1. INTRODUCTION

According to some analysts' estimates, the global contract research organisation (CRO) market will reach USD 90 million in 2026 from USD 50 million in 2021; it is expected to grow at a very fast annual growth rate, according to many over 10% per annum.

The growth of the market is mainly attributed to the increase in research and development expenditure, outsourced activities and the increase in the number of clinical trials. However, the limited availability of qualified professionals is currently a major obstacle to market growth.

Healthcare providers have focused on adapting to the difficult transformations triggered by the COVID-19 pandemic. Clinical research plays a crucial role in the development of diagnostics and therapies to combat the ongoing covid-19 pandemic, through rapid and accurate clinical trials and the collection of robust and reliable results in a variety of large-scale settings. Intense global research collaborations between stakeholders and industries involving all countries are driving this significant market growth.

Based on type, the contract research organisation (CRO) market offers discovery/early phase services, clinical research support services, laboratory services, regulatory services and post-approval services (Real World Research). The clinical research services segment is the largest in the market and is expected to register the highest growth rate during the forecast period.

On the basis of end-customer type, the contract research organization market is mainly segmented into pharmaceutical companies, biotechnology companies, and medical device companies. The pharmaceutical and biotechnology companies segment holds the largest share in the market and is estimated to witness the highest growth rate during the period 2021-2028.

In this context, the market value of CROs as companies operating in Italy has not yet been officially quantified. There are no reliable studies or estimates of the economic value, expected growth rates, degree of market penetration and the level of employment it generates.

This paper aims to follow up on the survey carried out by the Italian Association of Clinical/Contract Research Organizations (AICRO) " AICRO Survey 2019 - The state of member CROs", which provided a very first and partial account of the state of the art of the major CROs in Italy, before the pandemic period.

This analysis summaries some macroscopic structural, operational and financial indicators, mostly derived from original AICRO studies.

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2. ECONOMIC CONTEXT INDICATORS

In the last 15 years, the Italian economy has shown a fluctuating trend. From 2008, the year that is considered the beginning of the economic crisis, and up to 2014, GDP has recorded significant declines. Suffice it to say that in 2008, GDP stood at € 1,637,699 million, and then we had to wait until 2015 to see values even higher than 2008. The trend was erratic, with major falls in production and then, from 2015, an economic recovery began, which was then halted by the pandemic. The dramatic drop in 2020 was followed by a recovery in 2021 and, according to known forecasts, the recovery in 2022 is considered to raise GDP values above pre-pandemic levels, with further growth expected in 2023, subject to the effects of the Ukraine crisis.

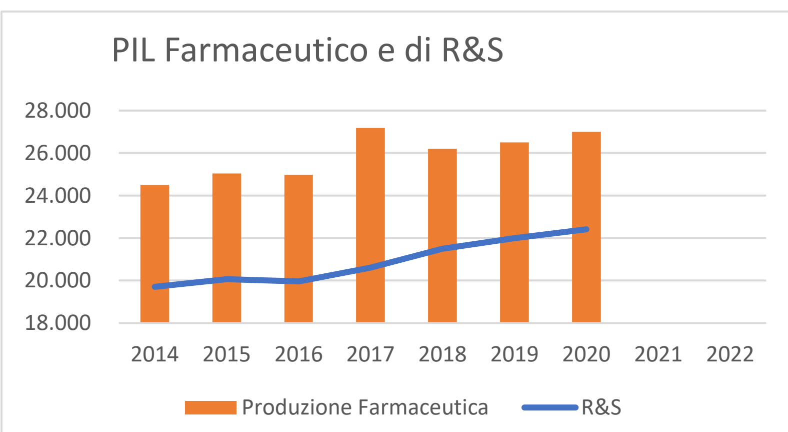
According to data from ISTAT and the Bank of Italy, the crisis has hit SMEs hardest, unlike large companies, which have managed to consolidate their assets, even recording capital increases.

In 2018, businesses in industry and services remain predominantly very small (0-9 employees). In fact, there are 4.1 million micro-enterprises, accounting for 95% of active enterprises and 43.9% of employees. Large enterprises (those with at least 250 employees), which account for 0.1% of the total, account for 23% of employees.

