the economy by creating highly qualified or knowledge-intensive jobs and improving the health and well-being of the population. From 1990 to 2004 net present gains amounted to $78 billion from a net present cost of $20 billion, a return on historical investment of $3.90 for every dollar invested.

Australia's GDP was $2.6 billion larger as a result of historical medical research and welfare was $1.5 billion higher than it would have been in the absence of biomedical research. In particular, independent clinical trials produce economic benefits for public investment, as can also be seen from a 2017 publication that estimated the impact of funding awarded by the NCI Southwest Oncology Group (SWOG) and used to conduct 23 positive trials from 1965 to 2012 by enrolling 12361 patients. Through 2015, these trials made it possible to gain 3.34 million life-years at a cost of $125 per life-year gained. Some calculations have been made for Italy too on the economic gains for the Italian National Health System from the participation of hospitals in a clinical trial, showing a multiplier effect of at least 1:2 (each euro is worth about 2.2 for the Italian National Health System) in terms of savings for avoided costs and drugs. It would be a strategic move for Italy to advance clinical research and promote independent research, investing as requested for example by FADOI, the Italian Federation of Internal Medicine Hospital Executives, at least a fixed amount of at least 1% in non-profit research) given the quality of human resources available in public facilities that can be appealing to private sponsors and competitive in gaining access to funding from non-profit organisations.

Italian Legislative Decree no. 52 of 14 May 2019 does not seem to seize on favourable circumstances. While, on the one hand, it tries to address the main challenges of clinical research today, on the other hand, it has bottlenecks that discourage sponsored and non-profit clinical trials. Moreover, it does not provide for any economic investment to implement the provisions. There seems to be little awareness in Italy that the current international and national situation of clinical research is not the fruit of improvisation, but is a historical process affected by contexts and specific decisions and which today is facing new challenges to be governed through an articulated understanding of the factors at play and trying to predict the changes. Discussions on clinical research tend to lack historical depth, which helps to understand its origins and how it has come to take on its current face and problems. Clinical research began to take the form it would in the 1950s, after the invention and use of randomised clinical trials (RCTs) to prevent drugs from being used based on few uncontrolled experiences or testimonies. Drug manufacturers were initially reluctant to invest in RCTs, believing they could continue to use expert observations and case reports as evidence to sell medicines. Following the thalidomide tragedy, the Kafauer-Harris Amendment (Drug Efficacy Amendment) was introduced into US legislation in 1962. According to it, new drugs had to be effective based on "adequate and well-controlled investigations" in order to be approved. Since the 1970s, the Food and Drug Administration has been requiring RCTs for the approval of a new drug, followed by Europe and Japan.

Inevitably, the pharmaceutical industry became the main sponsor of RCTs and in the 1990s it had largely replaced governments and academic medicine as the primary producer of RCTs. In the meantime, RCTs went on to become the "gold standard" of medical research, despite the limitations of usability, i.e., inadequacy for all those situations that could not be standardised in a statistical design or where the use of controls would be ethically inadmissible.

Of course, controlled observations or pathophysiological knowledge produced by laboratories have continued to be used, while scientific and technological advances or the availability of large databases have led to the integration of methodologies to make more effective comparisons.

However, RCTs have proven to be organisationally convenient and the regulatory framework has found it instrumental to harmonise clinical research on the model of RCTs worldwide.

Medical research has become almost exclusively collaborative and RCTs have progressively become a bureaucratic and corporate effort, requiring costly infrastructure for research design, patient recruitment and care, record-keeping, ethical review, statistical analysis, etc. Costs have therefore risen, and the time needed to bring a drug to market has become longer. At the beginning of the 21st century, a Phase III RCT cost $30 million.

