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The Technological Transfer and the spin-offs' creation in healthcare industry

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INTRODUCTION

In the third millennium, the ability to compete at the global economy level will largely depend on the possibility of generating "innovation", that is, the ability to develop new products, apply new technologies, and successfully access new markets [Jones-Evans et al., 1999]. Technology is the real engine of progress and wealth creation, and it is common opinion that it represents on the one hand the opportunity to improve the services and products offered, on the other a threat in the event that companies fail to stay in step with technological advancement [Dorf and Worthington, 1990]. Companies have always invested heavily in internal research and development departments to create innovation and provide sustainable growth [Chesbrough, 2006], following what has been called a "closed" innovative approach. However, at the end of the 20th century this model cracked, and a number of contextual factors caused the shift from a "closed" to an "open" approach.

The rising costs of R&D, in conjunction with the shortening of product life cycles, has made it more difficult for companies to justify large investments in innovation. At the same time, technological convergence [Levinthal, 1998], the growth of inter-organizational relations [Hagerdoorn, 2002] and the strengthening of Intellectual Property regimes have led to a more open vision of the management of technological innovation. Several trends show how external sources are becoming increasingly relevant in the innovative strategies of the business world. The knowledge necessary to innovate, in fact, is today generally more dispersed and fragmented over a greater number of actors [Chesbrough, 2006], since the products include a wider set of technologies, and the categories of subjects involved in the innovation process are they are progressively diversifying.

Open Innovation is the term with which Henry Chesbrough defines this phenomenon, distinguishing two mirror levels: on the one hand, Inbound Open Innovation, that is, the practice of exploiting the technological discoveries of other players and gaining a competitive advantage, on the other, Outbound Open Innovation. The latter approach suggests that companies, instead of relying on internal paths to reach the market, may seek external organizations, with business models more suitable for commercializing a given technology [Chesbrough, 2006].

Faced with an ever-increasing interest on the part of the business world in the themes of open innovation and a progressive expansion of the markets for technology, one can ask at this point whether there are organizations that are more suitable than private companies to take the road the external exploitation of technology. Businesses can be inhibited by a series of factors inextricably linked to operating in a highly competitive environment. The literature, therefore, has focused in recent years on a category of organizations with structures and objectives that are completely different from those of the business world, but which at the same time constitute an important source of technological innovation: universities.

The University role

Since the early 1980s, an intensification of collaboration between universities and businesses has been observed [Levy, Roux and Wolff, 2007], which has quickly become the subject of an economic, political and social interest, as well as an integral part of the debate that revolves around the relevance of universities in today's world [Horowitz, 2007]. History highlights how the scientific community has always provided and conveyed knowledge to the socio-economic system, both through scientific publications and through training and the mobility of human resources. Cesaroni et al. (2005) recognize that since the 1980s there has been a profound evolution of the international context which has led to an overall rethinking of the role of the University. This transformation took place following a set of contingent factors, among which we must remember:

1. The reduction of public funding for research which has introduced the need to find alternative sources in the private sector;
2. The growing interest on the part of companies, even small ones, to access sources of external knowledge;
3. The increasingly widespread "scientification" of technologies: in many industrial sectors some research results represent real components of the innovative process
4. The emergence of new disciplines as a result of the hybridization of pre-existing disciplines;
5. Greater social expectations towards the University, which is required to act in line with regional or national priorities in the field of economic development.

To these, the growing recognition of knowledge as a strategic resource of competitive advantage must necessarily be added. This configuration of the relationship between the scientific system and the industrial system characterizes the process of knowledge production according to the "Mode 2" conceptualized by Gibbson et al. (1994).

The European university scene (and not only it) has been strongly influenced by the advent of the so-called "knowledge society" (van der Zee 1996; Strain and Field 1997; Delanty 2001) which has determined a substantial transformation of the main institutions of knowledge production and among them above all the universities. The missions, the services to be offered and the functions to be performed have changed, because university institutions, as structures for the production and transmission of knowledge, play a decisive role in the context of the knowledge society.

When looking at universities as centers of knowledge, it is possible to distinguish three "roles" or "missions" [Martinelli, Meyer and Von Tunzelmann, 2007]. Initially the university was conceived as an institution with the aim of providing a high-level education (teaching mission), later adopting a knowledge generation function (research mission). In both these levels the institutes maintain greater autonomy of action and can be seen as indirect ways for technology transfer [Horowitz, 2007]. In recent years, especially in the 1990s, the university has begun to take on a "third mission", namely that of contributing in a more direct way to economic and social development.

Similarly, the main Public Research Bodies (EPR) have also invested efforts and resources in technology transfer. With the term Third Mission we mean the generation, transmission, application, and safeguard of knowledge for the direct benefit of actors and groups outside the core academic bodies. Being presently considered fundamental

co-actors in the knowledge transfer process, to the productive sector and service (McQueen and Wallmark 1982; Chiesa and Piccaluga 2000; Benneworth and Charles 2004; D'Este, Mahdi and Neely 2009), academic institutions do not cover anymore this role only by granting patents to outsiders, but are more dedicated to promotion, creation and support of new enterprises for the economic and social exploitation of scientific research results, an aspect considered the Fourth Mission of universities (Geiger 2006; Kretz e Sá 2013).

In this way, universities have begun to actively contribute to economic development, transforming themselves into "entrepreneurial universities". Clark [1998, 2004] identifies 5 necessary conditions for the change towards what is called an "entrepreneurial university":

- an expanded perimeter, which goes beyond traditional university borders, and which includes interdisciplinary offices or research centers in more flexible organizational contexts;
- an adequate incentive for academic staff;
- an integrated entrepreneurial culture;
- a diversification of the origin of the funds;
- a strengthened leadership center.

Tijjssen [2006] explains how there is a common trajectory that universities follow in embracing their "third mission" through a model that is divided into three successive phases, one after the other. In the first phase, the university conducts basic research, identifying, at the same time, possible links between research activities and business opportunities. A gradual evolution leads the university to recognize the commercial potential of its knowledge-assets. Phase two, concerns an initial development of commercialization possibilities, in which the university explores the compatibility between its assets and the needs of potential users. Finally, in phase three, the university secures the rights claimed on intellectual property, conducts market studies, draws up business plans, transforming itself into a sort of company, without however the legal status of a company and the objective of generating and maximizing the profits. By going through the three phases, the university approaches an increasingly business-oriented logic, gradually acquiring new managerial and organizational skills, as well as new structures.

This model of "entrepreneurial university" has placed the problem of industrial and commercial enhancement of the technologies produced by the research activity at the center of attention, in order to benefit both in economic terms and in terms of image.

The university world fits into the economic world by generating and transferring knowledge, and to do this, universities must necessarily equip themselves with dedicated and specialized structures in the management of technology transfer: the Technology Transfer Offices (TTO).

According to what was written in the 2018 Netval Report, the first TTO of universities were established in the 1990s, but it is only between 2001 and 2008 that most universities have established a specific office, with a boom in the years since 2004 to 2006. One of the many reasons why there has been this peak in the aforementioned years is the entry into force of Ministerial Decree 593/00 and Legislative Decree 30/2005 as well as the Ministerial Decree of 5 August 2004, n. 262 art. 12, which respectively sanctioned the possibility of acquiring ministerial

funding for the activation of spin-offs, the rules in the field of intellectual property protection and the possibility of obtaining co-financing for state universities that intended to establish or support internally "industrial liaison office". By now, in fact, almost all universities and public research bodies have a formalized TT structure.

The Technoloy Transfer mechanisms that the university can implement can be identified in three main ways (Coccia, Rolfo, 2002; Compagno, 2006):

i. The dissemination of knowledge through scientific publications
ii. The training of a workforce with high transversal specialized skills
iii. The commercialization of knowledge, which can take place through multiple operational mechanisms.

These latter mechanisms translate into new ways of economic exploitation of research, among which the main ones are:

a. Research spin-off companies, which were created with the aim of bringing the results of applied research to the market (Consiglio, Antonelli, 2003; O'Shea et al., 2005, 2006);
b. Joint University - Enterprise research projects (Cohen et al., 2002);
c. Advanced business consulting services (Agrawal, 2001; Compagno et al., 2006);
d. Protection of intellectual property - through patents and utility models (Hall, Ziedonis, 2001; Mowery et al., 2002) - and transfer or license of the related rights.

CHAPTER 1: THE TECHNOLOGY TRANSFER

Based on the definition of the Treccani Encyclopedia, technology transfer is "the set of activities carried out by research centers aimed at the evaluation, protection, marketing and commercialization of technologies and, more generally, the management of intellectual property developed in 'scope of research and development projects conducted by the academic world".

In summary, the Technology Transfer (TT) defines the process of converting scientific discoveries into products and processes that companies can make marketable.

The technology transfer system seeks to bring together the demand (businesses) and supply (universities and research centers) of technology.

The exploitation of knowledge has become a foundational asset for assessing the competitiveness of a country, and growth policies increasingly emphasize the crucial role of intangible resources, such as skills and innovative ideas. In this context, technology transfer is a very important activity to pursue objectives of economic and social progress, as well as being an instrument of strategic importance as a source of funding for university research (Villani, 2018).

The possible activities that fall under the definition of technology transfer in its various forms are:

- Support for the creation of spin-off companies
- Management of intellectual property;
- Management of licensing activities;
- Dissemination of information and announcements;
- Request for information and advice;
- Participation in mixed working groups;
- Management of research and consultancy contracts;
- Management of seed capital funds;
- Management of science parks and incubators;
- Management of research funds;
- Provision of technical services.

The function of technology transfer understood in a broad sense, therefore, is a way to speed up the impact and the wide dissemination of new knowledge both in society and in the market. In general, however, the most cited technology transfer activities are those that are commonly classified into two main categories:

i. the patenting of research results and the licensing of the related intellectual property to existing companies
ii. the development of new so-called "research spin-offs".

1.1 The technology transfer process

The process of technology transfer comes to life when the researchers have achieved a research result, and must therefore, together with the Technology Transfer Office (TTO), evaluate the path to be taken among several alternatives summarized in Figure 1.

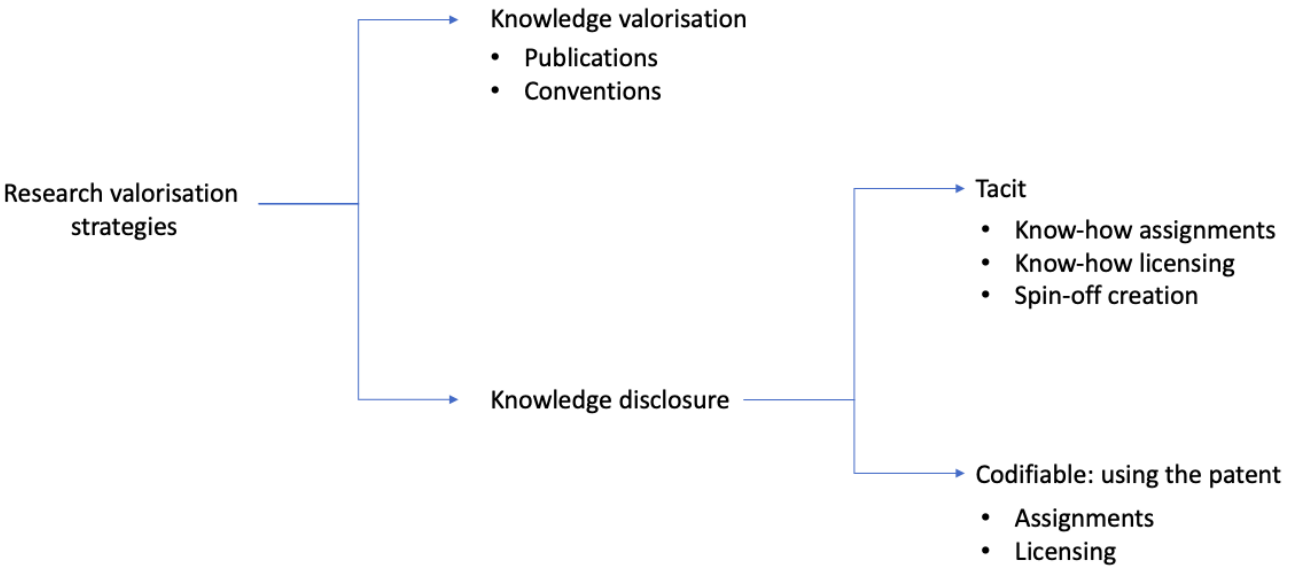

Figure 1: Research valorisation strategies - Source "Tesi di Laurea Magistrale - Politecnico di Torino"

On the one hand, it is possible to opt for the dissemination of the knowledge produced without any legal protection with the desire that it be freely used; this can be done through publications or conferences. This option is chosen both when it is not believed that there is an economic potential to be exploited, or in the wrong cases, which should not be taken as an example, in which the researchers decide to publish the result, in search of immediate prestige, but burning every possibility of legally protecting the result, by eliminating the novelty requirement, required for patents.

On the other hand, there is the opportunity to adopt legal protection tools for the inventions obtained and try to promote them. In this case, you may find yourself at a crossroads depending on the nature of the invention. If the result obtained is of a codifiable nature, it is possible to evaluate the details for patenting the invention and consequently to think about which strategy to use, such as the definitive assignment or the assignment under an exclusive or non-exclusive license.

If, on the other hand, the result is tacit in nature and the codification necessary for filing the patent application is therefore impossible, other strategies can be used, such as: the transfer of know-how through consultancy services by the personnel with knowledge, or in alternatively, the inventors, who are the holders of tacit knowledge, could decide to create a company based on their research results, in this case the collaboration of the TTO can be of considerable help, for the phase of setting up spin-off companies.

Summarizing from this example it is possible to identify the main activities for the enhancement of a research result: the protection of intellectual property that involves licensing or assignment of the patent, the creation of spin-off companies, the stipulation of research contracts with which to transfer knowledge.

These three mechanisms mentioned are the most widespread, but it is important to underline that they do not represent a complete list of all possible transfer activities, nor are they mutually exclusive to each other.

Here the focus will be on the activity concerning the development of research spin-offs.

1.2 The technology transfer offices and their role in the TT process

Technology Transfer Offices (TTOs) act as a formal interface between universities and various external organizations including business, government, and other research facilities. Although the functions of the various structures may differ between different universities or research institutions, and even from country to country, the TTOs are dedicated to coordinating all aspects of technology transfer activities, from the development and subsequent dissemination of patenting policies and strategies, to the actual management of business relations and licensing activities, up to the organization of forms of support for academic start-ups [Jensen et al., 2003, Rasmussen, 2008, Louis et al., 2001]. Regarding this last point, Wu [2007] shows that many TTOs provide assistance in drafting business plans, in contacting venture capitalists and in recruiting start-up teams.

The ultimate goal of TTOs is to reduce the barriers that culturally separate the academic world from the industrial world and to facilitate interactions between the two subjects. In particular, the offices can contribute to spreading awareness among the academic reality of the benefits that technology transfer activities can bring, for example by organizing seminars, conferences and events in order to sensitize researchers on Intellectual Property and commercialization issues [Baldini, 2010].

To adequately carry out this set of tasks, the professionals involved in the TT process must possess a series of specific skills, including in-depth knowledge of patent and legal matters, strong negotiation and marketing skills, skills related to database construction and networks of personal contacts, and an easy understanding of the market and business activities [Charles and Howells, 1992]. Finally, TTOs must understand both the culture and functioning of academic research and that of the private business sector, and use their experience and skills to be able to make the two realities communicate with each other [Powers and McDougall, 2005].

The TTO, therefore, can be considered a catalyst as it intervenes in the process of technology transfer to accelerate it but without modifying it and acts as a trainer, translator and facilitator of the process.

The TTO manager must consequently interpret the various request messages or the specific expectations of the parties involved; he must be able to dialogue with all the actors in the process and to do this he must be able to understand the different objectives and carry out the various preparatory activities. [Conti, Granieri and Piccaluga, 2011]

As regards the organization of the TTOs, there is no single form of organizational structure in an absolute sense, however, it is possible to note two prevalent trends linked to two macro factors. The first concerns the lifetime of

the TTO (or more generally the lifetime of the technology transfer activities). The second is related to the process or activity to be implemented. Regarding the latter trend, we can note an outsourcing of functions related to the enhancement or marketing of research results or patents and, instead, an internalization for technology transfer activities such as scouting and the selection of inventions / technologies to protect.

A reference point for classification in terms of organizational model is represented by the ownership structure of the TTO and consequently by the relationship with the university or with the research body.

The TTO can therefore be classified as from the following list:

- An internal office at the university / research institution;
- A for-profit company controlled by the university / research institution;
- A non-profit organization controlled by the university / research institution;
- A profit company linked to the university / research institution by a formal agreement;
- A non-profit company linked to the university / research institution by a formal agreement

It is therefore clear that there is the possibility of structuring the technology transfer activities according to different approaches.

The TTO is therefore the structure that mainly deals with the management and transfer of intellectual property belonging to the University or EPR in which or for which it works, and which plays a fundamental role in the relations between public research and the market.

It is possible to identify several names attributed to identical structures:

- Technology Transfer Office;
- (Industrial) Liaison Office;
- Knowledge Transfer Office;
- University Industry Linkage;
- Contract Office;
- Office of sponsored research;
- Patenting and Licensing Office;
- Business Development Office;
- Office of Technology Licensing.

In truth, many of these structures have the same objectives and carry out the same processes but from the simple name it is possible to guess the emphasis both in terms of strategic direction and operational activities of the TTO.

1.3 Skills in the field of technology transfer

Having clear the concept of technology transfer and TTO, it is possible to deduce that to strengthen the development and affirmation strategy, it is necessary that institutions such as universities or research bodies have

at their disposal skills of a certain caliber and of a high quality; this necessarily calls into question the questions relating to university and professional training.

The creation of skills in the field of technology transfer must be approached with reference to two possible levels of interest and actors:

- universities and public research bodies which, as their mission, generate knowledge, technology and, progressively, intellectual property which must be protected by carrying out all the activities functional to the transfer;
- companies that should acquire and exploit knowledge and technology.

Institutions that generate knowledge should ensure such a level of literacy on the issues of intellectual property protection and technology transfer in the public and private sector, such that students and doctoral students can become future managers and / or future researchers in conditions of knowing whether, how, when and why to protect the fruit of one's own (and that of colleagues') intellectual activity.

The European Commission, in fact, has set the goal of ensuring that every european student of scientific subjects receives a basic level of education on intellectual property by completing their higher education; therefore, the matter of intellectual property protection will no longer be the exclusive prerogative of the legal faculties [Conti, Granieri and Piccaluga, 2011].

Even companies, typically the larger ones, carry out (industrial) research activities, for which they have similar needs to those of universities and public research bodies as regards the generation and protection of knowledge and technology. At the same time, they also have diametrically opposed needs with respect to the technology transfer carried out by the public body, because they are placed on the side of those who buy and therefore represent demand.

Whatever the point of view from which to address this issue, it is easy to conclude that these skills are essential for the very success of any technology transfer strategy. Knowledge of the respective points of view should, ultimately, favor the meeting, which is difficult, between supply and demand for innovation.

The functional model of the TTO is based on a set of activities starting from the invention up to the stipulation of a license agreement with a company or the creation of spin-offs. In detail, the TTO begins by dealing with the coding of Intellectual Property (IP) through protection usually by means of a patent in order to make it suitable for transfer. Once the Intellectual Property Right (IPR) has been acquired, the TTO can proceed with the commercial enhancement that can take place through Licensing PI, which leads to the stipulation of a license agreement (licensing), through the creation of spin-offs or through negotiation of research or development contracts (Contract Research Negotiation), which involves obtaining external financial support.

In the specific case in which the ultimate goal of the TTO is the creation of a spin-off, given that the latter can be created on the basis of the non-formalizable or protectable know-how developed by the researcher in the course of his activity at the university, you will not need a patent or IPR, but the input will only be the IP.

The Contract Research Negotiation process, on the other hand, will have as its object the research skills of academic staff and will lead to the definition of research contracts with a financing company, aimed at finalizing, in application terms, those same basic skills, or research results. The result will be a new IP which presumably will be suitable to be protected and then commercialized to feed the entire process again.

Taking into consideration all aspects of the quantitative assessments to which we are and will be subjected, it is also appropriate to find the balance between the securities to be abandoned because they are commercially unattractive and those to be maintained.

1.4 Life cycle and phases of a Technology Transfer Office

From an operational and process planning point of view, some phases of the activities managed by the TTO are distinguished:

- Phase I: patent culture. The TTO informs and involves the internal staff of the EPR / university in order to make the management of its research results more aware and responsible.
- Phase II: the selection of patents and the creation of new businesses. The TTO begins the real management of the patent portfolio and of the first spin-off companies.
- Phase III: research monitoring and agreements with the industrial world, enhancement through licensing.
- Phase IV: the management of intellectual property in the various forms of cooperative research, through an evolution of the patent protection and exploitation strategy.
- Phase V: the growth of spin-off companies and access to risk capital. In this phase, on the one hand, a series of policies must be developed related to the investment and divestment of the EPR / university in the share capital of the spin-off companies, but also to the conflict of interest and competition of the research staff involved in the phase start-up of the spin-off company. On the other hand, spin-off companies must be selected and supported in the growth phase.
- Phase VI: the diversification of services, the new organizational forms of the TTO, new business models for the management of intellectual property. All the various forms of property rights to protect the research results must be evaluated, as well as the various organizational forms of management of macro processes or individual process activities.

From some empirical evidence we can see a trend in Europe of partial outsourcing of some activities, such as marketing or negotiation for licensing according to the type of patents in the portfolio and its critical mass and the possibility of drawing on specific skills within the EPR.

In the perspective of the future Horizon Europe program (European Framework Program for Research and Innovation, whose objective is to strengthen scientific and technological excellence by creating a European research space) the role of technology transfer will be key for supporting the creation of an innovation-friendly environment that makes it easier for great ideas to be turned into novel products and services.

1.5 The impediments to technology transfer

The novelty and the difficulty of the technology transfer matter is evident since there is no single professional figure who controls all the required knowledge. Indeed, a competent figure in the fields of law, economics, technology, organizational studies, knowledge management, sociology of science and many other aspects would be needed.

Siegel et al. [2003] emphasize, in fact, that one of the main difficulties complained of by industry managers during collaborative relationships with universities is represented by the lack of understanding that researchers have of business rules and principles. This brings to light the intrinsic conflicts between "open science" and "private science", due to the different perspectives, respectively of the academic and industrial world, through which the process of innovation and diffusion of new technologies and knowledge is seen [Fabrizio, 2006]. These perspectives may differ due to:

- **Differences between goals.** Those who work in the academic context are strongly oriented towards the development of knowledge and the related publication and dissemination activity. A possible negative effect seen from the researchers? perspective, in fact, consists in the danger that the TT could lead to a delay in the publication of new scientific results [Blumenthal et al., 1997], and damage the teaching function of the university, as commercialization constitutes a time-consuming activity [Louis et al., 1989, Stephan, 2001]. Furthermore, the researcher often works in contexts that tend to be mono-disciplinary and over relatively long periods of time. Finally, he covers a multiplicity of very different functions, such as research, teaching, administrative and collegial activities. On the contrary, those who work in the company are oriented towards the industrial use of knowledge, work on complex and interdisciplinary problems, have very short investment horizons ahead of them and are active on a relatively limited set of functions;
- **Different nature of knowledge.** The literature has repeatedly emphasized the different nature of the knowledge developed and used in the fields of research and industry: explicit and codified in the first, tacit and not codified in the second. This difference requires a work of "translation" and "absorption" of knowledge by the company, so that it can integrate it into its processes and then use it.

