Towards a More Competitive Italy in Clinical Research: The Survey of Attitudes towards Trial sites in Europe (The SAT-EU Study™)

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ABSTRACT

BACKGROUND: Italy is Europe's third largest pharmaceutical market, yet it ranks only ninth in the number of NIH-registered clinical trials per capita. The aim of our study was to explore stakeholders' perception of Italy as a place to undertake clinical trials, and to estimate the potential economic impact of selected reforms in terms of incremental trial activity.

METHODS: The Survey of Attitudes towards Trials in Europe (SAT-EU Study) was an anonymous, web-based survey, which systematically assessed factors impacting clinical trial site selection in Europe. Estimates of Italian economic impact were developed in collaboration with AICRO (Association of Italian Contract Research Organisations).

RESULTS: Responses were obtained from 485 professionals in 34 countries (15% residing in Italy) representing over 100 institutions, spanning BioPharma, Clinical Research Organizations (CROs), Medtech, and Academic Clinical Trial Units (CTUs). Italy ranked tenth of twelve in terms of accessibility and transparency of information required to run clinical trials, and last with respect to predictability and speed of Ethics Committees. Costs of running clinical trials were not considered critical, whereas, fragmented and slow approval process was. Streamlined centralized trial authorization would translate into an estimated 1.1 billion Euros of incremental trial investments over three years.

CONCLUSIONS: Clinical trial professionals consider Italy's governance of clinical research suboptimal, among the worst in Europe, and indicate that much could be done to make Italy more attractive for clinical trial investments. The present study also provides evidence about stakeholders' willingness to invest in trials and its economic consequences, provided effective reforms are put in place.

Key words: Clinical trial competitiveness Europe; clinical trial competitiveness Italy; clinical trial governance Italy: clinical trials Italy; Italian health policy.

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INTRODUCTION

From 2000 to 2012, 8'139 clinical trials were undertaken in Italy, 58% of which multicentre [1]. Italian trial sites may be considered attractive as Italy is Europe's third largest BioPharmaceutical market, [2] and Italian investigators prominent in terms of publications and medical society leadership [3].

Despite this, propensity to undertake clinical research in Italy is facing challenges. The number of clinical trials undertaken in Italy fell 21% from 2008 to 2012 [1]. But is the slowdown in Italian clinical research simply part of a European trend?

According to EudraCT (EU clinical trial database), Italy has decreased its share of total European trials from 18.5% in 2008 to 17.7% in 20122 [2]. In terms of clinical trials registered in the US National Institute of Health's (NIH) database, Italy ranks last of nine European countries in the number of NIH-registered trials per capita [4].

Why then is Italy a less attractive place to execute trials, considering the size of its market and the excellence of its investigators? This research question has not been fully investigated. Only one study has looked at these issues, with research limited to industry employees working in Italy [5], whereas much of the money invested actually comes from international trials generated or administered outside Italy.

The aim of this paper is to explore the reasons why Italy is considered a less attractive place to run clinical trials compared with other European countries, and to estimate the economic impact of potential reforms in terms of number of trials executed in the country. We have recently shown that ease of approval and investigator-dependent factors dominate clinical trial site selection at European level, while costs and government financial incentives appear less important [6]. Here, we focus on results pertaining to Italy's comparative performance, desired improvements, and their possible economic impact.

METHODS

The first research question on Italy's attractiveness for clinical research was addressed via the Survey of Attitudes towards Trial sites in Europe (The SAT-EU Study™), an anonymous, web-based cross-sectional survey engaging key stakeholder groups involved in clinical trial site selection, i.e. BioPharma companies, Medical Device manufacturers, Clinical Research Organizations (CROs), and academic Clinical Trial Units (CTUs). The SAT-EU Study™, detailed methods for which have been reported elsewhere [6], was a non-profit collaborative effort to systematically assess factors impacting clinical trial site selection in Europe and in Italy. Four categories of levers impacting trial site selection were identified and tested for their relevance: environment-, investigator-, hospital/unit-driven levers, and costs, for a total of nineteen levers, as previously reported [6]. The survey also explored perceptions of the Italian trial environment in comparison with eleven EU countries, and explored desired improvements and their potential economic impact in terms of trial execution decisions. The survey also sought participants' feedback with respect to areas for future improvement, and on the potential impact of reforms on clinical trial activity.