Today, the cost estimates for the overall development of a drug range, depending on the characteristics of the

research, between $150 million and $1.8 billion, and it takes 10 to 15 years for a new medicine to be approved. The high costs are often used to justify the rise in the price of medicines. The economic aspect of RCTs implies that sponsors are based in geographical areas, so they tap the interests of industrialised regions rather than developing ones, and even in richer areas the challenges faced by sponsored research are obviously those that give rise to an economic return and cannot relate to public health emergencies, such as the shortage of antibiotics. With the aim of reducing the weight of RCTs and speeding up drug approval in the United States, the *21st Century Cures Act* was approved by the US Congress in December 2016, but it was perceived as a favour to pharmaceutical companies: critics argue that the industry did not have this need, given that a third of all drugs in the United States are approved based on a single clinical trial with an average of less than 700 patients. While the law's intent was to stimulate the use of more realistic evidence (real-world evidence) in drug validation, rather than evidence collected in artificial experimental settings, there is concern that the law will only lead to a broadening of the indications for use of existing drugs.

In this context, strategies are needed to refocus the logic of clinical research, which methodological conformism has placed in the hands of industry.

The processes for structuring clinical trials in an ecosystem dominated by selective commercial pressures, resulted in the birth, in the eighties, of two types of organisations to support the industry. On the one hand, Contract Research Organizations (CROs), i.e., commercial partners of the industry that offered services by providing laboratories, clinical and legal services, monitoring of clinical trial sites, writing of articles, etc. Over time, CROs have taken on an increasingly strategic role and control a huge turnover (over $20 billion). Today, the industry relies on CROs to implement and manage clinical trials globally and, although CROs have no legitimate or commercial interest in the outcome of studies, they are more dependent on the industry because they would not exist without it. CROs have contributed to inventing a figure of principal investigator that is far from that of the traditional medical scientist who works in university hospitals: these non-academic physicians who work in the private sector on a contract basis do not see themselves as scientists and do not pursue the epistemological and ethical values of science but rather the economic returns established by the contractual ties with a private company. CROs have also been the driving force behind the relocation of trials to developing countries where conditions, also in terms of controls, are favourable: many countries are now competing to convince the industry and CROs that they ensure the ideal conditions for clinical research, even considering that the products tested will not be accessible to the population. As the organisational role of CROs emerged and prevailed, researchers also created collaborative networks, i.e., Academic Research Organizations (AROs), to conduct global clinical studies, necessary to find answers to important medical questions, as well as to ensure quality control over the results, their publication and discussion. These groups also focus on the management of the main national registries to collect data and influence the introduction of best practices, i.e., their inclusion in guidelines. Trials conducted by academic organizations have mainly focused on multimodal therapies, comparisons between different drugs and different drug combinations, the effectiveness of surgery and radiotherapy, the use of imaging methods: i.e., studies that do not aim to register or market new drugs but aim to improve the overall treatment, the understanding of the biology of a disease and the mechanism of therapeutic action. AROs have been widely used by the pharmaceutical industry as a scientific reference to ensure the quality of trials, as well as for the comprehensive management of clinical trials, including monitoring of the trial site, data management, statistical analysis, safety control, etc.

Standards for the design, conduct and publication of clinical trials have increased in recent years and while there has been an imbalanced relationship between pharmaceutical sponsors who fund a programme for the develop of a drugs or devices, the contract research organizations (CROs) that generally provide assistance in carrying out the process, the regulatory agencies and the world of academia, which, in particular, has seen its leadership as well as its oversight of the drug development process shrink.

Research based on randomised and sponsored clinical trials has undeniably produced progress in the quantity and quality of care, although it has been focused on drugs rather than on providing the biological explanations of diseases, preventing side effects for patients or curbing health care costs.

The objective of commercially targeted clinical research is to bring new, economically viable products to market as quickly as possible. To improve efficiency and reduce