These two differences explain some of the difficulties that are intrinsic to technology transfer activities, and which highlight the need to give birth to specific activities and institutions that know how to mediate between the objectives and languages of the two sides, academic and industrial.

A further factor that makes technology transfer difficult is that the latter presupposes a legal instrument of control through which such results can be conveyed to the market. From the management point of view, a means has always been the ownership of rights, that is, a juridical power over, and the consequent legitimacy to dispose of, certain resources. The regime of ownership of intangible assets depends on the rules of the state, so the issues of ownership can vary from one jurisdiction to another. At present, this intuitively represents a difficulty whenever individuals and institutions of different legal systems are involved within the same research group, because the

potential co-ownership of the research results could be supported by different rules. Obviously, the persistence of an unfavorable regulatory situation inevitably discharges on research institutions the role, not always easy, of finding a balance at the contractual level.

Another cause of uncertainty is the fact that, in the face of a few extremely significant financial successes, linked above all to the intrinsic value of some revolutionary technologies developed by university laboratories, the returns from TT's activity have been disappointing for many universities [Holstein, 2006], and this is a consequence only partially attributable to the "buying side", that is to the lack of commitment of the companies that receive a new technology, which leads them to underestimate a valuable Intellectual Property and not to exploit it adequately in commercial terms [Klien et al ., 2009].

CHAPTER 2: THE PROCESS OF VALORIZATION OF RESEARCH RESULTS

The realization of a technological innovation goes beyond the genius of an idea. As already mentioned, the strategies for research enhancement are manifold. Here we want, therefore, to proceed with a more in-depth narration of the processes of each strategy. In particular, it will deal specifically with the process of protection and enhancement of intellectual property, the process of creating a spin-off company and finally, the Contract Research Negotiation process.

2.1 The process of protecting and enhancing intellectual property

This process takes shape through the six different phases listed below:

- Identification of the IP: the enhancement process begins with the disclosure phase, that is, the researcher informs the TTO of the existence of a result that he believes is suitable for being patented. The TTO, therefore, should at this point carry out the scouting activity in order to promote greater consistency with national and European research strategies. In reality, however, this does not always happen, the TTO mostly plays a passive role by not implementing a formal control over the research activity. This is due to the fact that this activity is expensive in terms of man / hours and therefore is not always sustainable in the short term.

  The identification of the IP is formalized through the drafting of a disclosure form (DF): the document is compiled by the researcher with the support of the TTO and is intended to briefly describe the invention to be patented. In some cases, there are some variations to the IP identification phase. In particular, disclosure does not take place only through the TTO but, through an initial simplified documentation, also through the university structures that deal with the management of research contracts and that immediately carry out an assessment on the ownership of the IP, verifying whether it can be attributed to the university or, on the contrary, it is up to the funding organization.

  A problem may arise in this phase as not all researchers are interested in the patenting and subsequent commercialization of the technology, especially when they mistakenly believe that these activities may delay the publication of the results of their research. The problem is mitigated by the action of the TTO which acts through:

  - the publication of patenting guides and the organization of courses aimed at academic staff in order to spread a culture based on IPR;
  - the drafting and implementation of procedures for the evaluation of patent requirements that are as streamlined and fast as possible in order not to excessively delay the moment in which it will be possible to publish.

- Filing of the patent application: if the disclosure phase has achieved positive results and authorization is obtained to proceed, the phase leading to the filing of a patent application begins. The TTO in this phase is in charge of selecting a law firm-agent (patent attorney) who will be in charge of the formal drafting of the patent document. Generally, most TTOs opt for a first national filing in order to be able to quickly draw up a first application and obtain the priority date, and then, after obtaining the first response, decide to proceed with the extension of the patent at European level. However, nothing prevents you from modifying the application before the extension or possibly withdrawing and reformulating it according to the information received.

- Patent enhancement (out licensing): The process involves the execution of a series of sequential steps that lead to the negotiation of a license agreement by which the use of the patented technology is granted to a third party compared to the university.

- Marketing: The marketing activity aims to promote the marketing of the patent to businesses or, more generally, any organization interested in technology. It is ideally placed after the filing of the patent application but in reality, it is a phase that begins already during the evaluation of the patent requirements.

- Organizational evolution: from In to Out: The output of this phase consists in the selection of a small pool of possible interested licensees with whom to undertake the negotiation phase.

- Negotiation: Negotiation provides for a first intermediate output consisting in the selection of the company that will become the licensee and subsequently the finalization of the licensing agreement. In this phase the economic terms of the contract are agreed. Typically, the payment takes the form of a flow of royalties linked to the volumes invoiced by the licensee, which is then divided between different subjects as specified by the intellectual property policies developed by the universities.

2.2 The Contract Research Negotiation process

The process involves the implementation of two sequential macro-phases: marketing and contract negotiation:

- Marketing

  This is the activity that aims to enhance research skills towards the industrial sector: it is therefore a question of favoring the matching between the research or technology demand expressed by companies with the offer expressed by researchers. The TTO is certainly in a privileged position to carry out this activity given the contacts it is potentially able to generate, both with researchers and with the business world. However, given the chronic scarcity of resources of these structures and the very high level of effort required, it is easy to find in the national context that the TTOs do not carry out this activity. Except

in exceptional cases, where the territorial thrust and need is very strong, there are in fact third parties, of various kinds, who try to carry out this task (associations, consortia, foundations, intermediaries and consultants).

The output of the marketing activity is, therefore, the identification and selection of industrial partners towards which to direct the subsequent negotiation activity.

- Negotiation

  This phase can see the TTO engaged in the total negotiation of the contract including the commercial aspects or only the aspects related to intellectual property. In this case too it is easy to see a strong lack of homogeneity at the international level, and within the community. In Italy it is unusual to detect strong negotiation activity, in the field of commissioned research, which may concern the definition of the economic value of a research project and the related negotiation. In Spain, on the other hand, it is very frequent that TTOs can intervene in this activity and phase of research management.

  The dynamics of management of research activities have always had a strong individualistic connotation as it is the single researcher who typically provides the interconnections with industrial subjects interested in his skills. The purpose of the research and its economic value are negotiated by the researcher with the client company. The negotiation of intellectual property clauses only requires less involvement of the TTO: when the TTO intervenes in the negotiation phase all the other aspects have already been clarified. If, on the other hand, the negotiation of the entire contract includes the confidentiality clauses and all commercial aspects, the latter is more complex and would require the ability of the TTO to know how to evaluate the value of the research and mediate between the parties, trying to mediate the needs expressed by the researcher or by the research group and by the funding company, trying to safeguard the interests of the university or the research body both in relation to the activity of commissioned research and the protection and enhancement of its results and related industrial property.

  As already mentioned in the previous paragraphs, companies typically tend to want to ensure ownership of the results that will originate from the execution of the research, both for a matter of greater control and certainty of the rights connected to them and for greater management capacity, from a technical point of view, of the protection and enhancement strategies of the related industrial property rights.

  The research group, on the other hand, tends to underestimate the value of future industrial property and its related future cash flows because it is more interested in obtaining immediate funds for its research.

  The problem therefore arises for the TTO to act trying to safeguard the present interests of the research group but also paying attention to the longer-term interests of the research body (also linked to royalties that could be generated).

  Fortunately, in the last decade it is possible to find at an international level a convergence of interests, procedures and tools for the joint management of the various forms of property rights generated in the numerous opportunities for cooperative research between universities and industry.

  In Italy too we can cite decisive steps forward towards a simpler and more equitable collaboration between universities and industry. This certainly thanks to greater awareness and responsibility, both at the

institutional level and of the individual researcher, in the management of research results and their protection but also to the development of appropriate regulations and procedures under the coordination of TTO managers.

2.3 The process of creating a spin-off company

To better understand the spin-off creation process, it is essential in the first instance to clarify and define the spin-off concept.

Generally speaking, the term spin-off refers to the establishment of a legal entity (joint stock or limited liability company) starting from a pre-existing company, with respect to which a bond of sharing technological methods and skills is maintained as elements essential for its creation. The idea behind a spin-off is in practice to start a new entity by capitalizing on the know-how of the existing company. Depending on the type of derivation, it is possible to distinguish:

1. Industrial spin-offs: individual or corporate entrepreneurial activity that arises from an already established business;
2. Academic spin-offs or research spin-offs: companies that arise from the capitalization of skills and research activities developed within research institutions.

In particular, the term "public research spin-off" usually refers to a new economic unit created by a university or other EPR. More precisely, in Italy, Legislative Decree 297/99 was the first provision to deal with this issue - albeit indirectly - without however providing a precise definition. Also, the D.M. 583/00 defines the procedural methods on the basis of which the facilities provided for by Legislative Decree 297/99 can be requested for spin-off companies, without however defining what exactly is meant by this expression. More generally, it emerges that to date there is no official and unambiguously accepted definition of a spin-off company of public research.

However, a widely adopted and widespread definition in Italy is that according to which a spin-off of public research is "a company operating in high-tech sectors consisting of (at least) one professor / university researcher or a doctoral student / contractor / student, who has carried out multi-year research activities on a specific theme, object of the creation of the company itself".

According to this definition, a company can therefore be qualified as a spin-off of public research if the following three conditions occur simultaneously:

- the presence in the ownership structure of at least one person who has carried out research for a period of several years (at least three) in the academic field, with a structured (permanent) position or not;
- the start of a "for profit" business;
- the production and / or marketing of high-tech products and / or technologies and / or services based on results of research carried out at the university or other EPR of origin.

There are also multiple definitions of spin-off companies at the international level. Most of the field analyzes internationally follow the two-dimensional approach of Clarysse and Moray, according to which an academic spin-off is a new enterprise formed (a) by academic staff or students who have left the university for set up the business or who set it up while still in service at the university, and / or (b) based on a key technology (or idea) that is transferred from the original EPR.

At European level, a group of experts commissioned by the DG Research of the European Commission (CE) to work on the topic of metrics for knowledge transfer, as part of its final report, defined the spin-off company as "A new company expressly established to develop or exploit IP (Intellectual Property) or know-how created by the PRO (Public Research Organization) and with a formal contractual relationship for this IP or know-how, such as license or equity agreement. Include, but do not limit to, spin-offs established by the institution's staff. Exclude start-ups that do not sign a formal agreement for developing IP or know-how created by the institution". According to this definition, the existence of a contractual relationship between the original EPR and the spin-off company in relation to the IP transfer is considered an essential element.

Below is a list of definitions of the term "spin-off" divided by university, in order to have a more complete picture of what is the global vision.

AUTM - The Leading Association in Technology Transfer

The terms spin out and new venture are not well-defined and mean a range of things to a number of people. Fundamentally, both terms refer to a company that has licensed technology from a university or research institution in a transaction in which the university or research institution has received equity ownership in the licensee. Some institutions have organized affiliated entities with funds and expertise in organizing and managing new ventures.

Harvard Law school

"A spin-off involves the separation of a company's businesses through the creation of one or more separate, publicly traded companies. Spin-offs have been popular because many investors, boards and managers believe that certain businesses may command higher valuations if owned and managed separately, rather than as part of the same enterprise. An added benefit is that a spin-off can often be accomplished in a manner that is tax-free to both the existing public company (referred to as the parent) and its shareholders. Moreover, in recent years, companies have been able to tap the debt markets to lock in low borrowing costs for the business being separated and monetize a portion of its value."

Stanford University

Not all companies are startups or spinoffs. Indeed, the definition of a startup is still not clear. According to Wikipedia, a startup company (startup or start-up) is an entrepreneurial venture which is typically a newly emerged, fast-growing business that aims to meet a marketplace need by developing or offering an

innovative product, process or service. Although this can be seen as a good definition, Steve Blank, a Silicon Valley serial entrepreneur, has come with a more recent and probably better definition: Startups are temporary organizations designed to search for a scalable and repeatable business model. In complement, a university spinoff is a company founded by members of the university. Whether a spinoff is a startup or not depends upon its specific features. One can refer to Academic Entrepreneurship, one of the classical references about academic spinoffs.

Stellenbosch University (SU) - South Africa

In cases where SU should decide, in consultation with the inventor or the promotor of an idea, to exploit IP by means of the establishment of a spin-off enterprise, it shall be done by establishing a separate enterprise that shall normally be a subsidiary or associate company of "InnovUS Technology Transfer", and in which SU, the inventor or the promotor of an idea, and other possible partners shall own shares or members' interests according to a division that is agreed upon beforehand.

CRG, Spain

"Spin-off company is a new business entity formed to commercialize one or more related inventions generated from the research work from a parent institution. Forming a Spin-off company may sometimes be an alternative to licensing the IP to an established business. Licensing not always is possible or meaningful [...]. Creating a spin-off company around a technology has the potential to generate significant wealth as a large share of any profits made are retained by the company, with the inventors being shareholders in that company. Creating a spin-off may also be an appropriate commercialization route when there is a need to develop a technology further to extract its commercial value or when the team surrounding the technology is strongly entrepreneurial."

Universitat de Barcelona, Spain

"Generally speaking, spin-offs are companies that are created within a university setting and are the result of the research findings carried out by that university's own researchers. The university acts as an incubator and serves to support the spin-off in the early stages of its development"

Universitat Autonoma de Barcelona (UAB), Spain

"Company derived from the UAB (spin-off): a newly created company whose purpose is to exploit the results of UAB research, promoted and participated, with respect to social capital, by teaching and research personnel and research staff of the UAB, with the limits established by current legislation, but without the participation of the UAB in this capital".

Ghent University, Belgium

Technology driven spin-offs are based on proprietary technology of the university, in which the university has invested heavily, which is the result of technological and scientific breakthroughs that may be the result of years of basic research [...] The startup of such spin-offs is usually a complex and lengthy process that requires substantial financial means. The incorporation of the startup can be proceeded by an incubation stage within the university's research department to develop an industrial proof of concept, necessary to perform early market tests and to convince venture capitalists (VC) to invest. Such spin-off companies usually require a management team with the appropriate industrial experience to complement and to coach the often technology focused researchers/ entrepreneurs. Typically, the university will give exclusive access to its technology in return for shares and/or royalties. As this type of spin-off will be VC funded, it will be exit driven, leading to economic returns for the university through its ownership stake and through royalties."

Katholieke Universiteit Leuven, Belgium

What is a spin-off company? The creation of spin-off companies is one of the technology transfer mechanisms through which knowledge and/or intellectual property are transferred, by which research results are commercially exploited. This implies that the economic activity of a spin-off company is based on scientific knowledge or technological know-how developed within the university. The spin-off company translates these research results in commercial products and/or services. In short, in order to speak of a spin-off company, there has to be a transfer of knowledge or technology from the university to the spin-off company."

Université catholique de Louvain

A spin-off is a company born of a transfer of knowledge from the university to civil society, and thus also of the university's mission to serve society.

Vrije Universiteit Brussel, Belgio

"Spin-offs are start-up companies whose main activities are based on the formal transfer of research results originating from the university or university college. This transfer can take different forms (e.g. a license agreement or share capital participation) depending on the specific case."

Paul Scherrer Institute (PSI), Switzerland

"A spin-off company of PSI is a newly founded enterprise which is based on technologies or know-how created in the research activities at Paul Scherrer Institut whether or not former PSI employees are involved."

University of Vienna

"The University of Vienna actively encourages its scientific researchers to consider opportunities for commercialising technologies developed at the University. One such way is to start your own company to actively promote and commercialise your research. University Start-Ups: Start-up companies and established companies set up by staff and alumni of the University of Vienna."

Max-Planck-Gesellschaft (MPG)

"Spin-off companies have become one of the main channels for the transfer of knowledge and technologies from the MPG to industry in recent years. With a spin-off company, a license is transferred to the newly established company in which MPG staff are participating. As a general rule, the possibility that a license can be granted establishes the basis for the spin-off company. [...]".

Università di Oxford

There is no definition of spin-off, but the specific policy that is the responsibility of the University to decide whether to create a spin-off for the best exploitation of a technological innovation and that the participation of the University and the researcher is the result of negotiation among the parts.

Having clarified what is meant by spin-off, we can, therefore, continue by deepening the topic regarding the process of creating spin-offs.

The logical process of creating an academic spin-off (Fig. 2) can be theoretically traced back to that of any other corporate body (Catturi 2003), considering that it consists of a series of activities that follow one another following a temporal logic and that they converge towards a single final common goal. In fact, the development phase of the business idea arises from the previous academic research activity conducted by the subjects who decide later to start the spin-off, and which continues to persist even after its concrete activation. It is therefore possible to conclude that the point of origin of the spin-off (input) coincides with (and overlaps) the point of arrival of the academic research (output).

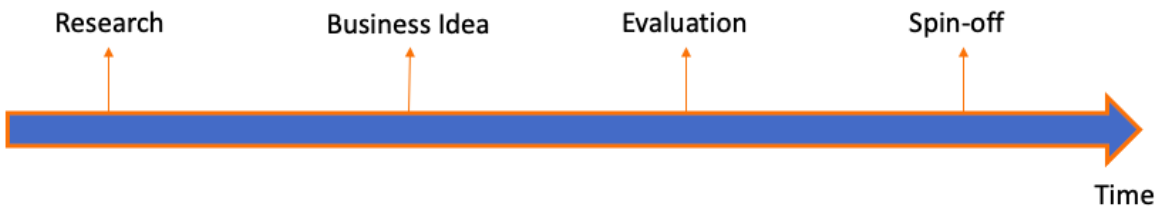

Figure 2:Academic Spin-off process creation – Source: Catturi (2003); Own elaboration

The process represented in the figure has an evolutionary, sequential and general character, in fact, many authors (Ndonzuau et al. 2002; Clarysse and Moray 2004; Degroof and Roberts 2004; Lockett et al. 2002) have articulated their own reworking of the phases of constitution of the university spin-offs, in order to give the process a certain degree of order and systematicity.

In particular, Clarysse and Moray (2004) mainly focus on the evaluation phase, which therefore precedes the creation phase of the spin-off, and which consists in a careful and reasoned control of the research results and of the ideas from which the spin-off originates, aimed at the consequent validation. They develop a "funnel" model (Fig. 3): there is a progressive narrowing of the process due to the selection of valid inputs which implies the relative rejection of those deemed invalid.

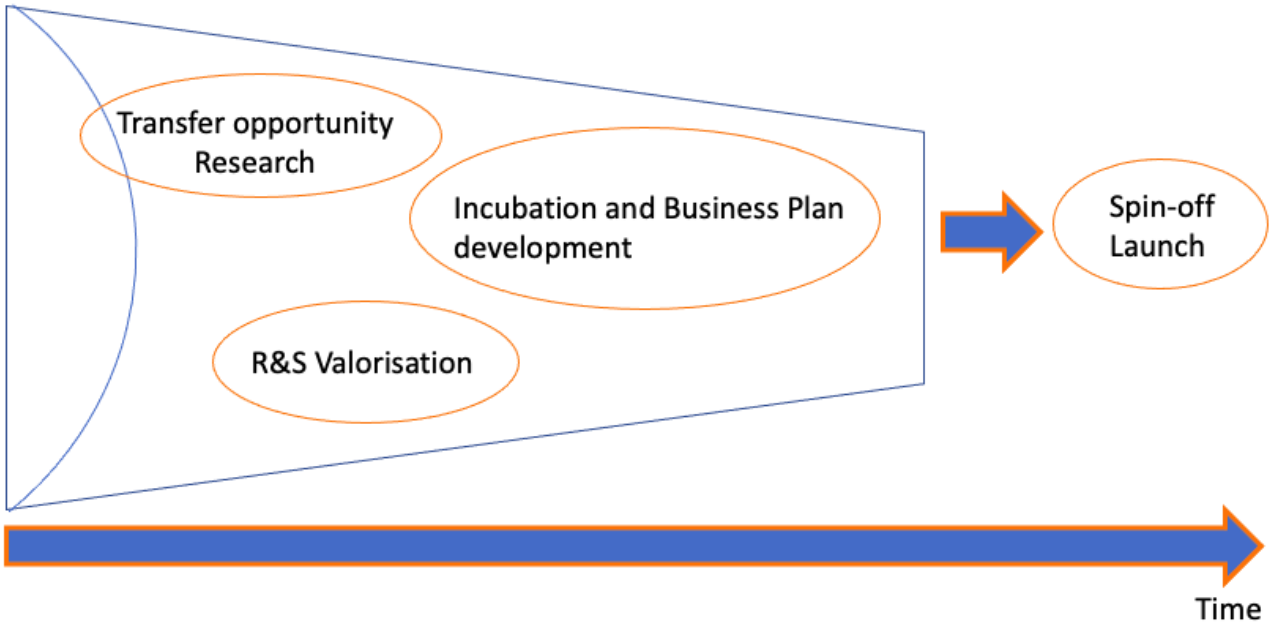

Figure 3: "Funnel" Model - Source: Clarysse e Moray (2004); own elaboration

As can be seen in the figure, there is a first phase of research during which a large number of ideas and projects are developed, of which, however, only a small part is effectively valued in a business idea, moving on to next phase of approval and definition of the project in which the method of valuing R&D is chosen. Subsequently, the business idea is subjected to verification and once approved it proceeds with its formalization through the drafting of the business plan.

Another interesting contribution is provided by Degroof and Roberts (2004), who develop a schedule that can be schematized in the following three phases:

I. Origination phase: in the first phase the main business idea is developed, in relation to which the search for opportunities is initiated by identifying a possible outlet market;
II. Concept testing phase: the second involves the evaluation and analysis of the feasibility of the business project;
III. Support phase: in the third and last phase, the concrete process of support for the spin-off by the parties involved started.

This scheme is very similar to the one described above. What differentiates this model from the previous one is the identification of four types of academic spin-offs in relation to existing support policies: absence of policies;

minimal selectivity / support; intermediate selectivity / support; comprehensive selectivity / support. These four levels of support and intervention of universities and institutions in the spin-off process influence the activities carried out in the three phases described above, determining a greater or lesser intensity of the same and the degree of involvement of supporters.

The model proposed by Ndonzuau, Pirnay and Surlemont (2002) is broader than those seen previously as it is divided into four rather than three phases (see Fig. 4).

These phases are part of a general framework, called "black box", which represents the concept of value creation considered as the final output of the academic spin-off and are the following:

4.1 Elaboration of the business idea starting from the research result;
4.2 Definition of the business project starting from the business idea;
4.3 Launch of the spin-off starting from the project;
4.4 Consolidation of the economic value generated by the spin-off.