In 2019, there are 4.304 million active enterprises, corresponding to 17.439 employees.

In this context, the pharmaceutical and research and development sectors have maintained growing trends, both in the crisis years and during the pandemic. It is these sectors that show continued vitality.

The figures provided for the pharmaceutical sector include the typical production of the sector and do not include the medical devices sector, which is also growing steadily. Similarly, the research and development sector as a whole includes both activities relating to clinical trials and research and development in other sectors, such as technology in general. However, the values are constantly growing.



Fonte ISTAT 2021 – Farmindustria 2021

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In these sectors the following is confirmed: the growth in employment levels and, compared to other sectors, the ever-balanced proportion of male (57%) and female (43%) jobs that is valid for both sexes, even for top positions. The level of education in these sectors is the highest, with 54% of graduates (industry average 21%).

3. CHARACTERISATION OF CRO IN ITALY

CROs with a presence in Italy are still represented by two macro-categories: Italian companies and those with foreign capital, but with offices in Italy. According to the latest information provided by AIFA (December 2019), at the Observatory (OsSC), 194 CROs operating on the Italian territory were registered, of which 106 were "Italian" and 88 "foreign". In the analysis presented here, we will limit ourselves to examining companies with a continuous presence in Italy and providing "classic" CRO services (Project Management, Monitoring, DM/Statistics, Regulatory Services and Start Up). It should be noted, however, that more and more often "contract organisations" within clinical trials also include companies that are very specialised in technology, IT and "niche" services. It is foreseeable that in the future these companies will work much more often in synergy with CROs and M&A activity will occur more frequently.

61% of the CROs surveyed are international companies, all of which have a presence in Italy. 39% are Italian companies, some of which are associated or "federated" with other companies abroad.

74% of CROs have their headquarters in Lombardy (82% in Milan), 17% in Lazio, and the remainder in other regions.

The characterisation of AICRO member CROs, with respect to type of business, reveals that the majority (60%) are "primarily" engaged in international business (i.e. generated abroad). 30% "mainly" deal with local business (i.e. generated in Italy) and 10% with business equally divided between international and local. A better quantification of the weight of locally generated business would allow to know more precisely the investments destined to Italy and consequently to understand and, in some way, measure the attractiveness of the Italian market for clinical trials.

The majority (60%) of the associates deal mainly with Interventional Clinical Trials (Phase I - IV). 40% declare a business equally divided between interventional, observational and other types of services.

The size of the companies seems to correlate with the type of business: in small companies locally generated business appears to prevail, while in medium-sized or large companies international (global) generated business prevails.

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a. HUMAN RESOURCES

CROs in Italy employed approximately 3,500 people at the end of 2020 who were specialised in technical functions related to the conduct of clinical trials (i.e. excluding staff and administrative services) of which approximately 3,000 were employed by AICRO member CROs.

Approximately 88% of the employees are employed by large CROs which constitute one third of the CROs surveyed.

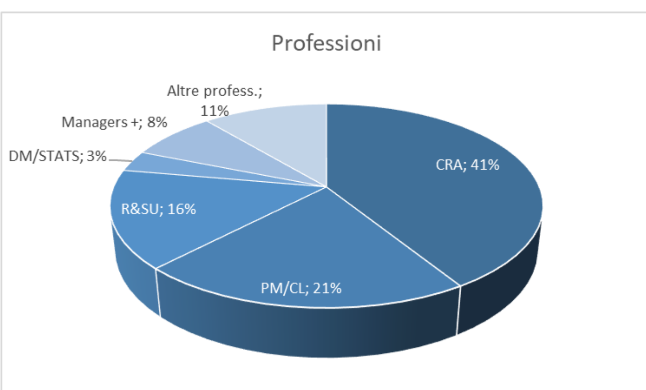
Females make up the majority of the workforce (approximately 75% of the total); this percentage rises to over 90% in management roles (source: AICRO survey).

The proportion of young staff is another characteristic feature of companies in this sector, with 35% of staff aged under 35. Approximately 95% of clinical trial management staff have a master's degree and at least one third of the total have a higher academic qualification (doctorate, master's degree, postgraduate diploma) (source: IQVIA RDS Italy).