costs, surrogate endpoints have been favoured over time, even when trials already in progress or the available data show that there is no substantial therapeutic benefit over existing drugs or increase in survival, not fully reflecting the needs and concerns of patients. Clinical studies funded by the industry have made it possible to develop and register important drugs, i.e., drugs that have a great clinical impact and are very profitable for the industry. The logic that has taken root since the 1980s in the development and regulation of new drugs has favoured the amount of data collected, over their quality, causing as stated above an exponential growth in costs, which largely depend on clinical trials required for approval. Moreover, thanks also to the grey areas of patent protection, the preference has gone to strategies that do not depend on an increase in clinical benefits or on a reduction of side effects and that do not impact on the high rate of failure of clinical trials. The industry has favoured the search for substantial profit margins, including the systematic use of CROs or changes in the indication of active substances to extend intellectual property protection. Innovative drugs, on the other hand, are increasingly being launched on the market at a cost that is seldom affordable even for high-income countries, forcing health systems and regulators to make difficult choices. Given the econometric data on the beneficial effects of clinical research, as mentioned above, in recent years the literature has shown that the costs of developing and selling drugs according to industrial strategies are not justified by therapeutic benefits. A study published in the *Journal of Economic Perspective* in 2015 examined a sample of 53 drugs approved by the FDA between 1995 and 2013 and showed that the growing trend in the price of these drugs cannot be explained by the benefits they provide. According to estimates, more than a third of new drugs reaching the market do not offer any therapeutic advance for patients, with many patents based on remixing old combinations or additional uses of existing ones. A study published in 2017 demonstrated that a very low percentage of RCTs that study the overall treatment of different types of cancer use criteria to recognise the clinical benefits according to the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS). Only 15% of the 277 RCTs that evaluated the systematic treatment of colorectal, breast, non-small-cell lung and pancreatic cancers published between 2011 and 2015 met the criteria of significant clinical benefit according to the ESMO-MCBS. The study suggests that researchers, funding agencies, regulatory agencies and the industry adopt stricter thresholds for significant benefits in the design of RCTs. Before 1970, clinical research in the United States was funded by public bodies. In 1991, 70% was commercially funded, but about 80% of the trials were conducted in university hospitals, where academic and financial controls supported the independence of researchers. In 2004, only 26% of the research was conducted in academic medical centres, the rest by for-profit companies. The trend continued, as it became increasingly obvious that when pharmaceutical and medical device companies financed research either directly or through private contracts, they would intervene to condition the design of the study and the published results. On 18 May 2000, the New England Journal of Medicine published a report based on interviews with specialists, titled "Uneasy Alliance. Clinical Investigation and Pharmaceutical Industry," which was accompanied by a scathing and since then famous editorial by Marcia Angell against the pharmaceutical industry titled "Is Academic Medicine for Sale?" The year 2000 can be considered a sort of watershed in the evolution of the social and political perception of clinical research. Two studies published in 2003 - one in the Journal of American Medical Association (JAMA) and the other in the British Medical Journal - found that commercially funded studies were 3.6 to 4 times more likely than non-commercial studies to report positive results for the sponsor's product. The chances that sponsored research found that the new drug was the treatment of choice were 5.3 times higher than studies funded by non-profit organisations. In addition, it was found that when researchers in industry-sponsored clinical trials had economic ties with the sponsor (as paid consultants or speakers), the likelihood that the trial results would support the use of the sponsored drug was 8.4 times greater. It was discovered that industry manipulations included the selection of people enrolled in a study to enhance the benefits of the drug and minimise the risks, including the study of the product on healthy people who took few other drugs and were therefore less likely to experience side effects. It was also found that in sponsored studies researchers frequently put their names at the bottom of articles that had been written by companies that contractually managed the trial and these articles were then sent to peer-reviewed journals. Conditioning by the industry to obtain economic returns from investments made in the first decades of development of clinical trials has also

involved the editorial boards of medical journals and committees of experts to develop guidelines for practice, through the presence of researchers with active financial ties to one or more companies that produce the drugs being tested or on the market.

In order to respond to obvious forms of corruption, transparency rules have been called for and introduced, i.e., to know when medical experts cited by the media receive funding for research or are paid for consulting services or reimbursement of conference expenses by pharmaceutical companies .

Increasingly stringent standards have been adopted by regulatory agencies and journals that evaluate and publish research results and to prevent clinical guidelines that inform the decisions of doctors from being influenced by commercial interests. Since around 2010, an increasing number of medical schools have been prohibiting faculty from being paid by pharmaceutical companies to give lectures and accept personal gifts, travel or meals. Some medical journals and publishers require companies to register studies in advance, before the results are known, so that negative outcomes are easier to track. Universities, regulators and journals have obviously been late in taking action to improve RCT transparency by requiring disclosure of conflicts of interest and registration of all clinical trials so that negative results do not disappear.