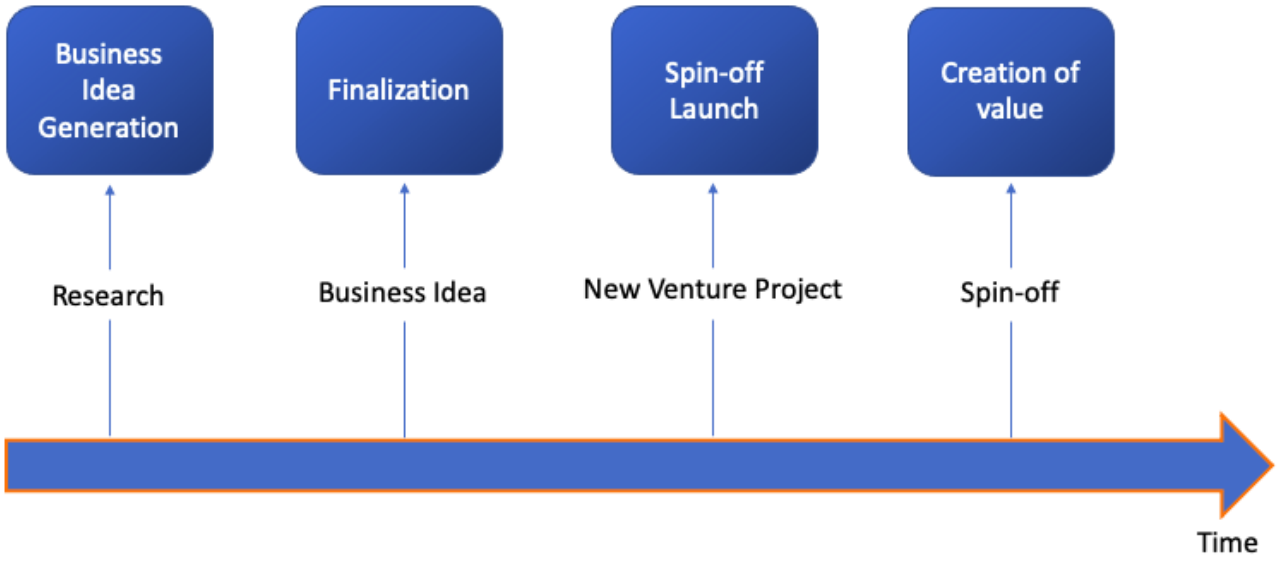

Figura 4: "Black Box" Model – Source: Ndonzuau, Pirnay e Surlemont (2002); own elaboration

Ultimately there is the proposal of Lockett, Vohora and Wright (2002), whose vision is broader than all, as it is structured in five phases:

- **research:** in this phase the main actors are the researchers who are dedicated to the definition of the business idea or the creation of intellectual property;
- **identification of the opportunity:** the methods of commercial exploitation of intellectual property are identified - through verification tests and market studies -; leads to the joint interaction between researchers and managers of the university offices in charge of managing intellectual property;

- **pre-organizational:** it consists of activities such as the definition of the object and the characteristics that will characterize the entrepreneurial initiative, the identification of the main resources to be used;
- **reorientation:** it is aimed at the actual analysis of the activities and the consequent redesign of the same in case of negative results;
- **sustainable growth:** the company detaches itself from the academic structure of origin, with the consequent and necessary redefinition of the relationships between the new business reality and the university, especially in terms of how the human resources involved in the project are used.

The authors emphasize that the transition from one phase to another involves the emergence of critical factors, important depending on the case, which must be addressed with appropriate and timely interventions.

The TTOs, in relation to the territorial context and in line with the mission of the institution, adopt different approaches, procedures and regulations for the management of the process of creating spin-offs.

Below it is possible to report and outline the different approaches in some models identified:

- The "low selectivity" model: characterized by low selection criteria and limited support for nascent spin-offs. The goal we want to achieve is to create as many spin-off companies as possible. TTOs that adopt this model are usually limited in size, do not specialize in a particular technological sector, have a limited number of financial resources, often anchored to the public resources available, and try more than anything else to create an "entrepreneurial" climate at the inside the university. These entrepreneurial initiatives can be important for regional development and for the formation of highly innovative clusters.
- The "high support" model: also characterized by low selection criteria, here new companies aspire to grow. Usually, the selection is made on the basis of growth orientation. Research institutions offer a high level of support for patenting, negotiation with companies, the availability of incubation spaces. The spin-off companies that receive this form of support are already born with a strong growth orientation and an aggressive commercial approach. Moreover, thanks to the organizational structure adopted, they have more ease in acquiring financial resources useful for growth from both public and private entities. Compared to the previous model, the number of businesses receiving support is more limited.
- The "protective" model: in this case, the public research bodies implement a greater selection of projects and the spin-offs are characterized by greater size and capitalization; in many cases, they aim to become leaders in their sector in a global market. To facilitate the pursuit of this goal, new companies are assured by the organization of origin a longer incubation process, so much so that spin-off companies usually abandon the EPR at a more advanced stage of their development cycle. While in the low-selectivity model, venture capital firms show no interest in spin-offs, it is different in this model, as new entrepreneurs are more market and growth oriented. In order to adopt the "protective" model, however, research activities at the highest international levels and high skills and human, physical and financial resources are necessary. For this reason, it is more likely that the TTO is detached from the university, maintains only formal links with it, and takes on a private form.

The three models differ from each other as they intervene in different phases of the spin-off creation process. While the low-selectivity model concentrates the actions only in the definition and approval phase of the business project, the high-support model reaches the stage of drafting the business plan, when the business idea is already well defined and have been prepared the main decisions in this regard. On the contrary, the protective model covers all stages of the process and the EPRs who decide to adopt this model must offer support to the nascent spin-off by following its entire evolution.

Clarysse et al. believe that the way in which resources are organized, during the incubation phases of the project, is decisive for the propensity for growth and the geographical extension of the market to which the company will want to aim, as well as for the services or products it will decide to offer, as well as for the strategies it will adopt to penetrate the markets and compete with competitors. In other words, the choice of the support model adopted by the EPR directly affects the characteristics of the spin-offs originating from the EPR itself.

The spin-off process can have as input the protected invention or the search result that is not protected or cannot be protected by any form of patent (know-how). In this sense, the process can be considered sequential to the PI protection process or be completely separated from it. The process involves the implementation of a series of successive phases that ultimately lead to the generation of the spin-off company.

As previously written, there is a strong lack of homogeneity in the concept or definition of spin-off companies both nationally and internationally. The differences, however, do not only concern the terminology (start-up, spin-off, university or academic) but also the goal for which a university or a research institution must support the entire process of business creation. This results in an equal variety of approaches and a different level of intensity of investments, efforts and resources made available.

For example, spin-off companies are considered to be any new initiative which from an organizational point of view is:

- a legal entity other than the entity;
- almost exclusively joint-stock companies;
- also alternatively:
    - with university participation as a member;
    - with the participation of a university professor / professor / researcher or technical administrative staff;
    - based on intellectual property rights or know-how developed in the university.

The created company (process output) is linked to a series of economic returns (dividends) for the proponents and for the university, due to equity participation. The economic returns for the university can also include any royalties in the event that the "core" technology is transferred to the spin-off through the signing of a licensing agreement. In this same case, alternatively to royalties, it is possible to structure a payment system that provides for the transfer to the university of shares of the new company. This last issue, also very delicate from a formal point of view, must be carefully taken into consideration in the transition to analytical accounting with the consolidated financial statements of the universities and all its holdings. In fact, in the recent past there has been

a practice of transferring or transferring know-how or intellectual property without precise estimates or appraisals of its economic value in exchange for shares in the share capital of the spin-off being established.

Shane, on the other hand, identifies a classification of academic spin-offs based on their needs and sources of funding. A first category includes spin-off companies that need minimal funding, since they are mainly based on self-financing. Examples of such spin-offs can be found in the software industry.

The second category, on the other hand, includes spin-offs that need a very large amount of funding to be able to produce a good or provide a successful service. In this case they are spin-offs operating in the biotechnology sector. The latter type of spin-off is potentially interesting for venture capitalists and business angels.

2.4 Spin-off companies as a tool for enhancing public research results

The spin-off companies of public research have for some years been at the center of intense attention by scholars and policy makers as they are considered crucial elements of the public-private technology transfer process (TT) and protagonists of the new phases of economic growth. It is indeed quite evident that spin-off companies have played a significant role in the industrial-scale development of new technologies not only in the United States but also in other parts of the world and most likely the same will happen in Asia in the near future.

In Italy too, the debate on the possibilities of further exploiting the results of public research that can be promoted through new academic entrepreneurship is very intense.
The phenomenon of the enhancement of research through the creation of spin-offs has grown a lot starting from what can be considered its date of birth in Italy, i.e. the end of the 1980s, despite the fact that some companies were also established in previous periods, representing a sort of ante litteram spin-off, when there was no talk of spin-off yet. The importance of spin-off companies has gradually increased with the emergence of the so-called "knowledge economy", characterized by intense competitive processes based on opportunity and the need to continually introduce new products and services with a high scientific and technological content. But if the new rhythms of scientific and technological research have made continuous innovation processes possible, they have at the same time put pressure on companies, called to identify and in fact choose some research paths to the detriment of others; or even not to choose at all for fear of making the wrong choice. Spin-off companies soon emerged as experimental subjects of the new results of scientific research, which they could develop on their own, or "incubate" for a certain period and then activate collaborations with pre-existing companies, often of large dimensions. More recently, spin-off companies have also become protagonists of the Open Innovation trend, inspired by Henry Chesbrough, and of regional economic development processes, which, despite the different terminologies used (learning region, triple helix, entrepreneurial university, etc..), essentially see Public Research Bodies (EPR) as sources of new innovative entrepreneurship. As already stated above, universities and EPRs currently play an important role in contributing to new entrepreneurial initiatives with a high technological content, thus giving shape to the third mission, which consists in contributing to the processes of economic development.

Currently, in the national context, satisfaction is felt for the results achieved, especially in terms of the number of companies created, of the scientific - technological sectors involved and also in terms of geographical spread throughout the national territory. We are therefore faced with an entrepreneurial phenomenon that presents numerous elements of considerable interest in terms of:

- enhancement, in the sense of "bringing the results of public research to application";
- closing the gap between public research and industrial innovation;
- transfer of technological solutions to small and medium-sized enterprises (SMEs) in non-high-tech sectors;
- creation of new qualified jobs for graduates in S&T subjects;
- acceleration of economic development processes on a local and regional basis.

In recent years, some universities have adopted measures to support entrepreneurship by increasing students' propensity to create businesses, promoting the creation of ad hoc support contexts for starting a business: fablabs, coworking spaces, contamination labs, etc. It is assumed that university policies can have great effects on the behavior of future entrepreneurs.

Recent evidence on students' entrepreneurial intentions, according to Saridakis et al., 2016, shows that approximately five years after graduation, the level of interest in business creation increases for graduates across all sectors. Other studies, Hassan and Wafa, 2012, show that there are significant differences in entrepreneurial intentions depending on the type of research carried out. Students following technical-scientific paths show a significantly higher interest in entrepreneurship than students with a more humanistic background.

Just as it is demonstrated that collaboration with industry represents a driver for the creation of a new business and both the cultural background and training on business issues can represent a sign of commitment for the university as well as a driver of start of an entrepreneurial initiative.

We are increasingly faced with growing evidence of the influence that the internal and external context of the university can assume as a stimulus to academic entrepreneurship and with respect to the entrepreneurial intentions of students [Colombo and Piva, 2012; Saridakis et al., 2016].

Since students generally do not have business experience, any kind of interaction with exponents of the business world combined with a first approach to market opportunities can encourage students to find industrial applications by pursuing an entrepreneurial career.

Another important factor, which may be relevant for PhD students interested in developing their own business, is access to entrepreneurial training courses. This type of training is still not very common in the three-year or master's degrees of a technical-scientific nature in Italy, but it is demonstrated how appropriate programs on the issues of developing a new business influence the creation of businesses by young students [Harris and Glibson, 2008].

Several studies have confirmed how these programs can increase the level of entrepreneurial interest among students and their entrepreneurial attitude. This growing empirical evidence has led to a rapid increase in the number of courses offered in higher education institutions around the world, demonstrating that entrepreneurial

education has a positive effect on students' ability to assess their skills and stimulate their aptitudes towards entrepreneurship.

2.5 The empirical analyzes on spin-offs in Italy

Since the early 1990s, numerous empirical investigations have been carried out on the phenomenon of spin-off companies in Italy. Thanks to the results of the surveys it was possible to identify the factors underlying the establishment of the spin-offs, highlighting above all the motivational ones of the pull type: the possibility of "doing fun things", which for various reasons the researchers could not do at the interior of the university; the achievement of personal success in terms of scientific prestige; the identification of an idea with ample development margins for the development of which it is necessary to have a high level of knowledge on the technical characteristics of the product and on the structure of the market. Among the push factors, on the other hand, the following were highlighted: intolerance for the academic environment in its most bureaucratic expressions; its low propensity to risk in the context of scientific activities; professional secrecy, sometimes imposed by private clients on occasion of collaborations with the university, in contrast with the desire of researchers to disseminate the results obtained and deal with the outside scientific world; economic reasons. Subsequently, numerous insights were provided by authors who carried out surveys on samples of companies of different sizes.

The results obtained by Grandi and Grimaldi showed how the network of relationships maintained by Italian spin-off companies was the factor that most affected the chances of success. Specifically, the key elements for the success of spin-off companies are the attitude of the founders to such interactions and the frequency in contacts with external agents. The empirical evidence reported by Cesaroni et al. show that, overall, universities and other home EPRs differed considerably in the support models provided to them.

rom the results of an analysis conducted by Iacobucci et al. about the growth processes of 160 public research spin-offs, created in Italy between 2000 and 2005, it is clear that only a small percentage of the sample shows significant growth dynamics, while the majority of companies have difficulty in transforming initial idea in a sustainable business on the market. In this regard, the authors note that in the italian institutional context, the main problem is represented by the difficulty for new businesses to raise adequate amounts of funds during the start-up and subsequent development phase. In organizational and managerial terms, the analysis identifies two other factors that contribute to generating these dynamics:

a. the imbalance in the team of founding partners towards purely technical skills at the expense of managerial and organizational skills
b. the lack of clarity in the definition of entrepreneurial orientation.

2.6 The current situation of spin-offs in Italy

In Italy, spin-offs appeared starting from the first half of the 1980s, when in other contexts - such as the US - the phenomenon was already widespread, having found first forms of application since the early 1900s. Furthermore, Italy has always been characterized by a smaller number of spin-off companies, when compared to other European countries - such as, for example, France, Germany and Great Britain. There are those who explain this aspect by the fact that they have aimed to aim for quality rather than quantity, thus aiming to create realities that are characterized by a real and effective potential for growth (Bozeman 2000; Cesaroni and Piccaluga 2003; Rostan and Vaira 2010; Prencipe 2016; Riviezzo et al. 2017).

However, it must be recognized that in Italy the phenomenon of research enhancement is recent, all the more so if we consider both technology transfer and technology transfer, through specific structures, Italian universities have only begun to deal with at the end of the past century (Algieri et al. 2011; Chiesa and Piccaluga 2000; Piccarozzi et al. 2013) and that in many academics there is still a tendency to avoid any mixture between research and the economic sphere.

This section aims to provide an updated picture of the state of the art of the creation of a research enterprise at a national level. The data comes from the XIV and XVI Report by Netval. Netval is an association made up of 64 universities and 15 EPRs and aims to represent a bridge between public research and companies interested in increasing their competitiveness through innovation; in collaboration with the Institute of Management of the Sant'Anna School of Advanced Studies, for some years now they have been collecting information on spin-off companies from public research in Italy which, according to the database of the Italian Spin-off platform, currently amount to 1,724 active companies.

The Netval reports show that the phenomenon of the creation of spin-off companies appears to be concentrated and consolidated mainly in the Center - North, but also expanding in the South and the Islands. In particular, as regards spin-off companies active on 31 December 2019, Lazio is the region with the highest number of spin-offs (11.9%), followed by Tuscany (11.7%) and Lombardy (10,0%) and Piedmont (8.8%). Lower, albeit high, levels of concentration are recorded in Emilia-Romagna (7.9%), Veneto and Campania (6.2%), Puglia (5.1%), Liguria (4.9%), Marche (4,5%) and Sicily (4.0%); lower percentage shares are found in Calabria (3.7%) and in the remaining regions.

With regard to the sectors of activity of the spin-offs active in Italy on 31 October 2017 (n = 1,373), about a quarter of these companies operate in the ICT field. The relative weight of this sector has progressively decreased over time and companies engaged in the sectors of innovation services have grown, followed by energy and the environment and life sciences. The decrease in ICT initiatives in favor of those for "innovation services" shows that ICT technology is now transversal to many other areas of final application. The biomedical, electronics, industrial automation sectors follow, while there are more modest shares for the nanotechnology sector, conservation of cultural heritage and - finally - aerospace.

Universities are increasingly moving towards the involvement of students (undergraduates in particular) and PhDs by planning their involvement in research projects and their participation in training courses on entrepreneurship,

possibly institutionalizing them, integrating and updating them from year to year. Many universities organize awareness-raising and promotion of business culture initiatives, in collaboration with the offices that take care of the training of the university's PhDs, especially in order to enhance the potential of particularly talented students with an entrepreneurial spirit. In general, there is still a strong need to increase the support activities for the growth and consolidation of spin-offs by enhancing the ability to select / identify the team even on an interdisciplinary basis.

Among the entities associated with Netval, a decisive role for the enhancement and development of research is played by some non-university research institutions, such as: AREA Science Park, ARTI Puglia, the Italian Aerospace Research Center (CIRA), the National Research Council (CNR), the Council for Agricultural Research and Analysis of the Agricultural Economy (CREA), the National Agency for New Technologies, Energy and Sustainable Economic Development (ENEA), the IDIS Foundation - City of Science, the Italian Institute of Technology (IIT), the National Institute for Nuclear Physics (INFN).

2.7 The reasons why to choose enhancing research by creating spin-offs

Although this is not a recent phenomenon, because it dates back to the beginning of the last century (Clark 1998; Etzkowitz and Leydesdroff 2000), it should be noted that the interest in the analysis of academic spin-offs seems to have spread among highly educated scholars only in the last few years. In Europe, moreover, attention to this method of exploiting the results of scientific research has declined not only in terms of regional policies - for which spin-offs are an important mechanism for building relationships between universities and businesses, as well as the creation of jobs and wealth -, but also the reorganization of academic structures, which aim at the maximum exploitation of university research results (European Trend Chart on Innovation 2002; Degroof and Roberts 2004; Doganova 2010).

In particular, the significant increase in the number of spin-offs registered in the university sector in recent years is primarily due to the new role now attributed to universities, increasingly motivated and induced by funding bodies (including the State) to open up to the commercialization of knowledge. product and to play the entrepreneurial role that now seems essential in a sector which is required to be competitive and even aimed at profit (Slaughter and Leslie 1997; Surlemont et al. 2001; Gumport 2002; Bok 2003). This is where an increasingly strong orientation to the market by universities arises, with relative modification of the management of available resources and sources of financing, as well as the degree of openness towards the complex (now changed and heterogeneous) of reference stakeholders (Steffensen et al. 2000; Piccarozzi et al. 2013). Another aspect that explains the exponential growth of these new structures, is instead linked to the widespread budgetary difficulties and the difficult availability of stable positions within universities (Fabbri and Rossi 2008; Rostan 2011; Geuna and Rossi 2013): this factor it encourages those engaged in scientific research to seek employment alternatives to traditional positions within universities such as to continue the research activity and therefore to necessarily broaden their range of activity, combining the traditional research function with that of an economic-

entrepreneurial nature. It is also important to underline that the autonomy of the universities now allows them to decide to favor and support the development of academic spin-offs.

By virtue of the centrality that scientific research appears to have in the field of technological innovation, in the last two decades the initiatives, both public and private, aimed at supporting the birth of spin-offs and supporting their long-term duration have multiplied (Lockett et al. 2005). However, there is a substantial inhomogeneity among scholars regarding the classification of approaches and intervention models that are progressively developed. In particular, two main models are identified in a report by the European Commission (2002):

- the "US model", which focuses on the strength of the formal and informal networks underlying the relationship between the university and the business, professional and financial spheres;
- the "Israeli model", which highlights the importance of the role played by the network of public incubators in the process of setting up spin-offs.

Again, the Austrian Ministry of Economy (Novakovic and Sturn 2000) proposes four models of European origin:

- the top-down approach (typical of Finland), which provides for the presence of national agencies geared towards financing incubators;
- the Swedish model, which describes a private network consisting of an incubator, a center for offering business support services and a set of lenders;
- the Swiss model (theorized within the University of Lausanne), for which various players gradually join together in a spin-off creation program;
- the Catalan model, in which the various university faculties, competing with each other for access to funds, are pushed to promote autonomous businesses; in this way "constellations" of entrepreneurial initiatives are created.

It seems useful to refer also to the typology proposed by Wright and colleagues (2006) which is divided into four different groups of interventions:

- interventions with low selectivity, i.e. initiatives promoted by public bodies with the allocation of scarce resources and arising from non-stringent selection criteria.

The spin-off is denoted as one of the entrepreneurial initiatives with the highest power of implementation for the transfer of technologies and academic knowledge, of which it would allow a more rapid and widespread diffusion towards the socio-economic context of reference. In addition, and increasingly, university spin-offs are harmoniously included among the most proactive and profitable agents in the creation, promotion and development of the knowledge economy. Although there are differences of opinion on the potential and income performance of a spin-off, the latter is unanimously and irrefutably qualified in terms of a knowledge / technology-based company, with a life cycle based on the assimilation of knowledge and technology and on the exploitation of a social capital that can be hoarded through interactions and relationships with internal and external stakeholders in the academic context.

Furthermore, in the fields of technology with a high rate of knowledge and innovation, in order to bring research results to the market it is not possible (or appropriate) to resort to the protection of intellectual property (with the relative publication of patents) or regardless of specific knowledge, almost exclusives, of the Researchers and their skills and international relations.

Spin-offs, therefore, could represent the main tool available to public research bodies to be an engine of territorial development, as they have intrinsic characteristics that make them extremely versatile and effective:

- generally develop products that are located on the technological frontier, with a high intensity of knowledge and offer innovative services that require very high skills or transversal or cross-sectoral know-how (eg biotechnology, bioinformatics, ...) which, normally, would require investments hardly sustainable for a small business or hardly available on the market at reasonable prices, or in the same business or operational context;
- they ferry onto the market, at least initially, technologies that would otherwise not be exploited (for the reasons mentioned above), costing the public body millions of euros in investments in research;
- enhance skills developed over years of research that could hardly have settled in business contexts characterized by much shorter cycles of return on investment;
- avoid the brain drain by giving the opportunity to many brilliant young people to test themselves in challenging and international areas;
- guarantee a direct link between the academic world and the production / market world, playing an active role within the company both from the point of view of the entrepreneurial and of the ecological university.
- allow a deep intersection with the science and technology parks;
- reduce time to market and sell an economic asset (knowledge) that allows other sectors to remain productive;
- if successful, they can return capital to be reinvested to the research institution / university and, in any case, increase its reputation.

The meaning and function of the economic enhancement of research through the spin-off is evident in that it represents the tool that allows the development of innovative processes and the competitiveness of the economic system in a more direct way. With the increase in the birth of these spin-offs in the italian territory, a favorable environment is being created for the emergence of new business initiatives, capable of selling and enhancing the results of research. These new businesses therefore carry out an important activity for the purpose of enhancing scientific research and technology transfer to the productive world and allow a link between the market and academic research capable of promoting innovation in the entrepreneurial fabric.

2.8 Factors preventing the development of spin-offs

Although in general the concept of spin-off is well received and recognized by almost all the common opinion, there are, however, some doubts about the real possibility of development of this particular type of business within the Italian economic context.

The factors that could put a brake on the development of this type of company would be represented:

- the high levels of taxation that characterize the fiscal policy which the legislation on innovative start-ups does not substantially remedy;
- the role played by italian institutions, which often claim to influence the choices of companies that are, even partially, under their influence, sometimes slowing down their development processes;
- the low rate of development of the Italian financial markets;
- the marginal role of "venture capital", an aspect that would not favor the growth (size and income) of Italian companies.

Furthermore, among the questions still open, there is the one concerning the degree of involvement of the university itself within the spin-off that operates in its orbit. Although some theorists believe that the involvement of universities in the life of spin-offs is beneficial for their growth, others believe that too close a bond could undermine the independence of the company and therefore the "entrepreneurial" character for which the spin - off was created or it could run the risk of slowing down decision-making processes so much as to make time to market so slow as to not fully exploit the competitive advantage of technological leadership determined by the novelty of the product. The fact is that, despite the pros and cons that lie behind the spread of spin-off companies, the basic idea is that the University, together with the other public research bodies, must play an increasingly central role. in their diffusion process.