Among the associates that have a global or international presence, a substantial portion of employees (24% of the total surveyed) have significant responsibilities in more than one country, mainly in the functions of project management or team leadership, while just over half of the total employees carry out their role on studies conducted in Italy.

There has been considerable growth in FSP (Functional Service Provider) models, which allow client companies to make use of specialised, directly managed resources for a contractually determined period of time. Currently, around 24% of the total workforce is assigned to FSP services.

The main professions reflect the relative distribution normally expected, with Clinical Research Associates (CRAs) continuing to be the most commonly used profession (with an estimated 1400).



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The global trends that point to a shortage of qualified resources to support the growth of CROs can also be seen in Italy.

The effort in training new resources and updating existing ones by AICRO member CROs has been remarkable, despite the fact that national legislation is particularly hostile and penalising in establishing requirements that are not equivalent in any other country in the world, thus making the activity of CROs operating in Italy less competitive.

The survey documents that members trained and certified 164 CRAs in the three-year period 2018 - 2020, but in 2021 alone this number rose to 150 and the trend is expected to continue in the immediate future.

Despite the growing demand for educated and trained staff, in several documented cases, the limits imposed on CROs by Italian legislation have prevented them from being able to recruit new staff who, although with adequate academic background, still need training in the field. It is not yet possible to make a precise estimate of these detrimental effects.

AICRO and its associates are active in various training initiatives in the university sector and have launched their own training course for young graduates.

b. IMPACT OF THE PANDEMIC AND PROSPECTS

The survey also collected the qualitative impressions of AICRO members regarding the impact of the pandemic and the actions put in place to mitigate its consequences in the short and long term.

The impression of sponsors' general attitude towards the launch of new studies and new investments during the pandemic period generally shows a moderately positive trend, with 79% of respondents believing it to be "unchanged" or "more proactive". Only 21% felt that customer attitudes were 'more conservative'.

However, the pandemic has produced significant changes in the way CROs work according to 74 per cent of respondents. In detail, the biggest changes are definitely in the direction of remote activities. Among the most frequently cited categories of change are an increase in occasional home working/smart working by staff, a shift in contractual arrangements towards permanent teleworking (home based positions), even for those roles previously excluded from these possibilities, and the introduction of new technologies enabling remote working and document dematerialisation. Although these changes may seem similar to those that have taken place in other sectors, it is important to remember the nature of pre-pandemic activities that involved physical travel around the country and operations that had to be done 'on site' or physically in the office.

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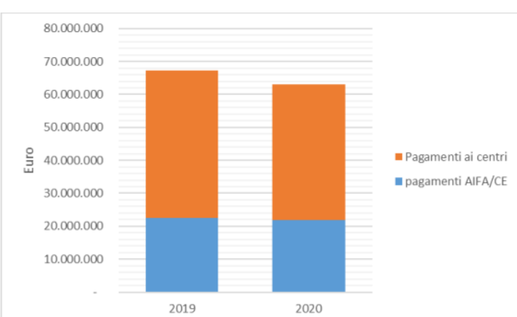
Categorie	frequenza relativa
Incremento dell'Home Working	21%
Incremento di attività di monitoraggio da remoto	18%
Aumento del personale home based	12%
Accesso all'home based per ruoli solitamente office based	12%
Aumento dell'archiviazione elettronica	10%
Introduzione di nuove tecnologie	9%
Presenza di personale in aree geografiche prima non considerate	7%
Diminuzione di percentuale di SDV	7%
Altro	1%
Introduzione di nuovi ruoli (i.e. In-House CRA)	1%

The activity of launching new studies does not seem to have slowed down during the pandemic period compared to the previous year, in fact, AICRO members launched about 380 studies in 2020 compared to 340 in the previous year (+12%) for a total of about 2500 participating centers (+6% vs 2019). Extrapolating the data of AICRO members to those of all CROs present on the territory in the last two years, one can confirm the previously hypothesized data on the management by CROs of well over half of the clinical trials activated in Italy, according to AIFA (672 clinical trials authorized by the Competent Authority in 2019).