In the uninformed or ideological public perception, the discovery of distortions due to commercial interests, i.e., profits that are put before the suffering of the sick, has cast a shadow of widespread corruption and conspiracy on the pharmaceutical industry (big pharma) and the impact of clinical research, including the increase in the cost of drugs, is attributed to. The conflict of interest issue, which is not a crime but determines a condition where the presence of secondary interests leads to the suspicion that not only the primary interest is taken into account, has reached levels of near paranoia. This is not the place to talk about it, but as a series of articles that appeared in NEJM in August 2015 reminded us, we should ask ourselves what really happened, since in the aftermath of the Second World War collaboration of researchers with industry led to the development of revolutionary drugs (e.g., antibiotics), while today it is only a sign of corruption. It is necessary, in the interests of the pharmaceutical industry, medical research and patients, to restore the conditions for transparent cooperation and on a renewed methodological basis.

Can independent research counter this phenomenon?

Medicine is experiencing a phase of profound changes both in the methods for collecting, validating and using new basic and clinical knowledge and in the collaborative and communicative challenges between doctors and patients or between medicine and society. These are developments that will bring further improvements in the treatment of diseases and health opportunities, provided that they are realised and socially perceivable, in the different contexts of health care decisions, more advanced guarantees of objectivity and efficiency, or higher scientific standards in the production, explanation and clinical use of information, and greater attention to ethics, or greater transparency and respect for the needs of patients and for the expectations of equality and sustainability in the delivery of treatments by healthcare systems. Developments in molecular biology make the use of science to adapt clinical research to plannable, methodological and practical objectives more critical.

In particular, clinical studies will increasingly have to take into account the individuality, on genetic and epigenetic bases, of the disease phenotype and the response to treatments: translational medicine will have to be incorporated into clinical studies if the objective is to be the precision/personalisation of treatments. Not only basic science, but also endpoints, statistical methodology and the infrastructural organisation of clinical research are experiencing advances made possible by the availability of new diagnostic technologies, and by more effective statistical approaches and computer algorithms to extract and process information.

New skills are also needed to supplement the different options for collecting and interpreting data of different types, i.e., to use them in decision-making processes for the benefit of patients and to have greater control over the failure rate of the clinical studies that have been undertaken. There are already stories of marketed drugs, e.g., Imatinib, that illustrate how the industry and academia can work together on an equal footing to push the boundaries of basic research and at the same time develop new, strategic drugs. The changes underway are questioning the existing model, opening up the vast body of clinical and biological data that can be obtained and used and, in the future, the evolution of statistical tools and smart algorithms to allow information to be used

more efficiently and in a way that works on the safety and benefits of patients. In the past, only structured data were collected in clinical trials to allow researchers to assess the efficacy of therapeutic procedures or interventions. Today, the typology includes biological samples, omics, personal metrics of patients aggregated with different technologies and collected to identify biomarkers that are potentially predictive for the therapy being studied. This approach is spreading, and interest is being focussed on the ability of omics to predict short- and long-term effects. These data will dramatically increase in quantity and predictive power when clinical trials will be combined and used to find answers to other relevant questions, including those not directly related to the main clinical trial questions. Artificial intelligence algorithms are beginning to be applied to this deluge of data and are currently being studied mainly by companies to improve the efficiency of clinical trials. However, they bear an extraordinary potential to improve research not focused on drugs, but on the best validated or most accurate knowledge, and on the benefits for patients.