CHAPTER 3: THE REGULATORY CONTEXT FOR THE CREATION OF SPIN-OFF

With the following chapter we want to provide an overview of the legislative reality starting from the first measures, up to the most recent ones, detailing the most explanatory and indicative articles.
Table 1 proposes the regulatory framework that, also indirectly, regulates the business creation activity as a result of the research.

REGULATORY PROVISION	MAIN NEWS INTRODUCED (UNIVERSITY AND RESEARCH)
LAW 168/1989	▪ Possibility of autonomous budget planning available ▪ Possibility of autonomous choice of priorities to be financed
Legislative Decree 297/1999	▪ Possibility of setting up companies for the industrial use of research results ▪ Possibility of employment of Professors and Researchers within the spin-offs ▪ Identification of the methods of financing the spin-offs
DM 593/2000	▪ Discipline of the procedures for granting state sources for the financing of research projects
LAW 240/2010	▪ Discipline of the role of university professors within the business world
DM 168/2011	▪ Definition of university spin-offs ▪ Discipline of the procedures for the participation of university staff in spin-offs
LAW DECREE 179/2012 LAW DECREE 3/2015	▪ Introduction of innovative start-ups ▪ Introduction of innovative SMEs
Legislative Decree 175/2016 "MADIA LAW" and following	▪ Determination of the applicability of the rules for the rationalization of public subsidiaries also to spin-offs after five years from the establishment
ANAC RESOLUTION 620/2018	▪ Absorption of university spin-offs into the orbit of public companies that must identify members with a public tender procedure in compliance with the rules on transparency

Table 1: The main regulatory measures towards the entrepreneurial university

The main contents of the measures referred to in Table 1 are briefly represented below.

LAW 168/1989

This is the first measure that went in the direction of a more entrepreneurial university, giving the possibility to universities to organize their activities in a more autonomous way. For the first time, universities were given the possibility of managing the use of the available budget, being able to define the priorities to be financed in total autonomy. Therefore, thanks to the regulatory provision in question, universities were able to decide the amount of budget to finance internal research, rather than to hire new teaching staff, rather than to renovate internal buildings or purchase new equipment. Law 168/1989 therefore represented a first form of autonomy that was granted by the central government to universities.

LEGISLATIVE DECREE 297/1999

The first regulatory hints can be found in Legislative Decree 27 July 1999, n. 297 which represents the fundamental regulatory act. The text, as part of the national research program, "governs interventions to support industrial research, related training and the dissemination of technologies deriving from the same activities". Through this rule we want to establish the procedural methods for the granting of some forms of facilitation, establishing the criteria underlying the public funding for basic research, i.e. the recipients of this funding, the forms of funding, the activities that can be financed and the role of the University staff. Therefore, the subjects authorized to benefit from them together with the activities worthy of intervention are set out in detail.

Among the recipients of the funding program, Article 2 includes the "companies recently established or to be established, aimed at the industrial use of the research results [...] with shareholding or competition, or in any case with the relative commitment of all or some of the following subjects: university professors and researchers, research staff employed by research bodies [...], as well as PhD students [...], on the basis of the regulations of the Universities and belonging [...]".

Article 3 of the aforementioned Decree, on the other hand, regulates the role of university research staff. In fact, it reads: "Research staff, [...] as well as university professors and researchers, may be temporarily seconded, pursuant to this paragraph, to industrial and similar entities, with priority for small and medium-sized enterprises companies as well as with similar subjects in the start-up phase, [...] at the request of the same subjects and with the prior consent of the interested party, for a period not exceeding four years, renewable only once. The seconded staff maintains the employment relationship with the person on whom they depend on and the related economic and contributory treatment".

Article 4, on the other hand, regulates the financing methods for the research activities set out in the previous articles. The main methods are:

- Non-repayable contributions
- Subsidized loans
- Interest subsidy
- Tax credits

- Tax Bonus, envisaged pursuant to article 7, paragraphs 1 and 4, of Legislative Decree no. 123.

No form of guarantee is required for forms of financing paid directly by MIUR.
With the Legislative Decree no. 297/1999, therefore, an attempt was made to encourage the creation of research spin-offs, introducing the possibility for public researchers to be directly involved or to take part in any other project for the transfer of research results from the world of universities to that of companies, maintaining in any case their role as researcher within universities. The decree in question, although it is now recognized as a starting point for a new discipline of the fruits of intellectual property, did not, however, provide precise provisions regarding the methods of creating spin-offs.

THE DM 8 AUGUST 2000, N. 593

To the Legislative Decree n. 297/1999, then followed the issue of the Ministerial Decree of 8 August 2000, n. 593, which governs the methods and criteria through which it is possible to draw on the state funds necessary to finance a specific research project.

LAW N. 240 OF 30 DECEMBER 2010

Following the evolution that has been witnessed at the context level, although the Legislative Decree 297/1999 remains the most important intervention in terms of spin-offs, a large-scale diffusion of the phenomenon has been reached such as to request specific regulatory intervention.
The most significant regulatory innovation is introduced in the matter of incompatibility, in implementation of the provisions of art. 6, c. 9, Law 30 December 2010, n. 240. The legal precept establishes the non-applicability of the rules on incompatibility with reference to the exercise of trade and industry through the establishment of spin-off companies. Consequently, a public employee, full-time professor and researcher, can work as an employee for the University and simultaneously exercise an entrepreneurial and managerial activity (NETVAL, 2013).
This law is called "Regulations on the organization of universities, academic staff and recruitment, as well as delegation to the government to encourage the quality and efficiency of the university system". In detail, Law 240/2010 focuses attention on the role of university professors and their relationship with the external business environment, providing clarifications on the legal status of university professors and researchers. Article 6, paragraph 9 states that "The position of professor and researcher is incompatible with the exercise of trade and industry, without prejudice to the possibility of setting up companies with the characteristics of spin-offs or university start-ups, pursuant to of articles 2 and 3 of Legislative Decree no. 297/1999, also assuming formal responsibilities in this area, within the time limits and according to the regulations on the subject of the university to which they belong". If on the one hand, therefore, Law 240/2010 prohibits permanent university professors and researchers from exercising the activity of entrepreneurs, on the other hand it opens up the possibility for the same professors to take on positions, even significant ones, in spin-off companies. off that are set up in order to market research products. Naturally, the participation of the Professors in the activities of the spin-offs must take place in the manner established by the national legislation and by the regulations issued by the individual universities, especially as regards the annual amount of time that they can devote to the activity of the spin-offs. If on the one hand, therefore, we want to ensure that teachers and researchers contribute, through their skills, to the

growth of spin-offs within the business world, on the other hand we try to set limits so that the teaching activity in the University was neglected. Article 6 continues in this way: "Full-time professors and researchers can carry out freelance and self-employed activities, including continuous ones, as long as they do not lead to situations of conflict of interest with respect to the university they belong to".

In summary, the regulatory measures cited up to now have had the main objective of defining the role that university professors and researchers are required to play within a panorama that saw them involved both in the university and in the corporate world. However, a regulation that would regulate the procedures for proposing, participating in or assuming formal responsibilities in companies with spin-off characteristics had not yet been enacted. However, this gap was subsequently filled with regulation no. 168 of 10 August 2011.

THE MINISTERIAL DECREE N. 168/2011

The Ministerial Decree of 11 August 2011, no. 168 is the intervention that most tried to refine the discipline, without prejudice to the reference to Legislative Decree no. 27 July 1999, no. 297 regarding the definition of spin-off, mainly trying to provide a solution regarding incompatibility. This decree essentially focuses on three key points:

- a new definition of university spin-offs, more precise and accurate than those issued in the previous rules and regulations;
- the basic procedure for creating a research spin-off;
- a third party in which the cases of incompatibility and conflict of interest of the subjects involved are set out.

The definition of spin-off is given by Art. 2 of Ministerial Decree 168/2011 which states that "in order to qualify as university spin-offs or start-ups, the companies referred to in Article 2, paragraph 1, letter e) of Legislative Decree no. 297 must be established on the initiative of the University or university staff or provide for the participation in the capital by the University, or the participation of university staff. The participation of university staff [...] can take place both in terms of participation in the capital and in terms of direct commitment to achieving the corporate purpose, offering the new legal entity the use of the know-how and skills generated in a research context". The necessary stakes are then placed to define a spin-off in order to distinguish it from a normal company, which are:

- the constitution must take place exclusively on the initiative of the University or university staff;
- participation in the spin-off of university staff must be envisaged, which can take place both in terms of participation in the capital and participation in the company activity.

According to the Ministerial Decree, the managerial and administrative positions of spin-off companies are precluded to:

- Members of the Board of Directors, professors and researchers who are members of the university commissions on research, research enhancement and technology transfer;
- Rector;
- Members of the Academic Senate;
- Directors of the University Departments;

without prejudice to the possibility entrusted to the self-regulation of the EPR to "[...] define the cases in which the professors and researchers in service cannot be authorized to set up spin-off or start-up companies, or assume formal management responsibilities, when the interested parties have specific roles within the university, such that the simultaneous exercise of the business activity could compromise the autonomy in carrying out the research and institutional function".

A further limitation is also placed on the exercise of activities in favor of the company by the subjects indicated in the event that there is a "[...] conflict with the regular and diligent performance of the functions related to the employment relationship with the University "In which case" [...] the professor and / or researcher, partner or non-partner, must immediately notify the University and at the same time stop carrying out the activity provided by the company".

With article 3 ("Procedure for setting up university spin-offs or start-ups"), on the other hand, we want to try a better definition and we want to make some aspects of the public research institute more uniform, setting out in detail some peculiarities of the spin-off constitution processes, in order to create a procedural basis common to all EPRs. In particular, as regards the procedures for setting up such companies, it is envisaged that each Entity has the decision-making power on the approval or rejection of the proposals for the incorporation of companies through the decision of the governing bodies of the Entity. In fact, it is stated that "the proposal for the incorporation of the company is approved by the University's [...] Board of Directors after obtaining the favorable opinion of the Academic Senate".

In order for the proposal to be admitted to the approval judgment, it must be expressly accompanied by a business project that presents:

1. The objectives of the business idea;
2. A financial plan;
3. The economic prospects and the reference market;
4. The innovative nature of the project;
5. The technological and scientific qualities of the project;
6. The description of the roles and duties of the professors and researchers involved;
7. The methods of any participation in the capital and the definition of the participation fee requested by the proponent (s) from the University;
8. Aspects relating to the regulation of intellectual property, made compatible with the regulations on the subject established by the University.

However, the approval procedures of the spin-off proposal are delegated to the University, by referring to the internal regulations, which define more specific procedures, especially in order to contain the timing of the assembly sessions and to streamline the project approval process. Therefore, it is common practice to provide for the establishment of Evaluation Commissions (generally made up of subjects competent in legal and economic matters) within the University which are placed upstream of the approval process having the task of examining the proposals for off and to assess its consistency with the general objectives of the University of reference. This is particularly necessary when the Entity's participation in the share capital is envisaged (in this case we are talking, as already seen, of university spin-offs), a situation in which an assessment of the associated risks is mandatory. Following the examination conducted, the Commission expresses its own evaluation of the project and communicates it to the governing bodies of the University for official approval (preliminary opinion of the Academic Senate and resolution of the Board of Directors).

LAW DECREE 179/2012 AND LAW DECREE 3/2015

The analogy between spin-offs as a new entrepreneurial initiative based on research and innovative start-up allows us to make a further reference to the discipline introduced by Legislative Decree 179/2012 art. 25, paragraphs 2 and 3, on the subject of innovative start-ups which have the aim of "[...] promoting sustainable growth, technological development, new entrepreneurship and employment, especially among young people [...]". Therefore, it is also possible to consider the spin-offs of public research among the recipients of the standard, even if not in a direct and specific way. In fact, the relationship between the two statuses is not always two-sided: a university spin-off does not necessarily need to comply with the fundamental requirements to define itself as an innovative start-up. For example, there could be the need to redistribute profits (or part of them) to remunerate the interventions or support of the originating entity. Just as, at times, it is the evolution, the business dynamics and the relationships with the research body that make the concepts superimposable. In fact, the Ministry of Health in the Decree no. This represents a cultural boost and an opening to several important opportunities.

Recently, the discipline has investigated some issues, albeit with indirect reference, relating to the type of companies being analyzed. In particular, paying attention to the form of the company being incorporated, explicit reference is made to Law no. 221 (conversion of Legislative Decree 179/2012) which identifies as innovative start-ups the joint stock companies under Italian law or in the form of a European company whose shares or shares representing the capital are not listed on a regulated market. In practice, there are many factors that lead to a preference for this legal form rather than others: among the advantages there is certainly the limitation of financial liability in the event of failure of the business project, the greater control deriving from the application of the provisions of the Civil Code on the matter of capital companies, and a clear identification of the roles and responsibilities of the shareholders and of the persons in charge of management power. Given the high degree of risk that normally characterizes the business of start-up companies, the choice of limited liability should favor their spread.
Subsequently, in order to overcome the time requirement and the issue of the prohibition of distribution of profits, the Decree Law 3/2015 (Investment Compact), converted into Law 33/2015, attributed a large part of the measures envisaged to the benefit of start-ups innovative to a potentially much wider range of companies:

innovative SMEs, that is to say all small and medium-sized enterprises operating in the field of technological innovation, regardless of the date of establishment, the corporate purpose and the level of maturity.

LEGISLATIVE DECREE N. 175/2016

More recently (Legislative Decree no. 175 of 19 August 2016, published in the Official Gazette on 8 September 2016 (no. 210), and entered into force on 23 September 2016, "Consolidated Law on publicly held companies", issued in execution of the legislative delegation referred to in art. 16 and 18 of Law 7 August 2015, n. 124 "Delegations to the Government regarding the reorganization of public administrations") the need was felt to review the legislation relating to the so-called "companies to public participation" with the aim of limiting its proliferation and setting rules that prevent its distortion from public utility purposes. The "Consolidated Law" arises, in fact, from the urgency of regulation and standardization of a matter that over the years has seen the succession of measures probably not homogeneous with each other and mainly aimed at containing public spending, with the aim of indirectly regulating the intervention of the Public Administration in the market.

With art. 1 the scope of application of the rule is immediately outlined: "the provisions of this decree concern the establishment of companies by public administrations, as well as the purchase, maintenance and management of shareholdings by these administrations, in companies with total or partial public participation, direct or indirect" while in the following paragraph 3, again in art. 1, it is envisaged that "for all that is not derogated from the provisions of this decree, the rules on companies contained in the civil code and the general rules of private law are applied to companies with public participation".

The direction chosen by the legislator was that of "[..] to *arrange that for the companies referred to in Article 4, paragraph 8 (companies with spin-off characteristics, university start-ups or with similar characteristics of research bodies) , the provisions of article 20 shall apply after 5 years from their constitution".*

The provisions of article 20 refer to the financial parameters that must be used by the Public Administrations when annually they will have to prepare a plan to maintain or not their shareholdings and, in the event of a negative outcome, submit them to "*a reorganization plan for their rationalization, merger or suppression, including through liquidation or sale".*

In order, the parameters that are specifically relevant are mainly four:

i. companies that have no employees or have a number of directors higher than the number of employees;
ii. equity investments in companies that carry out activities similar or similar to those carried out by other investee companies or by instrumental public bodies;
iii. equity investments in companies which, in the previous three years, have achieved an average turnover not exceeding one million euros;
iv. equity investments in companies other than those set up for the management of a service of general interest which have produced a negative result for four of the five previous years.

ANAC RESOLUTION 620/2018

In the debate triggered by the rules of the Madia Law, generated by the combined provisions of the articles of law mentioned in the previous paragraph and not yet addressed, the National Anti-Corruption Authority has recently been introduced with resolution 620 of 4 July 2018 which expresses an opinion, in response to a question posed by the CNR, regarding the applicability of the Consolidated Law on investee companies (Legislative Decree 175/2016 and subsequent amendments) to companies with spin-off characteristics or university start-ups established pursuant to Legislative Decree 297/1999 .

In fact, *"although the application of the Consolidated Law on investee companies does not fall within the competence of ANAC, the latter believes that, since these are issues of interpretation of art. 7 of the TU (Constitution of publicly held companies) where reference is made to the participation of the entity in the deed of incorporation - which obviously has a negotiating nature - the matter of public contracts from which legitimation would derive is necessarily called into question"* (Granieri, 2018).

The resolution of the ANAC implies that "for the purposes of setting up spin-off companies, in the form of joint stock companies in which a private entity also participates, the identification of the latter must take place through a public procedure (...) and with application of the provisions on transparency".

This determination, although theoretically correct, would seem to generate in practice a further increase in the degree of confusion due to the logic of a reasoning based only on the consequentiality of the fact that if the companies owned by the public administration are governed by the TU and the company spin-off is owned by the University / public body, the spin-off company is subject to the TU and the rules referred to therein, including those on public evidence.

Therefore, ANAC expresses an orientation which, despite the deliberately universalistic intention of the text, is not binding even for the entity that requested it, thus contributing only to generating background noise and uncertainty in a context that instead requires the exact opposite: a few simple, clear, unidirectional, homogeneous and incentive rules.

CHAPTER 4: ITALIAN IRCCS AND TECHNOLOGICAL TRANSFER

Having clarified, in the previous chapters, the concepts of technology transfer and spin-off of a general nature, we can now proceed with addressing these issues in a more specific context such as the clinical / health field.

Research and assistance in the health field represent activities of particular importance not only for their so-called "primary" objectives, that is, linked to the care of citizens, but also as regards economic development and innovation processes at the national. In particular, translational research, which includes the set of activities concerning the application of clinical research results to patient care, is a fundamental step for the development of innovation in the biomedical field. These activities require the involvement of personnel who work in various capacities in universities, in public research bodies (EPR) and in health institutions of various kinds. This is the set of people and organizations operating at the frontier of care and research activities, whose potential is enormous as they work daily in contact with the problems related to care and assistance; an area in which it is possible to conceive and test innovative solutions on which to activate technological enhancement and transfer actions, the ultimate aim of which is to improve the levels of healthcare for citizens and generate returns for the benefit of the entire country system.

The purpose of this chapter is to think about the potential, problems and perspectives of technology transfer in the healthcare area, wondering if there are possible analogies between what the university system has experienced in the last fifteen years on the subject of technology transfer - namely the transition from a poorly structured system to a more aware and organized one - and what the hospital system and clinical research in general are experiencing in this context.

The clinical innovation process was born with the identification of a medical need which, through a gradual approach towards the invention, develops towards the implementation of an innovative commercial solution (Yock et al., 2015). Before being introduced on the market and adopted in medical practice for patient care, clinical innovation must nevertheless undertake the processes of validation and certification, clinical trials and the regulatory implementation of reference (regional and / or national). Therefore, the clinical innovation process is characterized by a very long "time to market" and a high "attrition rate". These characteristics entail the need for major investments, so whoever identifies the innovative solution is usually unable to develop it independently to transform it into a product to be brought to the market. Finally, to this path is added the need to prepare a specific (regional or national) legislation for the product in question in order to be able to adopt it in the treatment of the patient.

Only in the health sector does the researcher have a triple specificity in himself, as he is at the same time researcher, user and experimenter. This represents a great opportunity since in other areas it often happens that the researcher expresses and develops ideas that are relatively far from the application areas, while in the sector in question the researcher almost always knows the specific needs related to the care practice (and in fact, of the market) that eventually it will use the innovative solution. The invention conceived by the researcher in the health sector, unlike

what often happens in other university fields, is often more consistent not only with technical-scientific requests, but also with those of a commercial nature. From these peculiarities, it is evident that the process of technology transfer in the clinical setting is different from what happens in the rest of scientific research.

When we talk about clinical innovation we refer to the introduction and/or development of tangible and intangible technological innovation. Tangible technological innovations refer to the biomedical/bio pharmacological field, understood as the development of new drugs, new biological and/or active chemical compounds, also including medical devices for diagnostic and therapeutic use; while intangible innovation refers to protocols, diagnostic or therapeutic strategies and medical management innovation understood as the organization of care pathways. If these are the inventions we are talking about, we realize how the field of clinical innovation represents one of the next challenges to be faced, as it has an impact on prevention, diagnostics, therapy, assistance and more generally on the well-being of citizens; the specificity of this sector, unlike others, is given by the fact that research and innovation in this area, in addition to generating progress and work, above all generate health, even beyond national borders.

The dynamics of technology transfer in the healthcare sector have strong and significant critical points. The strengths are represented by the quality of the research, the presence of state-of-the-art research centers and the network connection of the hospital centers. Furthermore, the innovative solutions proposed in this sector respond to specific medical needs and have a significant social impact in terms of reducing healthcare costs.

Analyzing the critical issues, it is highlighted the lack of a specific set of rules, already existing for universities, which determine the boundaries within which clinical research centers must carry out initiatives related to the enhancement of their research. Another criticality is represented by the training of researchers, who often do not have a clear vision of what their research work will entail in view of a consequent technology transfer. Added to this is also the difficulty, for the researcher himself, of having to carry out, together with the assistance task, also that of researcher and experimenter. Lastly, the criticality of the evaluation system of doctors/researchers and the funding system of the Institutes, still very attentive to the issue of publication rather than that of technology transfer, an attention that sometimes leads to a negative influence on the commitment to the transfer itself.

Research hospitals play an important role in the production and circulation of knowledge and represent organizations in which all the different benefits of research can manifest themselves (Salter & Martin, 2001). Research hospitals are, in other words, organizations that play an essential role in clinical innovation: production and dissemination of knowledge, connection of practice with science and technology, use and feedback on prototypes and concepts, and implementation of new medical routines, devices and procedures. At the same time, however, research hospitals occupy a delicate position in the political-health landscape. On the one hand, as health care providers, they must respect procedural logics, which lead research to support the best results and high-quality systems. On the other hand, as research structures, they are aware of innovation policy, which aims to promote research, science and technology-based innovations where industry is a key point. In interacting with these political logics, the research hospital must orchestrate a series of interests that do not always coexist harmoniously (Miller & French, 2016). These hospitals are particularly important institutions for facilitating the dissemination of tacit and codified knowledge, as they act as key users of innovations, being able to provide practical feedback on new

technologies and establish an organizational link between experimental research and basic research (Consoli & Mina, 2009). The theme of the enhancement of knowledge in the health sector does not emerge only from national planning documents, but also from recent international works that have analyzed the need for "research hospitals" (in Italy, the IRCCS), to equip themselves internally with a Unit Organizational for Technology Transfer (TTO) aimed at encouraging and speeding up both interdisciplinary collaboration and innovation in the healthcare field (Miller & French, 2016). These studies analyze how the creation of an organizational unit for technology transfer (TTO) aimed at encouraging, enabling and speeding up interdisciplinary collaboration and innovation in the biomedical field, has made it possible to coexist two different hospital logics research: on the one hand the logic of care and assistance, on the other the logic of innovation, aimed at the sustainability and competitiveness of the health system.

Within our national system, IRCCS can be considered as institutions with a wider role than the threefold, widely recognized function of health care, training and research; in fact, it is possible to identify the third mission thus identified for universities - albeit with appropriate modifications - as the "fourth mission" of hospitals and consider it as a mission of innovation and knowledge transfer (Rey-Rocha & López-Navarro, 2013). This mission is intended to include innovation in health technologies so that results can be transferred to society and thus contribute to economic and social development. The fourth mission thus transforms hospitals into "innovation actors and strategic development agents" as well as healthcare providers (Zawdie, 2010). This can be seen as the completion of the hospital's research mission, which includes healthcare, translational research, training and innovation in healthcare in patient care.