The activity of the centers, in terms of patient recruitment, instead seems to have been affected by the pandemic period. In fact, data on payments made to centers, to cover the costs of trials and for the treatment of patients, show a reduction in 2020 compared to the previous year. Overall, AICRO members made payments to centers of approximately EUR 41 million in 2020 compared to approximately EUR 44 million in 2019 (-8%).

In the same period, payments to AIFA and the Ethics Committees for study evaluation fees remained unchanged, with disbursements of approximately €22 million per year.

It is worth noting how important the disbursement for fees is becoming in relation to total payments (rising to 35% of the total in 2020).



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4. ECONOMIC ANALYSIS OF CRO IN ITALY

AICRO has carried out an analysis of the economic indicators of CROs in Italy. The analysis concerns a set of companies and is based on balance sheet data published in the years 2017, 2018, 2019 and 2020, and on information collected from the AIFA website and direct knowledge.

The identification of entities that can be defined as CROs was done by excluding companies registered as CROs in AIFA that have as their main object specialized activities in relation to the design and conduct of a clinical trial, such as, for example, companies dealing with electronic health records (e-CRF) and databases or managing experimental drug.

The companies identified are private capital structures, with registered office or legal representation in Italy, which is a prerequisite for access to the financial statements published in Italy at the Chambers of Commerce.

There are 46 companies (CROs) identified for the purposes of this analysis.

a. QUANTIFICATION OF THE CRO MARKET IN ITALY

Based on the values obtained from the analysis of the sample of companies as described above, the trend in revenues over the period 2017-2020 is summarized in the table below:

Andamento ricavi (approssimati, in 000 Euro)	
2017	**370,000**
2018	**380,000**
2019	**400,000**
2020	**411,000**

It appears that the market for outsourced CRO services has been growing substantially over the last 5 years and, at least until the end of 2020, has not been particularly affected by the effects of the pandemic, recording a steady average year-on-year growth of 4%.

These values are undoubtedly to be considered as defective, both because of the way in which companies are sampled and because the revenues generated by the activities in the territory of companies that do not file their financial statements in Italy are not known.

However, we believe that these values can represent, with sufficient approximation, the overall value of the CRO market, especially in trend terms.

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It remains to investigate the value produced by all those companies (specialised or CRO providers) that undoubtedly contribute to determining the total economic value of the clinical research 'chain'.

b. THE HEALTH STATUS OF CROs (marginality and balance sheet)

The 46 companies analysed were divided by size of turnover for 2020. Of these, 28 had revenues of less than 2 million, 9 had revenues of between 2 and 10 million, and 9 companies had revenues of over 10 million.

A few indicators in particular can give an idea of the health of CROs proper, in relation to the context:

- During the lockdown (2020) the turnover of Italian companies decreased by 11%, the pharmaceutical sector increased by 7.6% (source: CERVED) and, based on the estimates calculated with the survey presented here, CROs increased their turnover by 2.8%.

- The net profits recorded at national level, of all sectors, in 2019 amounted to 10.8% as a ratio of companies' net assets. CROs, in 2019, recorded a profit to equity ratio of 21% (source CERVED).

- Also, during the lockdown, domestic investments fell by 6.8%, while those made by CROs grew (over the period 2017-2020) by just under 10%, with a steadily increasing curve. In absolute terms, €18 million was invested by CROs over the four-year period (source: CERVED).

- Analyzing the pharmaceutical sector's investment in 2020 as a proportion of revenues generated, the figure is 8%. Comparing the investments made by CROs to the revenues generated, the figure for 2020 alone is 4%.

This figure expresses an overall constant net profit margin on revenues, with some slight decreases, but which testifies to a consolidated trend of mature production capacity. This also testifies to the fact that the pandemic did not affect productivity, according to the data available.

The reference market has slowed down due to the difficulties experienced by the Experimentation Centers in enrolling patients, caused by the impossibility of accepting them in hospitals, but, at the same time, the opening of the market for clinical investigations on medical devices, due to the entry into force of the new European regulations, has allowed an increase in the volume of activities.

As reported above, CROs employ about 3500 employees (2020 figure). Companies with revenues below 2 million employ 7% of the total number, companies with revenues between 2 and 10 million employ 9% and companies with revenues above 10 million employ 84%.