Questions and questioning methodology were carefully developed to avoid bias and were validated with London-based healthcare market research experts (The Planning Shop International), while a pilot survey was run to refine question strategy. Survey participants' feedback was gathered using a multiple-choice format, requiring respondents to provide a single response of rank; a response box allowed for free comments. The order of presentation of individual responses to questions was scrambled to minimise response bias. Two of the questions devoted to Italy sough to estimate incremental trial activity respondents would be willing to undertake in Italy over the next 3 years given defined reforms i.e. a) a general pan-European insurance for multicenter trials, and b) a single lead-authority providing a unique and binding Clinical Trial Authorization (CTA) for all sites within a multicentre trial.

The economic impact of reforms was explored combining SAT-EU data on stakeholder trial investment decisions, with AICRO data on costs associated with trials undertaken in Italy. Investments associated with multicentric trials executed in Italy were estimated on two levels: i) direct, patient-related costs associated with individual patient enrolment and, ii) overall trial costs, including trial set-up and central costs (such as CTA and EC

approvals, trial monitoring, statistics and report writing, investigator meetings, etc.). Since trial investments vary significantly by therapeutic area (TA) and by company involved, we sought the help of the Association of Italian CROs (AICRO) whose work spans a wide variety of TAs and companies, from large multinationals to small local players. Accordingly, AICRO surveyed their members on a voluntary basis providing information on trial costs and sizes for Oncology, Cardiology, Immunology/ infectious diseases, Neurology, as well as for "all other trials". Five major AICRO members provided information for each of five major TAs on: (a) average cost per enrolled patient (b) average number of patients per Italian trial site; and (c) average number of Italian sites per trial. We then used AIFA reports on the breakdown of trials by TA for 2007-2012 [1,2,7] to estimate the weighted average cost per trial executed in Italy. Finally, since direct patient-related costs per trial are only a fraction (50-75%) of total trial costs depending on trial size and design, we also developed an estimate of the total investment associated with the execution of a trial in Italy. We then used both numbers (direct, patient-related and total trial costs) to estimate the potential impact on trial investments given defined improvements.

Results are primarily presented descriptively as means, standard deviations, coefficient of variations and 95% confidence intervals (95% CI). Statistical significance of the differences among countries was tested by ANOVA. Statistical significance of the differences between Italy and each of the other countries was attested by paired t-test.

RESULTS

Respondent Demographics

Responses were obtained from 485 professionals in 34 countries (15% residing in Italy) representing over 100 different institutions, spanning BioPharma (53% of respondents) Clinical Research Organizations (CROs) (22%), and Academic Clinical Trial Units (CTUs) (18%). Participant answered 72% of questions on average.

In terms of hierarchy, 68% of respondents were in top-level positions, namely manager, director, vice-president, or department head. The majority of respondents were final decision makers, i.e. they were either the "overall final decision maker", or trial site selection decisions were "entirely at (their) discretion".

Perception of Italian Trial Environment

A statistically significant difference was found in respondents' perceived desirability to run clinical trials across twelve EU countries, namely Europe's top five healthcare markets (Germany, France, Italy, the UK, Spain), three main east-European markets (Poland, Hungary, Czech Republic), plus Netherlands, Belgium, Switzerland, and Austria.

In terms of accessibility and transparency of information required to run clinical trials, Italy scored tenth of twelve countries, since information required to get a trial site up and running is not easily accessible (Table 1). Differences among countries (F Statistics) are statistically significant and paired t statistics show significant differences between Italy and all other countries except the Czech Republic, Hungary and Poland.

With respect to predictability and speed of Ethics Committees (ECs) and Institutional Review Boards (IRBs), Italy scored last in a twelve-country ranking, with all differences among countries statistically significant (Table 2).

In terms of availability of equipment required to participate in a trial, Italy scored 9th, with all differences statistically significant (Table 3).

Evaluation of Italy's overall "trial capabilities"

Our results also show that Italy's overall "trial capabilities" are "average" compared to the other top four markets, namely Germany, France, UK, and Spain. Respondents attribute the greatest weight to the statement that Italy is in an "average position, not good, not bad", followed by the contention that "Italy is in the lowest quartile". The lowest weight was placed on the assertion that "Italy is in the highest quartile" (Figure 1).