A starting point for starting the innovation process is to create and spread the culture of technology transfer in research hospitals through cross initiatives (top-down and bottom-up) that aim to promote and spread the culture of the fourth mission.

With these premises, it is particularly important that the Ministry of Health is activating a series of project activities for the recognition of technology transfer activities.

The path of clinical innovation begins with a medical need that is identified in patient care. It is the medical need that stimulates the identification of innovative technical solutions that can be protected and enhanced. The prototype designed is compared with the standard of care by means of clinical trial protocols on patients in order to verify if it is the solution to the identified problem. Once the "proof of concept" data has been obtained, a further phase of validation and clinical experimentation is required which will allow the innovative product to be included in the current standard of care. Finally, the adoption of the product in the treatment protocols can only take place after the approval of a specific legislation that is perfected for each individual product used in patient care.

In the context of clinical innovation it is necessary, in other words, to demonstrate not only the usefulness of the invention, but also the effectiveness, efficiency and cost-effectiveness of the application to ensure that this practice (or device) is adopted as an innovative medical practice. In other words, it is necessary to perform both a health technology assessment analysis (HTA, "Health Technology Assessment"), and the inclusion in homogeneous diagnosis groups (DRG "Diagnosis Related Group").

The HTA process measures the impact of biomedical research and innovative technologies, which provide answers to health care problems, as also envisaged by the State-Regions agreement of 7 September 2016 relating to the updating of the Essential Levels of Assistance. HTA is a multidimensional and multidisciplinary approach for analyzing the medical-clinical, social, organizational, economic, ethical and legal implications of a technology through the evaluation of multiple dimensions such as effectiveness, safety, costs, social and organizational impact. The objective is to evaluate the real and/or potential effects of the technology, both a priori and during the entire life cycle, as well as the consequences that the introduction or exclusion of an intervention has for the health system, economy and society (Ministry of Health, 2017). The fields of biomedical research and HTA can therefore only represent a continuum of integrated activities useful for guaranteeing the best choices for citizens' health and the correct use of resources.

The DRG is the system which, based on diagnostic criteria (and any associated procedures), allows to classify all patients discharged from a hospital into homogeneous groups for the absorption of resources committed in order to remunerate each episode of hospitalization (Ministry of Health, 2015). The DRG is attributed to each patient discharged from a hospital, based on patient-specific variables: age, sex, type of discharge, main diagnosis, secondary diagnoses, procedures / surgeries. Innovative technologies that provide answers to care problems must be coded with a DRG in order to be affordable as hospital supplies or to be implemented in medical practice.

A modern healthcare system must be able to translate its values and research results into levers for the innovation ecosystem where, in recent years, there has been a growing focus aimed at prioritizing technology transfer as a key component in the value chains of the biotechnology sectors, pharmaceutical and social health.

4.1 The protagonists of the clinical innovation ecosystem

The ecosystem of clinical innovation involves, even in Italy, a multiplicity of public and private entities. It is characterized by the presence of various stakeholders, described below, included in a collaborative network between them.

- The National Health Service (SSN): a system of structures and services, managed through the collaboration between the State, Regions, Companies and Municipalities, which aim to guarantee all citizens, in conditions of equality, universal access to equitable provision of health care services.
- The Ministry of Health: organizer of the entire system of structures for the care of citizens and for prevention and supporter and financier of highly innovative research initiatives, plays a central role, in close connection with its subjects afferent and with external subjects. The functions of the Directorate General for Research and Innovation in health include, in fact, also the coordination of relations with other Ministries, universities and research bodies, public and private, national and international. Specifically, it is the Management that deals with Technology Transfer through the Internationalization and Promotion of Research Infrastructures Office.

- Regional Health Services (SSR): without prejudice to the coordination of the National Health Plan (PSN) by the Ministry of Health, they in turn include the regions and autonomous provinces of Trento and Bolzano, the local health authorities (ASL) and hospitals (AO). Furthermore, consider the role of the National Agency for Regional Health Services (Age.na.s.) in supporting the government policies of the State and Regions health services, through research, monitoring, evaluation, training and innovation activities.
- The Institutes of Hospitalization and Scientific Care (IRCCS): provide technical and operational support to the other organs of the NHS, for the exercise of welfare functions in order to pursue the objectives of the PSN in the field of health research and for training of the staff. The IRCCS, hospitals of excellence, pursue mainly clinical and translational research purposes in the biomedical field and in that of the organization and management of health services and carry out hospitalization and high specialty care services.
- Doctors: provide a fundamental contribution to research in the clinical field, carried out in Italy by various institutes, a fundamental point of passage for biomedical innovation, also due to the fact that it involves research and clinical practice in contact, for their nature, with the problems connected to the care and assistance of the entire country system. As part of the promotion of professionalism by the Ministry of Health and the identification, in conjunction with the Regions and other public administrations, of the needs of NHS personnel and health professionals, the definition of the relationships between the NHS and universities is included on the staff of hospital-university companies and basic and specialized training of health professionals as well as memoranda of understanding for assistance activities.
- Patients: they are at the center of activities aimed at making it possible to benefit from advances in science and medicine, in consideration of the changes in the health needs of patients themselves, framed in a health system, related regulatory environments and regulatory authorities in constant evolution. The Ministry of Health oversees to ensure that the research carried out is aimed at the public interest with a direct impact on the care of the patient.
- Universities, places for sharing specific knowledge and skills. Practices for exploiting research results, in a logic of complementarity of offer between the health system and universities, presuppose synergies between research, assistance, training and innovation functions. The specific purpose is to combine the quality of research with the quality of assistance.

These actors are joined by specialized companies and investors, who finance research projects by providing capital, and other players such as sector associations and foundations engaged in research promotion and enhancement activities.

4.2 Technology transfer in the clinical field: the Italian reality of the IRCCS

As regards the Italian reality, the Institutes of Hospitalization and Scientific Care (IRCCS) are hospitals of excellence that pursue research purposes, mainly clinical and translational, in the biomedical field and in that of

the organization and management of health services by carrying out high specialty hospitalization and care. Currently there are 51 IRCCS and they deal with clinical and translational research with the aim of finding an outlet in innovative therapeutic applications to be adopted in the treatment of the patient. Their activity concerns well-defined research areas, whether they have received the recognition of a scientific institute for a single subject (monothematic IRCCS), or for several integrated biomedical areas (polythematic IRCCS). The areas of excellence of the IRCCS are: cardiology; dermatology; imaging diagnostics; pharmacology; gastroenterology; genetics; geriatrics; infectious diseases; complexity medicine; neurology; neurorehabilitation; ophthalmology; oncology; orthopedics; pediatrics; psychiatry; rehabilitation (Ministry of Health, 2021).

Scientific Hospitalization and Care Institutes have a different legal nature, public or private (Table 1). There are 21 public IRCCS; they are public institutions of national importance subject to regional control and supervision by the Ministry of Health, which appoints their scientific director. Furthermore, at the request of the Region in which the Institute has the main headquarters of clinical and research activities, the IRCCS can be transformed into IRCCS Foundations of national importance, open to the participation of public and private subjects and subject to the supervision of the Ministry of Health. and the Ministry of Economy and Finance. There are 30 private IRCCS and they have greater freedom of action; the control on them is carried out only on the value of the researches carried out.

The region with the highest number of IRCCS is Lombardy, with 18 IRCCS of which 14 private, followed by Lazio with 8 IRCCS of which 5 private, Emilia-Romagna with 5 IRCCS of which 4 public, Veneto, Puglia and Sicily with 3 IRCCS, Friuli-Venezia Giulia, Liguria, and Campania with 2 IRCCS and Basilicata, Marche, Piedmont and Molise with one IRCCS.

Denominazione	Regione	Città	Natura Giuridica
Azienda Ospedaliero Universitaria	Emilia-Romagna	Bologna	Pubblico
Centro Cardiologico S.P.A. Fondazione Monzino	Lombardia	Milano	Privato
CRO - Centro di Riferimento Oncologico	Friuli-Venezia Giulia	Aviano (PN)	Pubblico
CROB Centro di riferimento oncologico della Basilicata	Basilicata	Rionero in Vulture (PZ)	Pubblico
Ente Ospedaliero specializzato in gastroenterologia Saverio De Bellis	Puglia	Castellana Grotte (BA)	Pubblico
Fondazione Ca'Granda – Ospedale Maggiore Policlinico	Lombardia	Milano	Pubblico
Fondazione del Piemonte per l'Oncologia	Piemonte	Candiolo (TO)	Privato
Fondazione Don Carlo Gnocchi	Lombardia	Milano	Privato
Fondazione G.B. Bietti per lo studio e la ricerca in oftalmologia	Lazio	Roma	Privato
Fondazione IRCCS Istituto Nazionale dei tumori	Lombardia	Milano	Pubblico
Fondazione Istituto Neurologico Carlo Besta	Lombardia	Milano	Pubblico
Fondazione Istituto Neurologico Casimiro Mondino	Lombardia	Pavia	Privato

Fondazione Policlinico San Matteo	Lombardia	Pavia	Pubblico
Fondazione Policlinico Universitario Agostino Gemelli	Lazio	Roma	Privato
Fondazione Santa Lucia	Lazio	Roma	Privato
Fondazione Stella Maris	Toscana	Calambrone (Pisa)	Privato
IEO - Istituto Europeo di Oncologia	Lombardia	Milano	Privato
IRCCS Centro Neurolesi Bonino Pulejo	Sicilia	Messina	Pubblico
IRCCS Centro San Giovanni di Dio Fatebenefratelli	Lombardia	Brescia	Privato
IRCCS Multimedica	Lombardia	Milano	Privato
IRCCS Ospedale San Raffaele	Lombardia	Milano	Privato
IRCCS San Raffaele Pisana	Lazio	Roma	Privato
Istituti Clinici Scientifici Maugeri S.p.A. SB	Lombardia	Pavia	Privato
Istituti fisioterapici ospitalieri - Istituto Dermatologico Santa Maria e San Gallicano Istituti fisioterapici ospitalieri - Istituto Regina Elena	Lazio	Roma	Pubblico
Istituto Auxologico Italiano	Lombardia	Milano	Privato
Istituto Clinico Humanitas	Lombardia	Rozzano (Milano)	Privato
Istituto delle Scienze Neurologiche	Emilia-Romagna	Bologna	Pubblico
Istituto Dermopatico dell'Immacolata (IDI)	Lazio	Roma	Privato
Istituto di ricerche farmacologiche Mario Negri	Lombardia	Milano, Bergamo, Ranica	Privato
Istituto Eugenio Medea	Lombardia	Bosisio Parini (LC)	Privato
Istituto Giannina Gaslini	Liguria	Genova	Pubblico
Istituto in tecnologie avanzate e modelli assistenziali in oncologia	Emilia-Romagna	Reggio Emilia	Pubblico
Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione (ISMETT)	Sicilia	Palermo	Privato
Istituto Nazionale di Riposo e Cura per Anziani	Marche	Ancona	Pubblico
Istituto nazionale tumori Fondazione Giovanni Pascale	Campania	Napoli	Pubblico
Istituto Neurologico Mediterraneo Neuromed	Molise	Pozzilli (IS)	Privato
Istituto Oncologico Veneto	Veneto	Padova	Pubblico
Istituto Ortopedico Galeazzi	Lombardia	Milano	Privato
Istituto Ortopedico Rizzoli	Emilia-Romagna	Bologna	Pubblico
Istituto per le Malattie Infettive Lazzaro Spallanzani	Lazio	Roma	Pubblico
Istituto scientifico romagnolo per lo studio e la cura dei tumori	Emilia-Romagna	Meldola (FC)	Privato
Istituto tumori Giovanni Paolo II	Puglia	Bari	Pubblico

Oasi di Maria Santissima	Sicilia	Troina (EN)	Privato
Ospedale Casa Sollievo della Sofferenza	Puglia	San Giovanni Rotondo (FG)	Privato
Ospedale infantile Burlo Garofolo	Friuli-Venezia Giulia	Trieste	Pubblico
Ospedale pediatrico Bambino Gesù	Lazio	Roma	Privato
Ospedale Policlinico San Martino	Liguria	Genova	Pubblico
Ospedale Sacro Cuore Don Calabria	Veneto	Negrar (VR)	Privato
Policlinico San Donato	Lombardia	San Donato Milanese	Privato
San Camillo IRCCS S.r.l.	Veneto	Venezia	Privato
SDN Istituto di Ricerca Diagnostica e Nucleare	Campania	Napoli	Privato

Table 1

In the field of health research, the IRCCS play an important role, assuming a function of driving the application of knowledge on clinical practice through a path of evaluation of paths and processes, the construction of diagnostic-therapeutic paths and guidelines, the assessment of costs and organizational processes, the impact on users so that health interventions are correct and sustainable. It involves moving from a generic concept of scientific evidence and a phase 1 transfer research model (called "bench to bedside") to a phase 2 transfer research to evaluate how scientific results work when applied in practice. This approach should become a reference cultural model for the entire National Health System (NHS). The next step is phase 3 transfer research which uses scientific, experimental and non-experimental methodologies to evaluate the relationships between health policy interventions and factors that can interfere with clinical and public health management strategies. In this way it is possible to address health problems starting from principles of evidence-based medicine, through research and transfer health strategy. Finally, the enhancement of the simultaneous presence of research and clinical skills cannot disregard the role of the IRCCS as promoters and evaluators of the innovation and standardization of diagnostic, assistance and organizational pathways that are truly transferable to other structures of the National Health Service, as well as to others structures of the SSN that propose these purposes. In this context, the role of the IRCCS appears crucial, called by vocation and by law to a strong integration between hospitals and laboratories, care and innovation activities (Ministry of Health, PNRS 2014-2016).

The issue of clinical innovation is therefore an important and delicate issue at the same time because it has several problems that affect the development of innovation. Although it is true that innovation in this sector generates social well-being, given the importance of the innovations implemented, in this context the potential innovators (the researcher, the doctor, the nurse or even the laboratory technician) are not rarely having to support their own research projects or having to independently seek dedicated research funds for the development of their own inventions or even more frequently they find themselves in bureaucratic complexities to face. Hence the support of the TTO, which can help the inventor in the various stages of innovation development at least in theory, because in practice, unfortunately, the TTOs, especially the public ones, are also experiencing inconsistencies in the legislative rules that regulate processes and complain about the excessive bureaucracy that slows down any phase of the research enhancement process.

The importance of the topic has led the Netval association to deal with technology transfer in the healthcare sector. Aware of the complexity of the issue and the critical issues connected to it, Netval came into contact in 2016 with the Ministry of Health. The importance of focusing the analysis on one of the players in clinical innovation in Italy, the IRCCS, emerged from the interaction between Netval and the Ministry of Health. The choice towards this type of institution is linked to two main reasons: the IRCCS include translational research and clinical assistance at the same time and are registered in a defined number.

The Ministry of Health has chosen to use the Netval questionnaire as a model for the first timely recognition of technology transfer in the IRCCS, because it is a model used for more than ten years by universities and research bodies. It therefore guarantees the uniformity of the data collected. However, the Ministry of Health simplified the questionnaire and adapted and integrated it with sections of specific interest for the IRCCS, in order to collect useful data for understanding the dynamics of technology transfer. The survey covers the three-year period 2016 - 2018 and the data collected were processed and published by Netval.

The analysis was aimed at understanding if and in what ways the IRCCS were active in the field of technology transfer: the number of active IRCCS was significantly increased compared to 2016. In fact, almost all the IRCCS are "operational" on technology transfer (43 IRCCS "are doing something" or "they are gearing up") and that only a small percentage (10%) does not carry out technology transfer activities nor have they planned to do so in the near future, by specific choice or for other contingent reasons. In particular, of the 51 IRCCS analyzed in 2018, 45% (23 IRCCS) declare that they carry out technology transfer activities using a specific Technology Transfer Office (TTO), which in such cases represents the organizational unit that deals with the enhancement of the search results. The number of TTOs present in the IRCCS has significantly increased compared to 2016, passing from 14 to 23 units.

In another 39%, the IRCCS do indeed carry out technology transfer activities, without however having a specific office, thus making use of other less specialized internal offices. Also, in this case (20 IRCCS) the number increased compared to 2017, where 18 IRCCS declared that they were carrying out technology transfer activities despite not having a specific office. Finally, in 6% of cases, the IRCCS do not carry out technology transfer activities, but plan to start doing so soon. Overall, therefore, during 2018 the actual commitment to the issues of technology transfer by the IRCCS which were taking action in this area in 2017 increased. In fact, in 2018, 43 IRCCS carried out technology transfer activities with a dedicated office or without an office; an increase compared to the 38 IRCCS in 2017.

The growing number of IRCCS that have approached these issues is probably attributable both to the implementation of ministerial indications in this sense, and to the ever increasing competitiveness that the IRCCS have to face in a rapidly evolving international scenario.

The year of establishment of the first TTO in an IRCCS is 1992, but it is only since 2010 that more and more IRCCS have begun to carry out technology transfer activities and to equip themselves with dedicated offices. The number has remained stable over the years, up to 2017, the year in which the largest number of IRCCS that have started technology transfer activities are registered. In fact, in 2017, 8 IRCCS started technology transfer activities,

of which 4 without a specific office and 4 with a specific office. 2017 therefore represents a significant year for the development of these activities in the IRCCS.

The IRCCS that carry out technology transfer activities are gradually creating internal notes/guidelines and specific regulations regarding various issues:

- ownership of inventions;
- management of economic returns;
- copyright ownership;
- conflicts of interest;
- patent licensing agreements;
- creation of spin-offs;
- collaboration with industry and contract research.

The main TTO missions are in order of importance according to the IRCCS:

- Support the patenting policies of research results and enhance the capabilities of the IRCCS to commercially exploit the rights deriving from its patent portfolio
- Promote the economic exploitation of the results and skills of scientific and technological research
- Promote technology transfer and economic development processes at local and regional level
- Spread an entrepreneurial research culture and support spin-off initiatives

As regards the various functions performed by the TTOs, it emerges very clearly that the two areas of most intense activity are intellectual property and licensing activities. In fact, all TTOs deal with intellectual property management and this data is constant over the years. Almost all the TTOs focus on the management of licensing activities (78%) although to a lesser extent than in 2017 (85%). Furthermore, most TTOs concentrate their activities in the management of research contracts in collaboration with international industry (78%), in participation in mixed working groups (75%), in supporting interaction with the industrial sector (74%) and in supporting business development activities (70%). In fact, many TTOs concentrate their forces on these six activities, leaving slightly in the background, but with rather high values, support for the creation of spin-off companies (65%), the dissemination of information and tenders (65%), the scouting of new inventions (61%), the management of research contracts in collaboration with the national industry (60%).

Among the remaining functions, it is useful to underline how the staff of the TTOs of the IRCCS are more dedicated in 2018 (61%) than in 2017 (55%) to the functions of requesting and disseminating information and consulting and to a lesser extent (57%) compared to 2017 (75%) to the management functions of research contracts with international industry.

Furthermore, it is useful to highlight the significant increase in activities related to CPD compared to 2017 (35%). In fact, in 2018, 55% of the staff of the TTOs of the IRCCS dedicated time to professional training activities. This data could be a positive consequence deriving from the increase in interest in technology transfer activities in this sector.

Less significant percentages can be found for agreements with seed capital funds or business angel networks (45%), the management of research contracts in collaboration with national (39%) and international (35%) industry. Finally, the management of clinical trial contracts (22%), the management of science parks (18%) and the provision of technical services (13%) represent marginal functions for the staff of the TTOs of the IRCCS.

With reference to the research enhancement process, the IRCCS offer support to their researchers mainly during the patenting process, in finding external funding, in negotiating with external parties, in identifying business opportunities, in licensing activities and in definition of the business plan. Less support is provided with regard to entrepreneurial activity, both in the creation phase of a start-up or a spin-off, and after the spin-off has been established.

The process of technology transfer in the IRCCS is therefore different from those described in the previous chapters, as can be seen by looking at Fig 5.

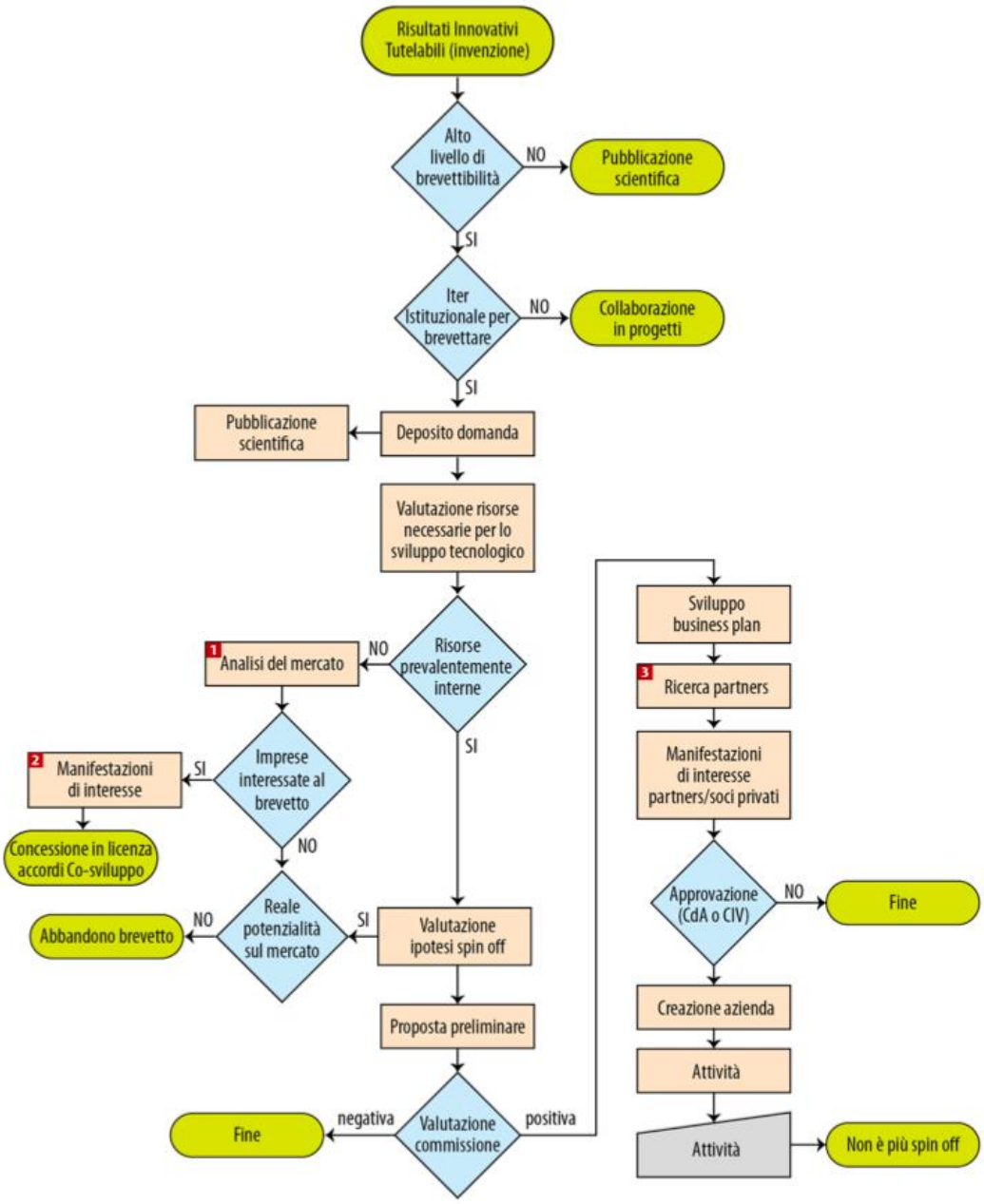

Figure 5: IRCCS Technologic Transfer process – Source: ***"Spin-off: Linee Guida per IRCCS"***

The launch of a spin-off, for the commercialization or enhancement of a patent or even a discovery, passes through both the evaluation of the TTO and through the evaluation of the board of directors which evaluates the pros, cons, profitability, feasibility and consistency with the rules governing the entity in question; this process, although necessary, could cause slowdowns in the business start-up process, with consequent delays in the enhancement process.