Artificial Intelligence (AI) will change clinical trials and represents an opportunity to strengthen the role and impact of non-profit research. AI is already being used in the design of clinical trials, i.e., to recruit patients, monitor the levels of adherence to the clinical trial and to reduce drop-out rates. In principle, AI can be used to more efficiently measure biomarkers that reflect the efficacy of the drug being tested or to identify and characterise subpopulations of patients who are most suitable for specific drugs. If less than a third of all phase II compounds reach phase III, it is not always because the drug is ineffective or dangerous, but because the clinical trial lacks enough patients or the right type of patients. At the level of clinical trial design, AI holds great promise for patients. For instance, AI-enabled systems could give patients greater access to, and control over, their personal data; coaching via AI-based apps could take place before and during tests, artificial intelligence can constantly monitor individual patients' adherence to protocols in real time, and, finally, AI techniques could help guide patients to clinical trials they may not be aware of. In precision medicine approaches, AI promises to have a strong impact, for example as the application of technology to improve the efficiency and accuracy with which professionals can diagnose, treat and manage diseases. It has already been tested in neurological studies. Image recognition algorithms can potentially identify relevant patient populations through a range of inputs, from handwritten forms to digital medical imaging. Artificial intelligence can analyse data from a failed clinical trial to discover and gain useful insight for the design of future trials. The use of AI features such as Machine Learning (ML), Deep Learning (DL) and Natural Language Processing (NLP) makes it possible to link vast and diverse datasets such as electronic medical records, medical literature and test databases to help the pharmaceutical industry improve clinical trial design and patient matching and testing, as well as patient monitoring during clinical trials. In-depth studies are needed to assess the privacy, security and accessibility of data, as well as the ethics of applying artificial intelligence techniques to sensitive medical information. Since artificial intelligence strategies have started to be applied to clinical trials in the last 5-8 years, it will very likely take more years in a typical drug development cycle of 10 to 15 years before the impact of AI can be accurately assessed.

The purpose of independent research is to make the method more rigorous and results more robust.
The strategies of industry-led clinical trials focus on products and tend to neglect many elements of ordinary reality to build an artificial one, functional to the result. Independent research, on the other hand, usually goes to great lengths to understand the limits of treatments and side effects, to optimise new therapeutic strategies, as well as to study important but less commercially attractive areas of research and health issues.
For example, it studies rare cancers, the use of drug combinations and multimodal treatment schemes, the impact of disease and its treatments on the human body, long-term patient follow-up, problems such as resistance to antibiotics, etc.
In the new era of molecular genetics, immunotherapy, gene therapy and regenerative medicine, basic and translational research plays a crucial role in identifying and developing new treatments and strategies against degenerative diseases as well as rare diseases.
The increase in biological knowledge over the last decade has been extraordinary, so the transition from the laboratory to clinic practice is more critical than before. This can be achieved by maximising access to biological material within a simple and efficient regulatory context, within an international framework. Several relevant issues will never be of interest to the pharmaceutical

industry, including surgery, radiotherapy, systemic treatment schemes with unpatented drugs and clinical trials on de-escalation... Independent clinical trials may produce results with an average follow-up of 140 months - which do not affect the industry. Independent studies can shed light on the side effects of treatments, which in some areas such as clinical oncology make it possible to understand the equivalence of shorter treatments with immune checkpoint inhibitor, which can also save costs. Independent research can meet the expectations of patients who are often excluded from clinical trials, even though they may benefit from them (e.g., patients with rare or metastatic cancer).

Independent research conducted by academia could particularly allow focussing on the relevant clinical benefit. Academic research can optimise therapeutic strategies. Many unsolved issues are not of interest to pharmaceutical companies.

Independent academic research can play a critical role in setting priorities and defining appropriate treatments in a transparent manner, based on sound science. Independent academic research fosters and accelerates the development of precision medicine, ensuring that research produces public, accessible and usable basic knowledge, enhancing the reach of knowledge through collaborative platforms, and providing patients with the most effective controls and the best information necessary to maximise their chances of accessing new clinical trials.

Independent research can support the industry and CROs, regulators and agencies for health technology assessment through specialised expertise, strategic visions, attention to needs ignored by commercial research, as well as through the development of new methodologies and accepting the challenge of using big data.

Well-designed, fully independent, academic clinical trials can help society and patients embrace new approaches such as adaptive licensing and the implementation of new treatments, including off-label uses in clinical situations of ignored needs, optimising the administration of currently approved therapies, supporting research outcomes, reducing side effects, and addressing surgery and radiotherapy. Independent research also supports initiatives to reduce side effects, to explore surgery and radiotherapy as adjuvant treatments, to conduct population-based research and to build and share registries.