In terms of overall "trial site desirability" Italy ranked 7th of 9 countries in an overall trial site "desirability" measurement. This indicator incorporates both trial performance and market size. Accordingly, Italy outperformed only two small markets, Austria and Switzerland, while

TABLE 1

ACCESSIBILITY AND TRANSPARENCY OF INFORMATION REQUIRED TO MAKE TRIAL SITE SELECTION DECISIONS (N = 296)*

	ITALY	GERMANY	FRANCE	SPAIN	UK	AUSTRIA	BELGIUM	NL	CH	CZECH R.	HUNGARY	POLAND
MEAN	69.9	78.7	73.3	72.5	77.0	73.1	74.6	75.9	74.3	69.5	69.4	70.3
STD DEV	7.9	9.6	9.3	8.7	9.9	9.3	10.0	9.2	9.7	9.8	9.7	9.8
COEFF VAR	11.2%	12.2%	12.7%	12.0%	12.9%	12.7%	13.4%	12.2%	13.0%	14.1%	14.0%	13.9%
95% CI	(69.0-70.8)	(77.6-79.8)	(72.3-74.4)	(71.6-73.5)	(75.9-78.2)	(72.0-74.1)	(73.4-75.7)	(74.8-76.9)	(73.1-75.4)	(68.4-70.6)	(68.3-70.5)	(69.2-71.5)
ITALY VS OTHER COUNTRIES												
DIFF (MEAN)	-	-8.75	-3.41	-2.60	-7.09	-3.14	-4.63	-5.95	-4.32	0.41	0.51	-0.41
PAIRED T STAT	-	-13.974	-6.245	-5.171	-5.840	-5.113	-7.076	-9.894	-6.785	0.618	0.776	-0.622
SIGNIFICANCE	-	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No

ANOVA		
	Num	3552
	Adj R-sq.	0.085
	F	30.91
	Prob > F	0.000

* Legend: Degree of satisfaction. ranging from 0 (lowest score) to 100 (best score)

TABLE 2

PREDICTABILITY AND SPEED OF ETHICS COMMITTEES AND INSTITUTIONAL REVIEW BOARDS (12 COUNTRY COMPARISON)*

	BELGIUM VS. ITALY	GERMANY VS. ITALY	NL VS. ITALY	UK VS. ITALY	CH VS. ITALY	AUSTRIA VS. ITALY	FRANCE VS. ITALY	CZECH R. VS. ITALY	SPAIN VS. ITALY	HUNGARY VS. ITALY	POLAND VS. ITALY
DIFFERENCE (MEAN)	-10.00	-9.84	-9.22	-6.49	-6.42	-5.99	-5.12	-4.32	-3.96	-3.62	-2.24
PAIRED T STAT	-11.172	-12.313	-11.496	-7.708	-7.414	-5.113	-6.985	-5.211	-5.360	-4.374	-2.946
SIGNIFICANCE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
NUMB OBS	230	247	244	242	206	206	250	213	250	210	224

ANOVA		
	Num	2.864
	Adj R-sq.	0.079
	F	23.40
	Prob > F	0.000

* Legend: Test for difference between Italy and comparator countries: from highest to lower Mean Difference. Degree of satisfaction. ranging from 0 (lowest score) to 100 (best score)

differences with Spain and Austria were not statistically significant (Table 4).

One specific question focussed on hospital-based trials in cardiovascular disease, the area that typically involves the largest and longest-running clinical trials. Respondents found the most highly desired improvement to be a reduction in bureaucracy, including optimized contracting with hospital administration, followed by streamlined Ethics review.

Impact of potential reforms

Optimization of EU level trial insurance for multicenter trials may have an impact on trial volume. While 40% of participants believe that "nothing much will change", another 45.4% of respondents believe that a pan-European insurance scheme would encourage them to activate an additional 1-6 trials sites in Italy over the next three years. Of these, 28% of respondents would add 3-6 trial sites.