4.3 Medical technology and Pharma industry

Medical technology is any technology used to save lives or transform the health of individuals suffering from a wide range of conditions. In its many forms, medical technology is already diagnosing, monitoring and treating virtually every disease or condition that affects us.

For the sake of this document, medical technology includes medical devices and *in vitro* diagnostic medical devices. Medical devices are products intended to perform a therapeutic or diagnostic action on human beings by physical means. In vitro diagnostic medical devices are products which provide medically useful diagnostic information by examination of a specimen derived from the human body.

There are more than 500,000 medical technologies currently available and they all share a common purpose: improving, extending and transforming people's lives. Medical technology can be familiar, everyday products such as blood glucose meters, sticking plasters, syringes or latex gloves. Alternatively, it can also be pregnancy tests, spectacles, wheelchairs and hearing aids. Meanwhile, at the high-tech end of the scale, medical technology includes molecular diagnostics, total body scanners, ultrasounds, life-supporting machines, implantable devices such as heart valves and pacemakers, neurostimulators and replacement joints for knees and hips.

The common thread through all applications of medical technology is the beneficial impact on health, quality of life and in society as a whole. Medical technologies contribute to living longer and better and empower citizens to contribute to society for longer. In so doing, they improve the quality of care and the efficacy, efficiency and sustainability of healthcare systems.

In the European Union, medical technologies are tightly regulated by laws that govern the safety and performance of devices across their lifetime, pre- and post-market. Over the next few years, the European medical technology sector will transition from being regulated under the current medical devices directives to two new regulations.

Medical technology is characterised by a constant flow of innovation, which is the result of a high level of research and development within the industry, and of close cooperation with the users. Products typically have a lifecycle of only 18-24 months before an improved product becomes available.

In 2016, more than 12,200 patent applications were filed with the European Patent Office (EPO) in the field of medical technology – 7.7% of the total number of applications –, still more than any other sector in Europe. 41% of these patent applications were filed from European countries (EU28, Norway and Switzerland) and 59% from other countries, out of which with the majority of applications filed from the US (38%).

In comparison, around 5,700 applications were filed in the pharmaceutical field and around 5,700 also in the field of biotechnology. While over the last decade the number of EPO filings in the field of medical technology has doubled, pharma and biotech patent applications were relatively stagnant.

The European medical technology industry employs more than 675,000 people. Germany had the highest absolute number of people employed in the medical technology sector, while the number of MedTech employees per capita is highest in Ireland and Switzerland. This high level of employment shows that the medical technology industry is an important player in the European economy. In comparison, the European pharmaceutical industry employs more than 740,000 people.

There are approximately 27,000 medical technology companies in Europe. Most of them are based in Germany, followed by the UK, Italy, Switzerland, France and Spain. Small and medium-sized companies (SMEs) make up almost 95% of the medical technology industry, the majority of which employ less than 50 people (small and micro-sized companies).

In Europe, an average of 10% of gross domestic product (GDP) is spent on healthcare. Of this figure, around 7.2% is attributed to medical technologies, i.e. less than 1% of GDP. The spending on medical technology is estimated to vary significantly across European countries, ranging from around 5% to 10% of the total healthcare expenditure. Expenditure on medical technology per capita in Europe is at around €203 (weighted average). The European medical technology market in 2016 is estimated at roughly €110 billion.

Based upon manufacturer prices the European medical technology market is estimated to make up 29% of the world market. It is the second largest medical technology market after the US (approximately 43%).

The pharmaceutical industry is the part of the healthcare sector that deals with medications. The industry comprises different subfields pertaining to the development, production, and marketing of medications. These more or less interdependent subfields consist of drug manufacturers, drug marketers, and biotechnology companies. The main goal of the pharmaceutical industry is to provide drugs that prevent infections, maintain health, and cure diseases. This industry directly affects the global population, so a number of international regulatory bodies monitor things like drug safety, patents, quality, and pricing. The pharmaceutical industry has made a great deal of progress over the last decade due to a research-oriented approach that has improved technologies, developed infrastructures, and increased research in the field of bioscience. Thanks to biotechnology, various formulations have been developed to cure or stop the growth of several major infections, including HIV and certain types of cancer. The global pharmaceutical industry was worth an estimated $1 trillion in 2014. In 2013, global pharmaceutical markets generated revenues of $980.1 billion. That year, North America (the US and Canada) contributed 41% of sales, while Europe contributed 27.4%. More recently, in 2018, the global pharma industry stood at $1.2 trillion, and the IQVIA Institute for Human Data Science expects $1.5 trillion by 2023.

International regulatory bodies for the pharma industry include the WHO (World Health Organization), the FDA, and the MHRA (Medicines and Healthcare Products Regulatory Agency). It is important for companies in the pharmaceutical industry to follow the policies set by these organizations. Regulatory bodies monitor not only manufacturers, but also drug sellers and prescribing physicians.

A number of questions arise when we think about the current state of the pharmaceutical industry:

- Why is there an increasing need for pharmaceuticals?
- Why have medications become so complex?
- What factors have led to the growth of the pharmaceutical industry?

Below, we explore these questions.

Worldwide, the average human life span has increased substantially over the last few decades. However, more infections and diseases have come along with this longevity growth. This has led to increased research on aging populations. The goals are to prevent infections and maintain health so that these populations can enjoy better lives.

Hectic daily schedules have led to unhealthy eating habits, a lack of exercise, less sleep, and other problematic lifestyle choices. This has resulted in high obesity rates, poor digestion, hallucinations, breathing difficulties, and other physical problems. Health supplements have been introduced to remedy all these issues, reduce the chance of getting sick, and meet daily nutritional needs through vitamins and minerals.
The middle class has been growing in both the emerging and developed markets. People in these markets have more disposable income and expect better healthcare solutions.
Chronic disease cases have risen in number. This has made people become more dependent on medications and health supplements.
Globalization and urbanization have led to increased environmental disturbances. These are major driving forces in the growing demand for improved medication and health supplements for each age group and geographic location.

The transition of Big Pharma from research managed largely "in house" to an open model, capable of capturing and internalizing the creativity and innovative technologies of small high-tech companies, has generated a clear change in the world of research and research hospitals. In this context, the role of the IRCCS, focused on excellent research, assumes a fundamental role through the entrepreneurial enhancement of the results of basic research.

CHAPTER 5: CASE STUDIES – CRO & IRCCS DE BELLIS

What is described in the previous chapters allows a better understanding of the following one. Here, through the analysis and comparison of two case studies, we want to highlight the problems and/or strengths concerning the development of spin-offs, starting from the opinion of researchers and managers of Technology Transfer Offices. The above case studies see two IRCCS as protagonists: the CRO (Oncological Reference Center) of Aviano - Friuli-Venezia Giulia - and the hospital specialized in gastroenterology Saverio De Bellis of Castellana Grotte (Ba) - Puglia, both public IRCCS. A questionnaire (see appendix A) was submitted to the heads of the technology transfer offices of both IRCSS and a questionnaire (see appendix B) to the researchers of each IRCCS, in order to be able to appreciate the opinions on the topic dealt with so far. from several points of view, thus having a broader and more complete vision of the real, practical and current situation regarding the enhancement of research in the aforementioned Scientific Hospitalization and Care Institutes.

Let's start by analyzing the point of view and the answers that the researchers of both institutes have given.
The subjects interviewed were five researchers from the CRO of Aviano and six researchers from IRCCS De Bellis, for a total of eleven.
The first questions in the questionnaire concern gender, age, type of contract and educational qualification. The researchers of the CRO of Aviano are mainly if not exclusively men (one, in particular, did not have any data about it), ranging in age from 45 to 74 years, three are graduates in medicine and surgery, one in biological sciences and one in the pharmacy, three have a permanent contract and two indicated "Other type of contract". Moving on to the researchers of the De Bellis of Castellana Grotte, there are four women and two men, aged from 39 to 48, of which four graduates in biological sciences, one in veterinary medicine and one in bio-health sciences, five have a contract fixed term and one has a research grant. Although it is understood, it is better to underline that these data do not represent the totality of the researchers present within the Institutes, but it is a sample.
Although the two IRCCS present evident differences in age, gender, type of contract and educational qualification, there is one point in common: most researchers believe that the results of the research they are currently working on can be evaluated in order to start a spin-off.
There are two researchers who believe that their research cannot result in the creation of a spin-off: the first is studying the role of microRNAs in the intestinal inflammation process in order to use these RNA molecules as a therapy for chronic inflammatory bowel diseases. He explains that "As a result of the research I am dedicating, there could be the possibility of using the microRNAs identified as gene therapy for the treatment of inflammatory bowel diseases, but for the development of this type of therapies it is entrusted to pharmaceutical companies that have specific skills in the field. The results of the research could, on the other hand, be patented in order to sell the research results to the outside, obtaining royalties". While the second, who is working on pharmacovigilance, states that the idea of the spin-off in relation to his research is "Realizable only by hypothesizing applications on mobile or web, to follow patients in the reporting and management of adverse drug reactions. Path already attempted in various hypotheses of feasibility of projects but too advanced in the needs of resources to invest and personnel to hire or contract".

So, in both cases the factor that is preventing the spin-off from starting, if not just the idea of starting one, is the lack of financial resources and competent human capital. We will see later also through other answers that these two issues will be mentioned several times.

It should be noted, however, that in the first case to believe that the idea is not valid for the creation of a spin-off is a researcher with a degree in bio-health sciences who states in a second question of the questionnaire that "I have never considered the idea of being part of a spin-off because temperamentally I feel little predisposed to be part of an entrepreneurial activity as well as being poorly prepared in this field". These elements could explain why you would opt more for the patenting of research results and subsequent sale to an interested pharmaceutical company, rather than for the creation of a spin-off. It can be hypothesized that if the latter were to follow a training course concerning the field of entrepreneurship and if he were to compare himself with fellow researchers specialized in pharmacology, his answer to the question "Do you think that the results of this research can be evaluated spin-off hypothesis?" it would no longer be negative.

To assess how the "spin-off startup" topic is evaluated by the researchers, they were asked if they had ever considered joining one by starting one, and the results were quite positive: eight out of eleven respondents considered positively the idea of being part of a spin-off, against three who do not consider it a viable option.

A total of three out of eleven researchers answered "no" - all three from De Bellis - and they motivated this answer by stating that: "I have never considered the idea of being part of a spin-off since temperamentally I feel little predisposed to be part of an entrepreneurial activity as well as being poorly prepared in this field"- as seen before; "I worked mainly in IRCCS where this possibility was not foreseen at least until recently"; "Currently the times are not ripe. I need to consolidate the idea". Altogether they would all seem to be responses from people who if encouraged, enticed, trained and informed about the process of starting a spin-off and the opportunity a spin-off can offer, they might revise their opinion on it. This would result in an increased commitment by the IRCCS to promote the possibility of undertaking such an entrepreneurial activity through workshops, seminars, training courses, conferences and the like.

A sobering fact is found in the analysis of the question "Have you ever been part of a spin-off?".

It is clear that, although the largest number of researchers interviewed are inclined to the idea of taking part in the creation of a spin-off, in reality only a small part has had the opportunity to actually start one - or more - in previous years and none of these work for IRCCS De Bellis. This data is sobering as it shows that although there has been a sharp increase in the number of spin-offs born in recent years within universities, the number of researchers who have started a spin-off within the IRCCS remains, however, small - four out of eleven in this case - in fact, in 2018 only 8 spin-offs created by the IRCCS (of which 5 public and 3 private) were active out of a total of 1,695 spin-offs. This research enhancement tool should be exploited more, especially within the Institutes of Hospitalization and Scientific Care.

The four researchers who were able to be part of a spin-off were asked to offer their opinion on the factors that positively and/or negatively influenced its development. As regards the factors that have contributed in a favorable manner, all four consider the innovativeness of the project/product within a market interested in the proposed idea as the main factor; the second factor, not least, appears to be the availability of public funding. The impeding factors that implied the sale of the spin-off, on the other hand, arose only from the opinion of a researcher, who

states that "the legislation in force in the IRCCS - read the previous chapter, referring to Law 240/2010 and Ministerial Decree n. 168/2011 - due to possible "conflicts of interest" it precludes the possibility of creating spin-offs for researchers with exclusive contracts with the Institutes themselves". This problem is also shared by the two TTO managers, whose answers to the questionnaire will be seen later.

Furthermore, we wanted to ask for a personal opinion about the factors considered to be impeding the start-up of a spin-off from scratch. The factors identified by the researchers are six, of which three are the most problematic:

- Lack of entrepreneurial spirit of researchers; seven researchers cited it.
- Difficulty in acquiring sufficient funds; in six researchers have cited it.
- Too much bureaucracy; in four researchers cited it.
- TTO staff not sufficiently trained; in two researchers mentioned it.
- Difficult to enter the market; in two researchers mentioned it.
- Lack of innovation mentality in the Italian public and private system; only one researcher mentioned it.

All six factors listed confirm what we read in the literature and what even the experts in the sector affirm and indicate the need to intervene on several fronts such as:

- training of researchers and TTO staff;
- the streamlining of the procedures envisaged for the development of the spin-off project idea by modifying and updating the regulations in force today;
- the expansion of the network of investors and the increase in their involvement;
- the Italian mentality which on several occasions has proved adverse to change, and when it was necessary to implement it, it all took quite a long time.

Finally, each researcher was asked to express some suggestions addressed to their reference IRCCS in order to improve the promotion of their entrepreneurial activity. The proposals were as follows:

1. increase the staff dedicated to the TTO;
2. take advantage of greater resources for the management of preparatory actions for industrial / entrepreneurial proposals;
3. change the "Vision" of the Institute;
4. cultivate the entrepreneurial mentality of researchers, which instead, too often, is limited and bound to scientific publication.

It is evident how the theme of the little, if at all, entrepreneurial mentality of researchers is felt and recurrent. The researchers themselves are aware of how much this aspect has a negative influence on the success of research enhancement through the spin-off, and are however all equally willing to follow any training courses made available by the IRCCS to which they belong fill this gap.

Increasing the number of resources dedicated to the TTO could be a well-founded and fair suggestion, especially if the goal is to make the workforce as heterogeneous as possible, which is specialized in subjects such as Economics, Law, Management Engineering as well as in subjects medical-scientific, in order to have within the UTS figures who, in addition to evaluating the validity of the idea in the clinical context, evaluate the business idea in the round, analyzing the market of interest in order to understand whether this off looks promising or not in the long run.
Changing the "vision" of the Institute could be a drastic solution, rather, one could think of an integration of the same by including the entrepreneurial perspective of the IRCCS - which translates into the will and commitment to make research results marketable - which will be transmitted in cascade on researchers and more generally on staff.

After the analysis of the interviews addressed to the researchers, we can continue with the interview submitted to the heads of the Technology Transfer Offices of the two IRCCS under study. For the sake of completeness of information, in the case of IRCCS De Bellis it is a Research Enhancement Unit and not a TTO. The comparison between the two realities - totally different from each other - of which the points in common and not, will be underlined, aims to provide a starting point from which to draw corrective measures/actions to improve and resolve the issues that today make it difficult spin-off development is complicated.

A first difference is linked to the region to which the IRCCS belong, one is located in Northern Italy (CRO di Aviano) and the other in Southern Italy (De Bellis di Castellana Grotte). In the CRO of Aviano the technology transfer office was born in 2007, while only in 2020 the De Bellis of Castellana starts the Research Enhancement Unit. From this data it is easy to deduce how much more immature is the second IRCCS in the field of spin-off creation, in fact to date the CRO boasts 3 active spin-offs - out of 8 total - of which one started in 2019 and two started in previous years to 2018, while the De Bellis 0 - although both numbers are moderate overall.
The total amount of research funds available is markedly different, as can be seen in Table 2:

	2019	**2020**
CRO	€ 28.3 million	€ 31.7 million
De Bellis	€ 1.6 million	€ 2.1 million

Table 2 – Amount of research funds

and are the result of the sum of different items that we see represented in Table 3, in order to view in detail the extent of the difference in funds, knowing where they come from:

RESEARCH FUNDS	CRO		De Bellis	
	2019	2020	2019	2020
Funds from the central government (Miur, etc.)	€ 8.9 million	€ 13.2 million	€ 1.4 million	€ 1.5 million
Funds from the Region	€ 9.8 million	€ 9.4 million	€ 0.17 million	€ 0.20 million
Funds from the European Union	€ 0	€ 0	€ 10 Thousand	€ 0.11Mln
Contracts for research and consultancy financed by third parties and technical services	€ 0	€ 0	€ 43 Thousand	€ 0.22 million
Own funds of the IRCCS	€ 0	€ 0	€ 0	€ 0
Donations	€ 0.92 million	€ 0.86 million	€ 0	€ 40 Thousand
Other	€ 8.7 million	€ 8.3 million	€ 0	€ 0

Table 3 – Research funds

The delta that exists between one Institute and another is obviously wide. This figure is an example of what is happening today in Italy regarding the distribution of specific funds of the Ministry of Health destined for IRCCS: every year the IRCCS are subjected to an assessment based on 24 indicators which include data relating to research, assistance activities and technology transfer. On the basis of these quantitative assessments, each IRCCS receives a contribution for research expenses which is proportional to the percentage of output generated by each Institute. As already seen above, there are currently 51 IRCCS in Italy, scattered throughout the national territory, with a non-homogeneous distribution and apparently not linked to a precise map of needs. 50% are found in just two regions, Lombardy and Lazio, only 19 in the South (36%), 30 are private (58%), in the north private IRCCS prevail, some regions lack them. The amount of funding, based on current criteria, produces extreme variability, as it goes from contributions of many millions of euros, to the largest and most active IRCCS - such as, for example, in the case of the San Raffaele Hospital IRCCS - Milan (private IRCCS) which for the current research activity in 2020 received 13,043,670.65 euros of which 12,475,337.32 euros assigned on the basis of performance - a few hundred thousand - as in the case of Saverio De Bellis - Castellana Grotte (BA) hospital specializing in gastroenterology (public IRCCS) which received a total of 1,119,944.41 euros for the current research activity in 2020, equivalent to the share assigned on the basis of performance. For the first 10 IRCCS - less than 20% of all IRCCS - more than 40% of the allocated funds are envisaged (figure which can be verified by reading Table 4):

Institute	Total funding [€]	Share allocated on the basis of performance [€]	Legal nature
IRCCS San Raffaele Hospital - Milan	13,043,670.65	12,475,337.32	Private
Ca'Granda Foundation - Maggiore Policlinico Hospital - Milan	8,453,339.66	8,237,689.66	Public
IRCCS Foundation National Institute for the study and treatment of cancer - Milan	8,185,945.43	7,935,945.43	Private
IEO - European Institute of Oncology - Milan	6,934,619.67	6,559,619.67	Private
Bambino Gesù Pediatric Hospital - Rome	5,674,908.14	5,202,308.14	Private
Humanitas Clinical Institute - Rozzano (Milan)	5,555,257.69	5,038,857.69	Private
San Martino Polyclinic Hospital - Genoa	4,830,008.18	4,537,008.18	Public
San Matteo Polyclinic Foundation - Pavia	4,371,289.29	4,371,289.29	Public
Romagna scientific institute for the study and treatment of tumors - Meldola (FC)	4,248,638.30	3,820,263.30	Private
Total	**65,388,271.82**	**62,268,913.49**	
Total financial resources available for the year 2020	**161,801,912.64**	**154,972,165.65**	

Table 4

It is clear that most of the public financial resources end up in the portfolio of private IRCCS, which achieve greater results probably also thanks to their autonomy in the management of the available budget and their non-subordination to regulations that negatively impact IRCCS of a public legal nature.

Funding, as mentioned above, takes into account performance but not plans that meet needs at the level of the individual Institute, or in accordance with regional or national programs. It could therefore seem that this is a method that disperses the available resources rather than distributing them in an optimal way.

The Current Research activities of the Institutes, in line with what is reported in the National Health Research Plan 2018 - 2020, are evaluated and financed according to the breakdown of the following criteria:

A. Scientific production and relative efficiency and impact of scientific production (55%) - scientific publications are evaluated;
B. Ability to attract resources (10%) - the ability to obtain funds for research funding from Italian public bodies, the European Union, private bodies or foundations is assessed;
C. Assistance activity (20%) - the number of hospitalizations, the origin of the patients (% from outside the region or % of non-residents in Italy) and the complexity of the cases treated are assessed;
D. Ability to operate online (10%): the Institute must demonstrate its ability to be a point of reference, in the area of recognition, both in scientific and assistance activities, referring to the annual number of patients included in multicenter programs and to number of Regional Hub reference Care Centers by pathology and related activity;

E. Technology transfer (5%) - the economic value of the patents sold and licensed by the IRCCS in the last 3 years and the number of co-development contracts stipulated by the IRCCS are assessed.

This division is consistent with the dual institutional purpose to which they are preordained, the IRCCS present themselves as two-sided entities. From the point of view of assistance, as already mentioned, the IRCCS represent hospitals of excellence, usually specialized in sectors dedicated to the treatment of pathologies of national importance with a high social impact. From the scientific point of view, on the other hand, the IRCCS represent national research organizations, responsible for carrying out basic research, in accordance with the guidelines of the health research program. The technical and operational knowledge developed within the IRCCS are made available to the NHS, both in the exercise of the assistance functions and in the realization of the research objectives identified in the National Health Plan and in the training of personnel.

Despite the consistency with respect to the purpose of these Institutes, the evaluation method for the distribution of the funding listed above implies that the IRCCS is mainly dedicated to publishing and assistance activities, almost omitting the technology transfer activity whose results only affect for 5% of the total funding, in which more time and money should be invested in order to obtain further results for the scientific profile of the IRCCS itself.

There are also clear differences in the distribution of the time employed by FTE personnel (Full Time Equivalents) to carry out certain activities (see Table 5).

TIME BREAKDOWN OF ETP STAFF	De Bellis		CRO	
	2019	2020	2019	2020
ETP staff mainly dedicated to the protection of Intellectual Property (IP)	30%	30%	30%	30%
ETP staff mainly dedicated to research and consultancy contracts (with industry)	40%	40%	5%	5%
ETP staff mainly dedicated to licensing	10%	10%	30%	30%
ETP staff mainly dedicated to spin-off companies	0%	5%	5%	5%
ETP staff mainly dedicated to other tasks (e.g. management, finance, training, etc.)	20%	15%	30%	30%
Total	100%	100%	100%	100%

Table 5

First of all, these differences may be due to the fact that De Bellis has three FTE employees and the CRO, on the other hand, two. Secondly, it could also be deduced that since the TTOs are born in two different moments, the CRO in 2007 and the De Bellis in 2020, this may involve a different commitment in the activities shown in the table. An activity such as licensing, for example, takes time before results are obtained as at first the patent application must be submitted, then it is necessary to wait for it to be accepted and finally you can proceed to the negotiation phase for the sale of the license. With this it could be possible to explain why the CRO dedicates 30% of TTO staff time - with 3 licenses concluded in the year 2020 and 7 actives in the portfolio as of December 31, 2020 - while De Bellis dedicates only 10 % - with 1 license concluded in the year 2020 and 1 active in the portfolio as at 31 December 2020.