Collaborative independent clinical research platforms are better suited than commercial research to make patient rights compatible with constraints on access to new clinical trials and to optimise knowledge development. These platforms can provide guidance, for example, for cancer patients, making genetic and molecular profiling usable for clinical trials and adaptive licensing, a staggered drug approval process that allows a subset of patients with urgent medical needs to access new treatments first. These platforms could constitute a pre-competitive scheme to match the right cancer phenotype with the drug under investigation, before competitive development, while maximising the knowledge of patients whose tumours may not exhibit the relevant characteristics. The biological materials required for research are stored by independent collaborative platforms in non-proprietary quality biobanks with transparent governance and biomaterial sharing policies, inspired by the principle of sharing for drug development, rather than for commercial entities. High-quality collaborative research platforms are likely to become models for new research to shift the focus from research centred on drug development and registration to a truly patient-centred approach.

The aim is to find a suitable trial for a patient, rather than finding a suitable patient for a trial.

Patients are also likely to accept higher levels of uncertainty provided that the methodologies are defined, explained in a comprehensible way and controlled by agencies that have proven to be reliable. It is therefore possible to imagine, in the context of independent research, the use of Bayesian logic, preclinical reasoning, non-controlled studies, observational tests and analyses of retrospective cases, as well as anecdotal cases and traditional results of large or small randomised clinical trials. Adaptive clinical trials in general, with their potential for flexibility when properly applied, are today's frontier of clinical research.A cornerstone of independent research is scientific review by peers, i.e., scientists and statisticians, who have no direct or indirect interest in the research or results. Its purpose is to improve protocols and control data. Methodology, aims, statistical design, primary end points and scientific relevance are the main focus of the peer review. Peer review is not a perfect system, but it has been the only effective way to check the validity of research results or to predict the functionality of a methodology since the beginning of modern science. Independent research or-

ganisations are particularly attentive to the independent management of data and to database manipulation through the Independent Data and Safety Monitoring Committee or Board (IDSMC/IDMSB), which consists of an independent group of experts who monitor data related to patient safety and treatment efficacy while a trial is in progress. To eliminate potential bias, independent research adopts strict rules on analysis and reporting: all results, including negative and unfavourable ones, must be reported within a reasonable period of time, authorship must be predefined in the protocol and all authors must have access to the trial data. The circulation of knowledge between basic research and clinical practice is an essential precondition for continuous progress in understanding cancer biology and the development of new treatments. Many candidate drugs enter clinical trials without proper understanding and documentation of the biology of the targets, thus explaining the failure at later stages and dropout rates. Several stories, such as those of Gefitinib and Vatalanib, illustrate the problems that can arise in the absence of an adequate circulation of knowledge. In addition, it will be possible to reduce the number of clinical trials with a suboptimal design, an important benefit in itself, resulting in the reduction of the high dropout rate and of unnecessary exposure of patients to investigational treatments that will prove to be ineffective. Several areas need to concentrate limited resources and avoid duplication. Today, patient subpopulations can be selected in more optimal ways based on prognostic and/or predictive biomarkers. While technological development is improving the predictive value of tests, these markers can help to find the right doses for the target population. There is an increasing number of large banks of biological samples from patients participating in trials and having a consistent treatment history with related clinical and pathological data, which provide a unique opportunity for the retrospective analysis of archived specimens and prospective evaluation that can serve as optimal access to clinical trials based on target selection. The broader economic impact of precision medicine will be linked to the use of biomarkers to avoid unnecessary treatments and predict adverse drug reactions.

Independent research consistently produces clearer results and less false positive results, for the simple reason that the donor has no personal interest in the result. Regulatory authorities should therefore require the industry to have a clinical trial conducted by an independent research institute in each phase three of the core stage. This allows health technology assessment institutes to determine the actual value of a new drug. A comparison with existing treatments will increase the quality of research by expressly assessing the added therapeutic value of a medicine. Several governments, including Italy through AIFA, the UK and Belgium, are using different ways to fund independent clinical research.