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In other words, given that 28 of the 46 CROs with revenues of less than 2 million are analyzed, the following picture is obtained:

Tipologia di imprese (per fatturato in Mil Eur)	**Numero di imprese**	**Numero dipendenti**	**numero medio di addetti per impresa**
< 2	**28**	**245**	**9**
2≤ X < 10	**9**	**315**	**35**
≥ 10	**9**	**2940**	**327**
totale	**46**	**3500**	

This reflects the Italian characteristic. In fact, the predominance of small enterprises is a typical feature of our economy.

From the point of view of assets, CROs are capitalized, managed by a management prepared to face the management difficulties of our country. It is enough to think of the banking system, which on the one hand has been absorbed by the obligations due to the evolution of European regulations (Basle Accords in their various forms) and globalization, which has produced rules that are influenced by the logic of the more industrialized countries, on the other hand the obsolete approach to investors, so that in Italy start-ups do not find in banks an interlocutor able to accompany the company in the processes of reorganization or start-up of new business. In addition, the tax system and the bureaucratic/administrative apparatus is known to be a source of obstacles to development and speed of action, as would be required by the globalization of markets.

Nevertheless, the CRO companies analyzed, operating in Italy, have a presence of equity compared to debt whose ratio expresses solidity.

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5. CONCLUSIONS

The analysis of the CRO sector in Italy reflects its membership of a vibrant pharmaceutical and medical device market that, despite the 2008-2014 crisis and pandemic, has grown in both economic and employment terms with good prospects for the future.

Clinical trials on pharmaceuticals and clinical investigations on medical devices are both local and international processes, and Italy's participation in research projects suffers from national regulations, with regional interpretations, document management platforms that differ from each other, are complicated and are not particularly in tune or in synergy with the European ones, presenting itself as a useless replication of documentary work. In other words, the Italian bureaucratic regulatory system is much more complex and binding (without any real advantage) than the European provisions and those applied in most other countries. In this sense, an important process of revision and streamlining of the rules, agreed upon with the contribution of all research players, would be desirable and necessary in order not to penalize the market and national operators, making the system more competitive.

A great deal of attention must be paid to small companies, precisely because the European landscape requires a vision that cannot be limited to a local horizon. Therefore, from both a strategic and an organizational point of view, small companies should strive to increase their market penetration capacity and develop their organisation, adapting it to the constant international challenges.

At the beginning of 2022, Regulation (EU) No 536/2014 on clinical trials of medicinal products for human use came fully into force, significantly changing certain procedural aspects in order to improve transparency and competitiveness in the European Union. Significant delays in adapting Italian legislation to the requirements of this regulation seriously jeopardize Italy's participation in international studies, with potentially serious scientific, reputational and economic damage. An immediate reaction from the stakeholder community is required and it is essential that CROs have the opportunity to share experiences, proposals and participate in decision-making processes.

The experiences gained during the pandemic emergency have shown how the use of technologies and processes of "dematerialization" and "virtualization" push in the direction of substantial changes in clinical trial models (the so-called Decentralized Clinical Trials) that go in the direction of greater sustainability and greater involvement of patients while maintaining methodological rigour. On this issue too, CROs are an active party willing to define a methodological framework shared with other stakeholders. The ability to accept and indeed promote these changes will be a key feature of CROs in the immediate future.

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- Recommendations:
- It is essential to critically review all the national legislation in order to fully harmonize it with the European one, freeing it from the many limitations and constraints that do not allow a full and fast development of the Italian contribution to clinical research.
- In particular, the specific regulations for Italian CROs are penalizing, causing economic and organizational burdens and objectively limiting further development of the sector in Italy.
- The shortage of research professionals is now critical on the national scene. Greater synergy between academia and industry is desirable in order to provide modern training suitable for immediate employment in a sector of great added value.
- An understanding of the economic dimension of the sector is essential for better management of resources, investments and opportunities, especially for small and medium-sized enterprises. It is equally important to consider the economic benefits that the promotion of clinical trials can bring to trial centers.
- The advent of technological solutions and methodological innovations must be fostered and promoted. The ability of all stakeholders to face and accept change must become the hallmark of Italian clinical research in the future.

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