In the case of Intellectual Property (IP) protection personnel, both IRCCS take the same percentage of time, which is 30%. Although the percentage is the same, the results obtained are obviously different, as can be seen in Table 6:

N ° PATENT APPLICATIONS AND N ° PATENTS GRANTED	De Bellis		CRO	
	2019	2020	2019	2020
Patent applications: filed in Italy	0	1	2	1
Patent applications: filed in Europe	0	3	0	0
Patent applications: submitted to WIPO	0	0	0	2
Total number of patents: submitted in the year	**0**	**4**	**2**	**3**
Patent applications: nationalizations filed in Europe	0	3	0	0
Patent applications: Nationalizations filed in the United States	0	0	0	0
Patent applications: nationalizations filed in other countries	0	0	0	0
Total number of patents: nationalizations submitted during the year	**0**	**3**	**0**	**0**
Number of patents granted in Italy	2	1	1	1
Number of patents granted in Europe (EPO)	1	0	0	0
Number of patents granted in the United States	0	0	0	0
Number of patents granted in other countries	0	0	0	0
Total number of patents granted in the year	**3**	**1**	**1**	**1**

Table 6

An activity for which IRCCS De Bellis is most committed (40%) is the stipulation of research and consultancy contracts (with industry), against 5% employed by the CRO. This activity is useful for achieving:

- co-development agreements with companies that undertake to produce the products on which the IRCCS carries out research and tests them (in this case it is mostly medical devices);
- pure research agreements with other universities;
- material transfer agreement.

With these agreements, PIs or royalties are obtained in the case of medical devices.

Finally, as regards the time dedicated to spin-off companies, the percentage is again the same for both institutes, it corresponds to 5% and in this case the results achieved - or rather, not achieved - coincide (see Table 7).

SPIN OFF	De Bellis	CRO
	2020	2020
Number of IRCCS spin-off companies established during the year	0	0
Number of spin-off companies that ceased in the year	0	0
Total number of active spin-off companies	0	0

Table 7

These non-numbers are also due to the difficulties that public IRCCS encounter due to current legislation which is unclear, confusing, binding and impeding the development of spin-offs.

In particular, over the last two years the Ministry of Health has worked in collaboration with the heads of the TTOs of some (19) of the 51 Italian IRCCS, in order to create guidelines for the creation of spin-offs, since there is no legislation that indicates to public IRCCS a way to create spin-offs, moreover, each of them is subject to health regulations which vary according to the region they belong to.

First of all, it is necessary to clarify how a public IRCCS differs from a private one:

- The public IRCCS are real public bodies and are characterized by the greatest interference by the State (in the role of the Ministry of Health) on the progress of their management (appointment in case of need of the extraordinary commissioner, control of spending decisions and possible agreement with the loan disbursed, budget control etc.).
- Private IRCCS, on the other hand, have greater freedom of action and control over them is only on the value of the research carried out.

Let's see, therefore, in detail, what are the regulatory aspects that, according to the managers of the TTO themselves, have flaws and that should be implemented.

In the first instance, the lack of relevance of the latest legislative acts on IRCCS is lamented: "... Twenty years have passed, respectively, from what is still the main tool for promoting technology transfer policies for public research subjects (Bando del Legislative Decree 297-99), and 15 years from the legislative act that introduced the possibility, for the IRCCS, "In order to transfer the results of research in the industrial field ...", to "... establish and / o participate in consortia, partnerships or corporations, with public and private entities ..." (Legislative Decree no. 288 16-10-2003, art. 8.5)". In this regard, it is believed that a Director General and a Scientific Director to decide to invest IRCCS resources in a spin-off need "clear paths, defined on a scientific, legal and economic level, and updated in the light of the present scenario". With this assumption we see in detail the laws in force:

› ***Legislative Decree 10-2-2005 n.30*** *Industrial Property Code, pursuant to Article 15 of Law 12.12.2002, n.273 (* ***Legislative Decree 13-8-2010 n.131*** *amending the CPI)*

It is envisaged that for Article 64 concerning employee inventions "the industrial invention made in the fulfillment of an employment or employment relationship, in which the inventive step is envisaged as object of the relationship and for this purpose paid, the rights deriving from the invention belong to the employer". Also included is Art. 65 on "Inventions by university researchers and public research bodies" (so-called Professor Privilege). Professor Privilege is still in force only in Italy and Sweden, while the other countries have gradually abandoned it in order to instead adopt the *Institutional Ownership system*, which provides that the institution for which the researcher works becomes the owner of the results of publicly funded research, and, by owning the intellectual property rights, obtain the economic benefits that derive from the patent.

The ownership of the inventions generated by its staff within the laboratories is for any research institute the starting point for the process of technology transfer. It is also true if the latter presumes the establishment of a spin-off company by the IRCCS staff. In this case, therefore, the aforementioned legislative decrees imply that the spin-offs are assignees or licensees of IPR for the inventions of the IRCCS, both private and public.

Professor Privilege therefore represents a limitation/complication that can be easily solved with the abolition of the same, just think that in countries such as Denmark, Germany, Austria, Norway and Finland it has already been abolished since 2000/2007.

It could be thought of leaving to the IRCCS the faculty to manage the ownership of the search results through the employment contract in which it can be expressed in a specific way. This is done, for example, in the case of a private IRCCS, in which it is specified: "14.4 Considering that the duties carried out by the Doctor under this Agreement include medical and scientific research activities, also including a creative activity and inventiveness, for the performance of which the Employer - both directly and indirectly, through any affiliate - provides means and equipment, all intellectual property rights on everything created and/or implemented by the Doctor during the period of validity of the Contract, including, by way of example and not limited to, researches, studies, scientific discoveries, inventions, medical and surgical devices, methodologies and techniques of any kind, will be considered the exclusive property of the Employer, without prejudice to the Doctor's moral right to be recognized author and/or inventor of what he directly created and/or realized during the relationship. With this Agreement, the Doctor renounces, and in any case assigns to the Employer, any right connected to the works covered by intellectual property rights created during the employment relationship. The consideration for this waiver and/or transfer is already included in the remuneration referred to in article 9 above. In particular, but without limitation, the Doctor acknowledges and accepts that all electronic files created, transmitted or archived by the Doctor - or by another person at the request of the Doctor - on hardware or software owned, rented or in any other form belonging to the Employer, the Institute, or any affiliate, are and will be the property of the Employer (or related institutions) and the Doctor will have no right or claim of confidentiality in relation to the consultation, manipulation or any other use of such information from the Employer (or the bodies concerned).

14.5 Upon termination of the employment relationship, for any reason whatsoever, the Doctor must deliver to the Company all existing copies of documents, files, papers, reports, or other material containing intellectual property rights, whether on paper or electronically. If the Doctor wishes to keep a copy of the documentation or other material, the Doctor himself must make a specific request and obtain written approval from the Chief Executive Officer of the Company".

In 2018, the Ministry of Health distributed a standard regulation to all individual IRCCS who have begun to pay close attention to ownership. However, in the standard it was not possible to go beyond the tautologies researcher = who does research/inventor = who invents, so for figures such as fellows, undergraduates etc. there is a risk of discrepancy at the level of individual institutions. Furthermore, there is the problem of heterogeneous interpretations on the ownership of what is not patentable and interesting in a spin-off key.

- ***Legislative Decree n.502 / 1992***

Art. 9 bis. paragraph 2: "... the experimentation is adopted by the region, motivating the reasons for the economic convenience of the management project, for improving the quality of assistance and for consistency with the forecasts of the RDP and highlighting ...".

Public-private collaborative models in the field of health are regulated by this article 9bis, as definitively amended by Law no. 405/2001 and, as regards specifically the IRCCS, by art. 8, paragraph 5 and 6 of Legislative Decree no.288/2003.

- ***Legislative Decree 16-10-2003 n.288***

Reorganization of the discipline of scientific hospitalization and treatment institutes

Art. 8. Research and assistance functions: "5. In order to transfer the results of research in the industrial field and in any case safeguarding the public purpose of the research, the institutions and bodies governed by this legislative decree may enter into agreements and conventions, establish and / or participate in consortia, partnerships or capital companies, with public and private entities whose qualification and suitability is ascertained. In no case can any losses of consortia and investee companies be charged to the management of the entities. The aforementioned relationships must govern:

a) the methods of distributing profits connected with the possible patenting of the results and their exploitation, binding in any case their destination to the financing of institutional activities;

b) adequate rules of transparency of financial flows, with reporting obligations;

c) objectives and certain times for their achievement;

d) suitable methods of information, verification and control of the progress of the program by the governing bodies and management bodies."

Art 9. Instrumental activities: "1. IRCCS Foundations and untransformed Institutes may carry out activities other than institutional ones, provided they are compatible with the purposes referred to in Article 1, for which they can enter into agreements and conventions, establish and/or participate in consortia and partnerships or capital with public and private subjects, chosen in compliance with national and community legislation".

In "Spin-off - Guidelines for IRCCS" we read: "Legislative Decree 288/2003, implemented which essentially incorporates what has already been stated by the reform decree, introduces further possibilities with respect to public-private collaborative models on management trials referred to in Article 9 bis, in order to allow the transfer of research results in the industrial field. The dictates of Legislative Decree 288 therefore differ from managerial trials since it refers to commercial and economic development of knowledge, research and discoveries matured within institutes, whereas managerial trials, on the other hand, concern more strictly related aspects to the welfare nature as per paragraph 2 of Article 9 bis".

The purposes referred to in Art. 1 with which the compatibility of a spin-off initiative must be respected are: "... research, mainly clinical and translational, in the biomedical field and in the organization and management of health services, together with hospitalization and treatment of high specialty".

A further comment coming from the heads of the TTOs of the IRCCS on the aforementioned regulation concerns the lack of clarity about the authorization process in the event that a public-law IRCCS intends to implement spin-off "Instrumental Activities". The IRCCS under private law, enjoying greater autonomy, as already expressed above, have the right to direct the authorization process according to internal procedures approved by the IRCCS Board of Directors, such as for example specific regulations, on the subject of spin-offs, where existing. With reference to the prohibition of IRCCS to cover spin-off losses, the entrepreneurial dynamics and the corporate

configuration that characterize spin-offs make this prohibition difficult to reconcile, furthermore it is considered unconstitutional (due to the violation of the Leonine agreement, of the shareholders' agreements in application of Legislative Decree 231/2001) in the opinion of some notaries. The prohibition of coverage of losses pursuant to Legislative Decree 288/2003 implies inadequacy with respect to the governance models of the spin-off, especially in the case of entrepreneurial activity in the biomedical field, which requires the contribution and exploitation of synergies and contributions from private entities whose purpose is also the production of business profits.
Furthermore, the standard contains only a generic reference to national and community legislation for the choice of IRCCS spin-off members.
With regard to this legislation, each IRCCS should verify any applicable regional regulation, in the event of participation in the spin-off capital by the Institute, which therefore may have to report the initiative to the reference Region to comply with the authorization process.
An example is Friuli-Venezia Giulia which will legislate on "... implement initiatives for the dissemination and transfer of research results and for their economic enhancement" (LR 10-08-2006 n.14) conditioning the "Instrumental Activities "With the opinion of the Steering and Verification Council of the IRCCS and, in the event of a negative opinion, with the authorization of the Regional Council, adding that IRCCS members must be" ... public and private entities whose economic capacity is ascertained and financial".

- ***Legislative Decree no. 168 of 10 August 2011***

As already mentioned in the chapter in which a chronological excursus of the main regulations in force was carried out, this regulation concerning the definition of the criteria for the participation of university professors and researchers in companies with spin-off characteristics or university start-ups in implementation of what provided for in Article 6, paragraph 9, of Law 240 of 30 December 2010.
"Definition of the criteria for the participation of university professors and researchers in companies having the characteristics of university spin-offs or start-ups" which attempted to define the boundaries, especially in terms of incompatibility. The ministerial decree was issued in implementation of the provisions of art. 6, paragraph 9, Law 240 of 30 December 2010, which in regulating the incompatibility of the professor and university researcher provides that this status "... is incompatible with the exercise of trade and industry without prejudice to the possibility to set up companies with spin-off or university start-up characteristics, pursuant to art. 297 of 27 July 1999, also assuming formal responsibilities in this area, within the time limits and in accordance with the regulations on the subject of the university to which they belong, in compliance with the criteria defined by the regulation adopted by decree of the Minister pursuant to article 17, paragraph 3, of Law no. 400 of 23 August 1988". (Source: University-Business Observatory, CRUI Foundation Working Group n.3).
This decree allows the university professor and researcher to exercise trade and industry but imposing a ban on positions on the Board of Directors (including spin-off companies) for university employees, postgraduate scholarship recipients (MIUR), etc.; in relation to similar cases of potential collaboration with universities/CNR for the IRCCS, the different types identified by the Ministry of Health are reported in the Guidelines for spin-offs, in the context of the registry classification of authors of IRCCS articles, therefore potential inventors:

- Seconded to IRCCS/NHS following a University Agreement
- Seconded to IRCCS/NHS following the CNR Convention
- Seconded to IRCCS/NHS following an agreement with an Other Research Body
- University agreement with secondment at IRCCS/NHS (no contract) with obligation of at least 16 hours
- University agreement not seconded to IRCCS/NHS (no contract)
- University Professor with contract art. 6 paragraph 10 of law 240/2010 with the obligation of at least 16 hours
- University Professor with contract art. 6 paragraph 11 of law 240/2010 with the obligation of at least 16 hours
- University Professor with contract art. 6 paragraph 12 of law 240/2010 with the obligation of at least 16 hours
- CNR agreement with secondment at IRCCS/NHS (no contract) with obligation of at least 16 hours
- CNR agreement not seconded to IRCCS/SSN body (no contract)
- CNR agreement with free professional contract
- Agreement with Research Body with secondment at IRCCS/NHS (no contract) with obligation of at least 16 hours
- Affiliated Research Body not seconded to IRCCS/SSN Body (no contract)
- Affiliated Research Body with free professional contract

› ***EU Regulation No. 345/2013*** *of the European Parliament of the Council of 17 April 2013 relating to European funds for Venture Capital*

This regulation states that: "(1) Venture capital finances enterprises which are generally very small, in the initial stages of their corporate existence and which show strong potential for growth and expansion. ... By providing finance and advice to these businesses, venture capital funds stimulate economic growth, contribute to job creation and the mobilization of capital, foster the creation and development of innovative businesses, increase their investment in research and development and foster entrepreneurship, innovation and competitiveness, in line with the objectives of the Europe 2020 strategy ...".

It can be deduced that specialized investors, of the Venture Capital type, despite having the possibility of financing small spin-off companies dedicated to the commercial and economic development of knowledge, research and discoveries matured within the institutions, cannot, on the basis of to the EU Regulation, to directly finance an IRCCS, a part of the financing that usually characterizes this type of business is lost, as can be seen in Fig. 1.

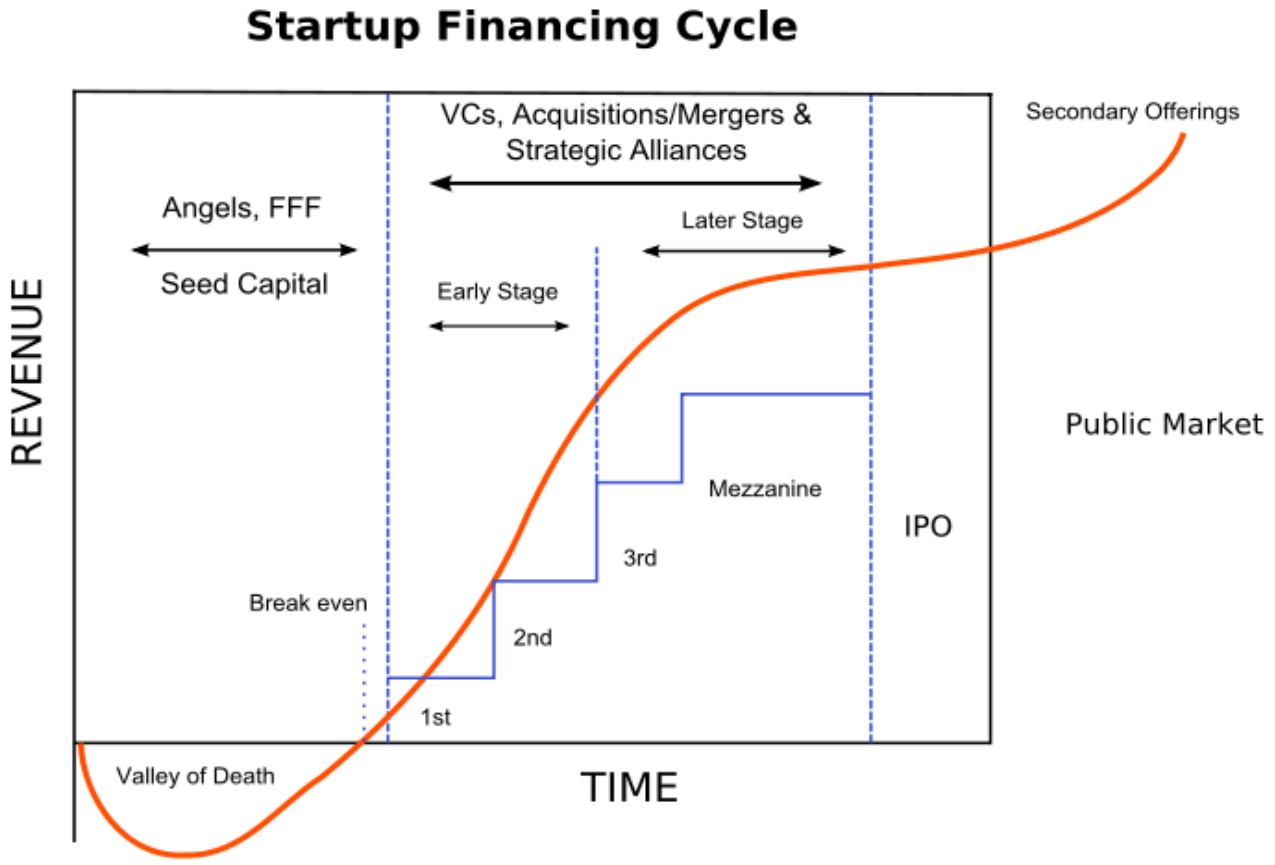

Figure 1 – Startup Financing cycle

The list of written rules is those personally considered among the most problematic, in the questionnaire addressed to the managers of the TTO I wanted to ask for a personal opinion on this issue.

The executive analyst of the research enhancement unit of the IRCCS De Bellis suggests that "for me the greatest constraint derives from ANAC opinions which highlighted the need for public evidence in the selection of the partners of the nascent spin-off. Furthermore, there should be a clear indication of the possibility for IRCCS to participate in the economic activities of the spin-off, without losing its basic condition as a non-profit organization". The ANAC opinion in question is the ANAC resolution 620/2018, already analyzed in the previous chapters, which implies that "for the purposes of setting up spin-off companies, in the form of joint stock companies in which a private entity also participates, the identification of the latter must take place with a public tender procedure (...) and with the application of the provisions on transparency" which generates a not low level of confusion and means that the spin-off company, in the event that it is owned by University/public body, it is subject to the Consolidated Law and the rules referred to therein as the companies in which the public administration has a stake are governed by the latter.

The head of the enhancement office of the Aviano CRO, an expert in legal matters, on the other hand, states: "When it comes to spin-offs, the interventions for the TTOs of public IRCCS such as the CRO Aviano cannot fail to be, in the first place, oriented to favor Ministerial solutions to legislative critical issues that have always strongly penalized the development of business ideas, starting from the very possibility of creating a business, if

promoted by IRCCS (public) employees. On various occasions, the teams of researchers-inventors of the CRO have ventured into enhancement paths where a preliminary opportunity such as business competitions (local, national and not; generalist or sectorial) also represents an essential step of adaptation in the form of business idea. In this, we cannot ignore the complexity of the skills required by the life science innovation chain (e.g. pharma, medical devices, but also apps in particular from a digital perspective) and the extreme difficulty for the IRCCS to enter into direct agreements with specialized investors and industry, all the more so since it has to completely disregard the existence of entrepreneurial teams. In reality, the teams of CRO inventor researchers have always clashed with regulatory criticalities that prevent them from realizing their entrepreneurship, as the formal and substantial involvement of these in spin-offs is, when not impossible, heavily penalized.

From Legislative Decree 297/99, and often then, the public IRCCS have been excluded or in any case penalized by the main reference regulatory instruments and related support mechanisms.

In a nutshell, making a parallel with Italian universities, it is as if the latter had been precluded from all the technological transfer that was generated by the creation of university spin-offs, triggered 20 years ago precisely under the auspices of factual involvement of EPR personnel supervised by MIUR - personnel who, conversely, if of public IRCCS such as CRO Aviano have significant operational limitations in industrial collaborations and spin-offs. As an example among many, certainly among the least penalizing, but not insignificant for this, we can cite art. 3 paragraph 4 of the MISE Public Notice of facilitation for the economic exploitation of patents, which expands the reimbursement of costs to 100%, making it clear, however, that they are spin-offs from entities supervised by MIUR only (but not IRCCS spin-offs therefore).

Specifically, the CRO, as a public IRCCS, has always had to comply with the prohibition for researcher / structured medical personnel from taking up positions in spin-off companies and the substantial prohibition for them to provide remunerated extra-institutional activities of the type of research on behalf of third parties, moreover, it is never possible to contemplate incubation in the Institute, not even pro tempore and figurative canons, for the rental of spaces and laboratories.

The public IRCCS CRO Aviano, in addition to not being able, as previously noted, to derive any benefit from certain funding calls, discounts in the planning, planning and implementation phase of spin-off projects the impossibility of actively involving its employees, such as medical managers and biology managers, bound to the exclusivity of the employment relationship in the National Health Service, also given the prohibitions on taking up positions in external companies.

The Entity therefore found itself in a position to launch entrepreneurial initiatives in the face of the competitive disadvantage of facing solutions that are often not practicable and various operational limitations.

The competitive disadvantages of the public IRCCS compared to universities and other EPRs ultimately constitute a competitive disadvantage for the country system"

In addition, the TTO CRO, as a suggestion in terms of policy to improve effectiveness and efficiency in the context of spin-offs, offers the following: "Encourage the approach of young people to business creation starting from the research results. Doctoral students have the goal of publication. Industrial doctorates are carried out in collaboration with existing companies. PhD programs could be created in which projects are selected for the

potential of the research to translate into business creation. These paths should then find space in the IRCCS and support from the TTO".

Still on the subject of regulatory aspects, other opinions were requested on specific issues concerning the institutional process for patenting; the expression of interest as a selection method for the choice of a private partner in the spin-off shareholder structure and, more generally, the definition of procedures for the establishment of the spin-off.

In the "Guidelines for IRCCS" we read:

- "In public IRCCS, the "Institutional procedure for patenting" decision contemplates the transfer of ownership by the inventor to the Institute. If this process gives a negative result, the inventor, maintaining the ownership of the invention, will be able to proceed independently or with third parties, or will be able to collaborate in research or co-development projects".

  In this regard, the heads of the TTO write:

De Bellis	These are two relatively parallel issues. The important thing is to provide for the possibility of creating spin-offs of IRCCS that are both participatory and, above all, accredited (without IRCCS direct participation in the corporate structure).
CRO	Given the persistent regulatory difficulties for public IRCCS, in theory it would be incentive in the sense that if the researcher sees too many complications, he maintains the IP and proceeds independently. In fact, however, the CPI continues to refer only to the patent proper, therefore it is difficult for an especially young researcher to consider taking on € 10,000 in patent costs, between Italian and PCT, moreover knowing that for every non-patentable IP, interpretations that are too risky arise. In the life science sector, the supply chain is very long and complex as well as finding licensees / industrial partners who cover the patent costs. It could therefore turn into a real incentive if associated with easier start-up activation.