Over time, data sharing has become a strategic element in the synergies that amplify the impact of clinical trials. In order to facilitate data circulation, medical journals call for authors to include a data sharing plan as part of clinical registration. Data from well-designed and well-conducted clinical trials are not only useful for the original purpose and secondary analysis by the original researchers, but can be used in a variety of applications, including the independent replication of a clinical trial, to avoid duplication, to generate or test new hypotheses, and to advance biological explanations and clinical practice. Indeed, it is widely accepted that giving credit to data generators is a key incentive for data sharing. In January 2016, the International Committee of Medical Journal Editors (ICMJE) recognised that it is an ethical obligation to responsibly share data generated by clinical trials as participants put themselves at risk. This position has been shared by foundations, government agencies and the industry, which finance trials. The IMCJE put forward as a condition for the publication of a clinical trial report in journals that authors be required to share, with others, anonymous data (including metadata) of individual patients and the results presented in the article (including tables, figures and appendix or additional material) no later than 6 months after publication. Today, the use of research data by people other than those who originally collected the data, called "data sharing," is encouraged by national laws and regulations on clinical trials, as well as by public and private bodies, journals, etc. The care of data and associated metadata collected during the original project, to make them available to third parties in useful forms, is a work that sometimes continues for decades and there is seldom academic recognition or reward for sharing data. For reasons of fairness and to encourage data sharing, those who initially collected the data should receive appropriate and standardised credits that can be used for academic progress, grant applications and other personal interests. This is why an acknowledgement system has

been suggested whereby data generators are identified and cited by means of a standardised designation differentiated from the designation of the authors of an article in peer-reviewed journals.

While improving or encouraging data sharing is a strategic objective, good data management is the key to promoting discoveries and innovations, as well as their integration and re-use by the scientific community after publication. The data have four potential owners: the patients participating in the trial, the public, the researchers and the clinical trial's sponsor. There is an urgent need to improve the infrastructure to support the re-use of academic data. A diverse set of stakeholders - representing academia, the industry, funding agencies and academic publishers - met in 2014 to jointly design and approve a concise and measurable set of principles called the FAIR Data Principles. The existing digital ecosystem that governs the publication of academic data often limits the possibility of reaping maximum benefit from investment in research. Also, research financing entities, publishers and government agencies have begun to require data management and plans to manage data generated in publicly funded research. In addition to adequate collection, annotation and archiving, management includes the concept of "long-term maintenance" of valuable digital data, with the aim that it should be discovered and reused in downstream studies, either alone or in combination with de-novo generated data.
The results of good management and good data management are therefore high-quality digital publications that facilitate and simplify this unceasing process of discovery, evaluation, and reuse in downstream studies.
In order to define the "good management of data", the objectives and expectations have been clearly set out, providing simple indications to inform those who publish and/or store academic data that could be of great use. Ideally, any anonymous data obtained in the context of clinical trials, including those sponsored by the industry, should be made available to other stakeholders in accordance with FAIR principles, i.e., Findability, Accessibility, Interoperability and Re-usability - in compliance with ethical, legal and social constraints. The goal is for them to serve as a guide for those who wish to better manage and leverage their data reserves. The FAIR Principles focus specifically on improving the ability of machines to automatically find and use data, as well as supporting their reuse by individuals. This commentary is the first formal publication of the FAIR Principles and includes the rationale behind them and some examples of their implementation in the community. Good data management is not a goal in itself, but is rather the key to knowledge discovery and innovation.

It is essential to train the next generation of clinical researchers, transferring key knowledge about nature and the organisation of the infrastructure needed to assemble databases, which will have to be used repeatedly to answer various questions and can potentially open the way to scientific discoveries without incurring new costs. It is an independent research task. The Workshop on Methods in Clinical Cancer Research, for example, is a training programme that introduces junior clinical oncologists in any oncology sub-specialty to the principles of a good clinical trial design. This workshop has existed since 1999 and is acknowledged and accredited for CME credits.
Over years it has improved the value of the training provided. Knowing how to design and conduct high-quality clinical trials is critical to the progress of new therapies. This seminar was set up to reverse the decline in the number of clinical scientists. The ultimate goal is to develop a strong and ever-expanding base of well-trained clinical researchers by providing them with the essential training to conduct better clinical and translational trial projects.
Participants propose a trial protocol when applying for the Workshop and complete writing the protocol during the Workshop. The development of the protocol is not intended to be a practical exercise as participants are required to make every effort to implement their own protocol. Patients too need to be informed about these approaches as they will be partners of the researchers in carrying out new approaches.

Recent scientific and technological advances require increasingly extensive collaboration. In a period of scarce public funding for basic and pre-clinical research and drug development (along with higher regulatory barriers), the results continue to be discouraging and call for new and collaborative approaches for continued success. There are examples of how clinical research is being reorganised to more effectively address the challenge of integrating the unmet health expectations of traditional research with the opportunities offered by

advances in basic research to overcome some of the obstacles on the path to the development of new drugs. The recent history of three diseases - cystic fibrosis, multiple myeloma and type 1 diabetes mellitus - illustrates how collaborations between academic institutions, foundations and companies have evolved to meet the challenges. Given the high failure rate in the development of new therapies in the pre-clinical phase, also called the "valley of death" for this reason, and given that therapies for certain conditions may have limited market value, the pharmaceutical industry is reluctant to launch early-stage programmes for the treatment of so-called orphan diseases. Based on programmes developed by federal agencies in the United States to catalyse innovation and reduce barriers to early development of new therapies, foundations dedicated to promoting research on individual diseases have developed a new approach to bridge the preclinical gap, which has been called "venture philanthropy": it consists in entering into collaborative agreements with the industry and federal agencies to share the financial risk of therapeutic development, shorten the translational pipeline in the initial phase and advance research with the primary aim of responding to expectations of care for patients. Foundations and their partners have accelerated the initial development by providing access to patient populations for clinical trials and assistance by disease-specific experts in the design of clinical trials, which has helped bridge the gap between different plans in the process of discovery and therapeutic validation. These collaborations, between foundations, academic centres, federal agencies, the industry and patient advocacy groups, have achieved major successes by leading the way in improving patient outcomes. In each of the cases mentioned, none of the main advances achieved could have been made in a timely manner if the partners had worked independently. Advocacy groups and foundations are finding creative ways to create synergies between the efforts of many partners to accelerate progress. Accessing funding for these new models remains a challenge, but with powerful partnerships and the success of some of the cases that have paved the way, there are now precedents to continue to promote and support innovative partnerships.

Conclusions

The reasons why, in the Western world, political and economic investments should be made in clinical research, favouring a strengthening of the so-called independent component, and why Italy, in particular, should reorganise its own regulatory and infrastructure system for clinical trials, lie in the fact that this responds to patients' demands for innovative, safer and more effective care and contributes, by increasing competitiveness and attracting investment, to the efficiency and sustainability of the national health service, as it increases the degree of appropriateness of clinical choices. In particular, independent research is focussing on so-called unmet clinical needs and on the integration and use of scientific knowledge in the development of new therapies, concentrating on both efficient strategies for data production, management and use and on tailoring new therapies for individual patients. In this sense, non-profit research emphasises the importance, both scientific and ethical, to study populations (and diseases) neglected by sponsored research, which aims to bring a product for sale to the market. Independent research has an interest in comparing new therapies with those already established and in pursuing objectives, such as treatment safety and the adequacy of diagnostic pathways, and in developing observational research models or models seldom pursued by industrial sponsors, and possibly adhering to the real world. It is strategic to promote the integration between research and training, taking advantage of the opportunities of a changing research (personalisation of therapies, artificial intelligence, patient-centred care and ethical issues).

Non-profit research is therefore instrumental both to the improvement of health care and to the economic and social development of the community in which it is conducted.

From this point of view, it is a strategic resource for the Italian National Health System, complementary to industrial research, and drives innovation and therefore qualitative developments for university medical departments. Italy should invest in clinical research also because of the competitive advantage of hosting researchers who are among the best in the world.

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