Table 8

- "The expression of interest as a selection method, without the possibility of derogation, to choose a private partner in the shareholder structure of the spin-off is a critical factor in the development and enhancement process".

  Opinion of the TTO managers in this regard:

De Bellis	Free choice should be left, perhaps motivating the reasons for selecting a partner rather than another which could be, for example, economic, planning, research continuity reasons and the like.
CRO	To our knowledge, the public IRCCS that have set up spin-offs in which IRCCS has a share in capital are only CRO and Ca 'Granda. The CRO took two years to complete various audits, including those aimed at justifying the presence of a co-founding industrial partner. In this last regard and with reference to the spin-off experience participated by the IRCCS Ca 'Granda Ospedale Maggiore Policlinico Foundation, it should be considered that the head of the TTO reports the Lombardy regional law that makes the MDI mandatory to select these partners. As a starting point for resolution, perhaps together with universities, CNR, ENEA, etc., a unique MDI format could be reached.

Table 9

Finally, it was asked whether in order to simplify the process of creating a spin-off, the definition of procedures (which must be followed by the UTS for the formation of the spin-off) valid at national or regional level is considered more useful, and the responses were as follows:

De Bellis	Certainly we need a general national framework, within which each IRCCS must have the possibility of setting personalized limits, but always with a view to promoting the birth of self-entrepreneurship from within.
CRO	Nationally.

Table 10

However, despite the evident and heartfelt difficulties regarding the creation of spin-offs/start-ups from the CRO and thanks in particular to the initiative of its researchers, we have witnessed the creation of some entrepreneurial realities (which we see in Table 11):

Company name	Business sector	Year of establishment	Company headquarters	Website
SEDICIDODICI Srl	Cardiovascular diseases	2005	Via Roveredo, 20 33170 PORDENONE	www.bloodclotfinder.com
EVtech s.r.l. (Before ISITEC Srl)	Manufacture of electro-medical devices	2011	Corso Garibaldi, 9 33170 PORDENONE	www.isitecinnovation.com
PHARMADIAGEN Srl	Biomedicine, Pharmacogenetics and pharmacogenomics	2009	Via Roveredo, 20 / B 33170 PORDENONE	www.pharmadiagen.net
BioFuture Medicine Srl	Oncology and Nanomedicine	2016	Via Roveredo, 20 33170 PORDENONE	www.biofuturemedicine.com
LightHouse Biotech srl	Oncology, pharmaceuticals	2019	Via Roveredo, 20 33170 PORDENONE	https://lighthousebiotech.com/

Table 11

In relation to the active spin-offs, it was asked to tell for each spin-off the historical path taken to start it and to keep it active with the aim of being able to possibly use it as an example of modus operandi to be replicated. Below is the path covered.

SEDICIDODICI Srl

Founded in 2005 by CRO researchers and local entrepreneurs to bring advanced technologies for the assessment of hemostasis on the market, it holds Patents in the field of diagnosis and pharmacological monitoring of thrombotic, ischemic and hemorrhagic pathology. Sedicidodici is supported by Italian Angels for Growth to further develop smart clot device.

We started from the idea of product innovation (medical device), which was patented and from which synergy arose between the CRO researchers who achieved the invention, in a completely autonomous way within the IRCCS, and entrepreneurs locals passionate about the project. They simultaneously participated in competitions for business ideas. From a procedural point of view and the relationships between business teams and IRCCS, there was a need to define the relationships in terms of ownership of patents and the opportunity for technical-scientific collaboration, to be formalized following the typical decision-making process in the IRCCS thus ultimately acquiring the favorable opinions of the Scientific (proposing), Administrative and Health managers, the latter in the staff of the legal representative General Manager last signatory.

EVtech s.rl. (Before ISITEC Srl)

Founded in 2005 as a start-up, it is a company dedicated to find solutions for automated compounding pharmacy essential to patient safety. Isitec exports its products throughout the world.
The path taken is the same one taken by Sedicidodici.

PHARMADIAGEN Srl

It was born in 2009 as first Italian spin-off addressed to fight cancer through pharmacogenetics with the aim to provide molecular biology services, both standard and custom, focused especially on genomic profiling.
Pharmadiagen Srl has lived a different path, probably unique as the first experience of public IRCCS co-founder-shareholder (Newronika Srl, linked to IRCCS Ca 'Granda, differs in that it is also activated on the basis of the legislative instruments MURST Legislative Decree 297/99, L 593/00 for university researchers, therefore not employees of the NHS, and because it also has the relevant university as a shareholder). The steps for Pharmadiagen were participation in competitions for business ideas and a parallel verification of the authorization process that lasted two years. The only legislative reference on the subject for the IRCCS (of Aviano) provided for the authorization of its highest advisory body (Advisory and Verification Council - CIV) and, if this had not expressed a favorable opinion, alternative authorization from the Friuli Region -Venice Giulia. The CRO adopted a first preliminary resolution to give evidence of the desire to create the participated spin-off, and then, months later, the definitive resolution for entry as shareholder co-founder.
For safety, the CRO, in addition to the favorable opinion of the CIV, also considering the unprecedented and complex situation from a legal point of view, also asked for and obtained written feedback from the Region (Health Department) to certify the awareness of the initiative and as a clearance.
In 2016 Geneticlab Srl is booming and acquires control of the company Pharmadiagen.
Pharmadiagen Srl is now a subsidiary of the Synlab Group, the largest European medical diagnostics group.

BioFuture Medicine Srl

BFM is a star-p focused on developing new molecular kits for research and diagnostic application in the field of age-related diseases and food, with expertise in molecular and cellular biology, medicinal chemistry and nanomedicine. In 2017 the company became a spin-off of Ca 'Foscari.

The year 2015 was functional to the creation of BioFuture Medicine (BFM), founded by researchers in 2016 at the CRO, as an innovative start-up with possible collaborations with the CRO of Aviano, the Technological Pole of Pordenone and the Ca 'Foscari University of Venice. The company builds on the consolidated experience of its founding researchers in the field of biology and translational medicine. A co-founding researcher, meanwhile, while continuing to collaborate with the CRO, became a professor at the Ca 'Foscari University and BFM was recognized as a spin-off/start-up of the university.

LightHouse Biotech Srl

LightHouse Srl, based on the definition of Spin-off contained in the Guidelines distributed by the Ministry of Health at the end of February 2020, it is not excluded that the company may fall within this definition. For now it is more pertinent to refer to it as a "start-up", established in the local science-technology park in Pordenone, engaged in the development of a machine where part of the research activity has also involved CRO researchers and know-how for some years.

In addition, cases of *best practices* relating to the management/activation of spin-off companies are added.

The CRO's participation in competitions for business ideas, although not assiduous, translates into positive results, counting, out of a total of 8 entrepreneurial teams promoted over the years by the IRCCS researchers, 6 finalists awarded including 3 winners of the Start Cup FVG/Start-up FVG and 1st place in the "Il Sole 24 Ore" National Innovation Award.

Four spin-offs / start-ups, promoted by CRO researchers and based at the Pordenone Technological Center, have obtained, respectively, record funding from the Italian Angels for Growth for over 1 million euros with machinery in production for clinical validation, commercial agreements and devices already placed in hospitals in Italy and in various countries, significant growth in turnover from advanced molecular diagnostics services, obtaining POR-FESR type private-public collaborative grants.

While serving a regulatory fabric that essentially precludes many public IRCCS employees from promoting spin-off initiatives and participating in them, thereby compromising the main success factor, that is the human factor, the CRO has worked to overcome these problems by intensifying relations with the territory, in order to give continuity to the participation in business competition at least in relation to the unstructured staff of the IRCCS. In addition to the spin-off/start-up experiences in the table, two Startcup experiences, local (2012) and regional (section "Life Science/Ideas", 2015) also take on significance from the UTS point of view. Although it has become impossible for researchers to activate a new business due to the regulatory problems mentioned above, it has grown from those business plans and related ideas for product innovation, respectively onco-hematological diagnostic kits and pharmacy apps, their sensitivity to technology transfer, which over the years has resulted in negotiations with companies and investors for hypotheses of co-developments and also participation in calls for collaborative industrial research.

The questionnaire also wanted to "investigate" the type of incentives for technology transfer aimed at the TTO staff, to better understand whether measures were envisaged that could stimulate the staff to do better and to "produce" more and more. The answers were as follows:

INCENTIVES TO TT	CRO		De Bellis	
	YES	NO	YES	NO
Can staff receive financial incentives for the creation of spin-off companies (additional to the participation in the share capital by the IRCCS)?		✓		✓
Is involvement in technology transfer activity taken into consideration when evaluating the possibility of career advancement?		✓	✓	
Are incentives used to stimulate the involvement of researchers in technology transfer activities?	✓		✓	
Does the TTO staff receive financial incentives based on the results achieved in the TT support activities?	✓			✓
Can doctors get "sabbatical" periods to work in spin-off companies of which they are members?	✓			✓

Table 12

The CRO, however, added comments to some of the responses. To the second question in the table, as you can see, the answer is no, but it is specified that: "for 10 years the CRO management (doctors, biologists) has also been evaluated by the Scientific Director on the basis of the levels/capacity of technology transfer. However, considering that most of these employees often did not obtain this extra reward in the year due to the objective absence of TT activity (e.g., many clinicians), and the TTO is not aware that this prevented their career advancement, it is also difficult to objectify real progress if thanks to the TT criterion". To the third question, the answer is yes, plus "In theory from now on yes, having been introduced Ministerial indicators:

- from 2018, indicator and in IRCCS Three-Year Planning;
- from 2020, evaluation parameter in the Pyramid."

The fourth question specifies "Yes for permanent employee". And, finally, the last question is added: "theoretically possible, this case never occurred".

Also in this case, a personal opinion of the TTO managers was asked about any suggestions in terms of policy to further incentivize TT's activities.

The TTO CRO believes that it is necessary to define an innovation budget, administered and managed directly by the TTO; greater flexibility in hiring external consultants and purchasing software for office management and technology enhancement; involvement of the UTS in the definition of the research strategy of the IRCCS and in the evaluation of scientific production (starting from what was said by Prof. Riccardo Pietrabissa in an ASTP conference).

De Bellis, on the other hand, believes that "reward mechanisms should be envisaged for researchers who activate spin-offs; to optimize, as happened for the Italian University, the legislative system in order to allow the solution of the problems still present regarding conflicts of interest and exclusivity of the public employment relationship with respect to new spin-offs; strengthen the reward given to the staff of the "Research Pyramid" for self-entrepreneurship initiatives (patents and spin-offs)".

APPENDIX

APPENDICE A – Questionario per UTT

Sezione 1. Il profilo dell'IRCCS

Informazioni sull'IRCCS

1.1 Si indichi il budget totale annuale dell'IRCCS (in Euro)

Attività di ricerca

1.2 Si indichi il totale dei **fondi per la ricerca (compresi sia i finanziamenti pubblici che quelli privati, in Euro),** e – qualora disponga delle relative informazioni – ne suddivida l'ammontare tra le differenti fonti di finanziamento di seguito riportate:

- Fondi provenienti dal governo centrale (Miur, ecc.)
- Fondi provenienti dalla Regione
- Fondi provenienti dall'Unione Europea
- Contratti per ricerche e consulenze finanziate da terzi e servizi tecnici
- Fondi propri dell'IRCCS
- Donazioni
- Altro

Sezione 2. Il profilo dell'Ufficio di Trasferimento Tecnologico (UTT)

Informazioni generali

2.1 Presso il suo IRCCS è presente un UTT (più in generale, un ufficio che si occupi di trasferimento tecnologico)? Se sì, in che anno è stato costituito tale ufficio?

2.2 Il personale dell'UTT è specializzato per funzioni/attività?

2.3 Indichi per favore la ripartizione del tempo del personale ETP dell'UTT fra le seguenti funzioni *(il totale deve essere pari a 100%)*:

- Personale ETP dedicato prevalentemente alla protezione della Proprietà Intellettuale (PI)
- Personale ETP dedicato prevalentemente ai contratti di ricerca e consulenza (con l'industria)
- Personale ETP dedicato prevalentemente al licensing
- Personale ETP dedicato prevalentemente alle imprese spin-off
- Personale ETP dedicato prevalentemente ad altre mansioni (es. management, finanza, formazione, etc.)

2.4 Il personale UTT è in possesso di quale dei seguenti titoli di studio? *(è possibile indicare anche <u>PIU' DI UNA</u> risposta)*

- Giurisprudenza
- Economia
- Ingegneria *(specificare quale:* ……*)*
- Lettere (classiche o moderne) e/o Filosofia

- Lingue straniere
- Nessuno
- Altro

2.5 Il personale incaricato per la valutazione dell'ipotesi di spin-off è in possesso di quale dei seguenti titoli di studio? *(è possibile indicare anche PIU' DI UNA risposta)*

- Giurisprudenza
- Economia
- Ingegneria *(specificare quale: ……)*
- Nessuno
- Altro

Rapporti tra l'IRCCS e l'Ufficio di Trasferimento Tecnologico (UTT)

2.6 Qual è il rapporto tra l'IRCCS e l'UTT? *(è possibile indicare SOLO UNA risposta):*

- L'UTT è un ufficio interno all'IRCCS
- L'UTT è un'organizzazione *non profit* controllata dall'università/ente
- L'UTT è una società *profit* esterna ma controllata dall'università/ente
- L'UTT è una società *non-profit* legata all'università/ente da un accordo formale
- L'UTT è una società *profit* legata all'università/ente da un accordo formale

2.7 Quali interventi di policy istituzionali potrebbero migliorare l'efficacia e l'efficienza nell'ambito degli UTT?

Sezione 3. La gestione della Proprietà Intellettuale (PI)

3.1 Indichi per favore il numero totale delle domande di brevetto: presentate e – qualora disponga delle relative informazioni – ne suddivida il numero in base all'ufficio brevettuale di competenza:

- Domande di brevetto: presentate in Italia
- Domande di brevetto: presentate in Europa
- Domande di brevetto: presentate alla WIPO

3.2 Indichi per favore il numero totale delle domande di brevetto: nazionalizzazioni presentate e - qualora disponga delle relative informazioni - ne suddivida il numero in base all'ufficio brevettuale di competenza:

- Domande di brevetto: nazionalizzazioni presentate in Europa
- Domande di brevetto: nazionalizzazioni presentate negli Stati Uniti
- Domande di brevetto: nazionalizzazioni presentate in altri Paesi

3.3 Indichi per favore il numero totale di brevetti concessi e – qualora disponga delle relative informazioni – ne suddivida il numero in base all'ufficio brevettuale di competenza:

- Numero di brevetti concessi in Italia
- Numero di brevetti concessi in Europa (EPO)
- Numero di brevetti concessi negli Stati Uniti
- Numero di brevetti concessi in altri Paesi

Sezione 4. Il supporto alle imprese spin-off

4.1 Numero di imprese spin-off dell'IRCCS costituite nell'anno 2018/2019/2020

4.2 Numero di imprese spin-off cessate nell'anno

4.3 Numero complessivo di imprese spin-off attive

4.4 Con riferimento alle imprese spin-off attive, indicare la denominazione e il settore di attività e - se possibile - anche le altre informazioni richieste:

Denominazione impresa	Settore di attività	Anno di costituzione	Sede dell'azienda	Sito web

4.5 Con riferimento alle imprese spin-off attive, indicare quali sono stati i passaggi necessari per arrivare alla realizzazione di tali spin-off.

4.6 Potrebbe indicare la denominazione degli spin-off che non sono più attive, indicando se si è trattato di: fallimento, vendita, liquidazione, fusione, etc.?

4.7 Laddove l'interruzione dell'attività fosse stata dovuta al fallimento, indicare – qualora possibile – le ragioni che lo hanno causato e quale azione/misura/provvedimento avrebbe potuto evitarlo.

4.8 Quali suggerimenti avrebbe in termini di policy per migliorare l'efficacia e l'efficienza nell'ambito degli spin-off (numero di spin-off attivate, attività di accompagnamento alla crescita e al consolidamento degli spin-off, miglioramento nello scouting di idee d'impresa, ecc.)?

4.9 Ci sono stati casi di Venture Capitalists e Business Angels che hanno deciso di investire in spin-off nati dal suo IRCCS?

Se sì, come sono venuti a conoscenza degli spin-off?

Indicare uno o più casi di *best practices* relativamente alla gestione/attivazione delle imprese spin-off

Sezione 6. Gli incentivi al Trasferimento Tecnologico (TT)

6.1 Il personale può ricevere incentivi finanziari per la creazione di imprese spin-off (aggiuntivi rispetto alla partecipazione al capitale sociale da parte dell'IRCCS)?

6.2 Il coinvolgimento nell'attività di trasferimento tecnologico viene preso in considerazione nel valutare la possibilità di avanzamenti di carriera?

6.3 Vengono utilizzati incentivi per stimolare il coinvolgimento dei ricercatori nelle attività di trasferimento tecnologico?

6.4 Lo staff dell'UTT riceve incentivi finanziari in funzione dei risultati raggiunti nelle attività di supporto al TT?

6.5 Secondo il "Programmazione Triennale 2018-2020 Istituti di Ricovero e Cura Carattere Scientifico (IRCCS)" rilasciato dal Ministero della Salute, il finanziamento delle attività di Ricerca Corrente degli Istituti, sarà ripartito secondo i seguenti criteri:

A. PRODUZIONE SCIENTIFICA E RELATIVA EFFICIENZA E IMPATTO DELLA PRODUZIONE SCIENTIFICA (55%);

B. CAPACITA' DI ATTRARRE RISORSE (10%);

C. ATTIVITA' ASSITENZIALE (20%);

D. CAPACITA' DI OPERARE IN RETE (10%);

E. TRASFERIMENTO TECNOLOGICO (5%).

Si ritiene che tale criterio di finanziamento favorisca l'impegno nel e la crescita del TT?

Se no, quale dovrebbe essere la ripartizione ideale?

6.6 Quali suggerimenti avrebbe in termini di policy per incentivare ulteriormente le attività di TT?

Sezione 7. Networking

7.1 Si ritengono utili le piattaforme di networking dedicate agli spin-off (Knowledgeshare, Spinoff Italia, Netval, ecc.)?

Se sì, in che modo tali piattaforme apportano un contributo positivo alla creazione/realizzazione di uno spin-off?

7.2 Si ritiene necessaria la creazione di ulteriori piattaforme o sono sufficienti quelle già esistenti?

Se sì, perché? Quale "funzione" dovrebbe svolgere una nuova piattaforma in più rispetto a quelle esistenti?

Sezione 8. Procedure e normative per il processo di TT negli IRCCS

8.1 In "Spin-Off Linee Guida per IRCCS" si legge: "negli IRCCS pubblici, la decisione "Iter istituzionale per brevettare" contempla la cessione di titolarità dall'inventore all'Istituto. Qualora tale iter dia esito negativo, l'inventore, mantenendo la titolarità dell'invenzione, potrà procedere autonomamente o con soggetti terzi, oppure potrà collaborare a progetti di ricerca o di co-sviluppo."

Quanto scritto sopra potrebbe rappresentare un ostacolo o un incentivo alla creazione di spin-off? (Motivare la risposta)

8.2 In "Spin-Off Linee Guida per IRCCS" si legge: "La manifestazione d'interesse come modalità di selezione, senza possibilità di deroga, per scegliere un partner privato nella compagine sociale dello spin-off è un fattore critico nel processo di sviluppo e valorizzazione."

Indicare quali siano le criticità e, laddove possibile, suggerirne una o più spunti per la risoluzione.

8.3 Al fine di semplificare il processo di creazione di uno spin-off, si ritiene più utile la definizione di procedure (che devono essere seguite dall'UTT per la formazione dello spin-off) valide a livello nazionale o regionale?

8.4 Quali tra le norme oggi in vigore rappresentato il maggiore ostacolo allo sviluppo di spin-off e perché?

8.5 Viste e considerate le difficoltà dovute alle non poco chiare/non aggiornate/non sempre applicabili norme in vigore, si ritiene che una soluzione per lo sviluppo di spin-off possa essere quella di affidarne il compito direttamente ad un consulente esterno specializzato (es. MATERIAS)? (Giustificare la risposta)

APPENDICE B – Questionario per ricercatori

1. Il profilo del ricercatore

Informazioni sul ricercatore

1.1 Retribuzione totale annuale del ricercatore (in Euro) (anni 2019 – 2020)

1.2 Indichi per favore la tipologia di contratto:

- □ A tempo indeterminato
- □ A tempo determinato
- □ Contratto a progetto
- □ Assegno di ricerca
- □ Borsa di ricerca
- □ Contratto interinale
- □ Contratto di collaborazione occasionale
- □ Stage
- □ Altra tipologia di contratto

1.3 Indichi per favore il suo titolo di studio:

Attività di ricerca

1.4 A quale ricerca si sta dedicando al momento?

1.5 Ritiene che dai risultati di tale ricerca si possa valutare l'ipotesi di spin-off?

1.6 Se no, perché?

Sezione 2. Spin-off

2.1 Ha mai preso in considerazione l'idea di far parte di uno spin-off?

2.2 Motivi la sua risposta:

2.3 Ha mai fatto parte di uno spin-off?

2.4 Se sì, raccontare quando; con quale progetto; con quale università/ente/IRCCS:

2.5 Quali fattori hanno influito in maniera positiva allo sviluppo dello spin-off?

2.6 Se non più attivo, quali fattori hanno influito in maniera negativa allo sviluppo dello spin-off?

Sezione 3. Parere del ricercatore

3.1 *Trascorso un primo periodo, di norma compreso tra 3 e 5 anni, si suggerisce che venga interrotto ogni eventuale collegamento in essere con l'IRCCS per quanto concerne la logistica o l'utilizzo della qualificazione di "spin-off (accreditato) IRCCS": ciò richiede che l'azienda, alla fine di questo arco temporale, sia pronta a operare senza alcun tipo di sostegno da parte dell'Istituto.*

In riferimento a quanto scritto sopra, vi sembrano sufficienti dai 3 ai 5 anni per diventare indipendenti? Se no, quanto tempo pensate sia realmente necessario? Quale sostegno dovrebbe continuare a dare l'istituto per far si che lo spin off non fallisca?

3.2 *All'organico interno si aggiunge, all'occorrenza, personale esterno che integri le competenze dei dipendenti: ciò può avvenire, per esempio, in materia di gestione di impresa, economia e marketing, o anche nella stessa materia oggetto dello spin-off, laddove quest'ultimo nasca per valorizzare risultati della ricerca derivanti da progetti di partenariato.*

Quanto scritto sopra, secondo la sua opinione, può rappresentare un ostacolo/problema/complicazione o piuttosto un valore aggiunto? Perché?

3.3 Quali ritiene essere i fattori impedenti lo sviluppo degli spin-off (es: personale UTT non sufficientemente preparato, scarsa mentalità imprenditoriale dei ricercatori, troppa burocrazia, pochi investitori, ecc?)

3.5 Cosa suggerisce al fine di migliorare tale promozione (qualora si ritenga debba essere migliorata)?

3.7 Qualora lei fosse interessato allo sviluppo di uno spin-off, ma non avesse le competenze/conoscenze necessarie per intraprendere un percorso imprenditoriale, sarebbe ben predisposto nei confronti di eventuali corsi di formazione messi a disposizione dall'IRCCS stesso?

3.8 Se no, perché?

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