TABLE 3

AVAILABILITY OF EQUIPMENT WHICH MAY BE REQUESTED TO SELECT A TRIAL SITE (N = 296)*

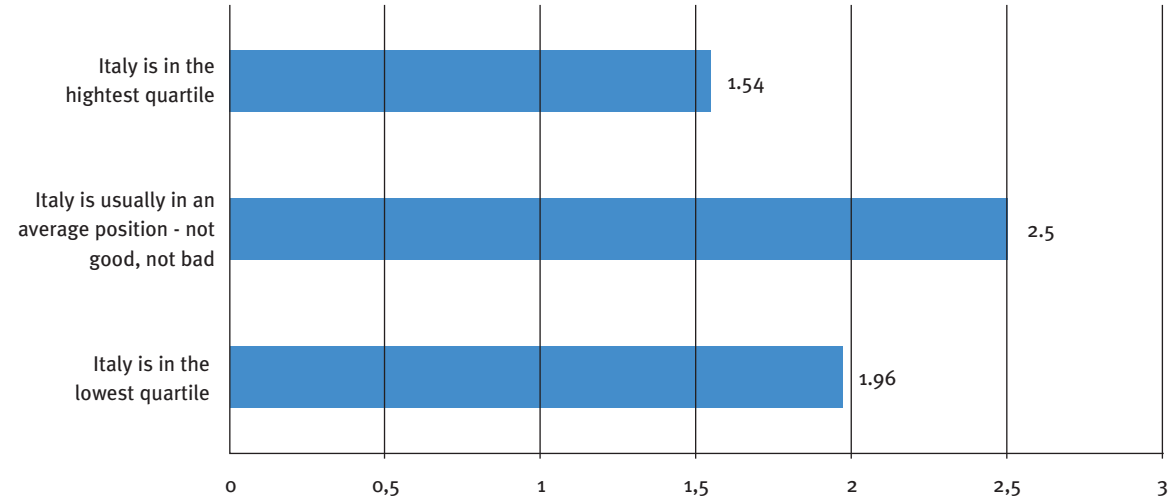
	ITALY	GERMANY	FRANCE	SPAIN	UK	BELGIUM	NL	AUSTRIA	CH	CZECH R.	HUNGARY	POLAND
MEAN	74.2	81.7	77.8	74.9	79.3	77.5	79.2	76.7	79.1	70.6	70.0	70.5
STD DEV	8.9	8.4	8.5	9.0	9.2	8.8	8.9	9.3	8.8	9.3	9.4	9.4
COEFF VAR	12.0%	10.2%	10.9%	12.0%	11.6%	11.3%	11.2%	12.1%	11.1%	13.2%	13.4%	13.4%
95% CI	(73.2-75.2)	(80.8-82.7)	(76.8-78.7)	(73.9-76.0)	(78.2-80.3)	(76.5-78.5)	(78.2-80.2)	(75.7-77.8)	(78.0-80.1)	(69.6-71.7)	(68.9-71.0)	(69.4-71.6)
ITALY VS OTHER COUNTRIES												
DIFF (MEAN)	-	-7.50	-3.55	-0.71	-5.03	-3.28	-5.00	-2.50	-4.83	3.58	4.26	3.75
PAIRED T STAT	-	-13.9738	-12.9738	-1.5647	-8.8895	-6.1341	-9.4587	-4.2545	-8.7271	6.3235	7.5940	-6.6536
SIGNIFICANCE	-	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

ANOVA		
	Num	3552
	Adj R-sq.	0.14
	F	56.19
	Prob > F	0.000

* Legend: Degree of satisfaction. ranging from 0 (lowest score) to 100 (best score)

FIGURE 1

ITALY'S OVERALL TRIAL CAPABILITIES VERSUS OTHER TOP 4 MARKETS (GERMANY, FRANCE, SPAIN AND UK) SCORED (ON AVERAGE) BY THE LEVEL OF AGREEMENT WITH THREE STATEMENTS (N=296)*



* Legend: 3=Rarely; 2 Sometimes; 3 Most of the time. Differences in scores (highest vs. average, highest vs. low, average vs. low) were all found statistical significant.

More significant is the finding that a unique and binding clinical trial authorization (CTA) would encourage 56% of survey participants to activate additional trial sites in Italy, with the highest weight placed on 3-4 additional trial sites (21% of respondents), followed by 5-6 additional trial sites (19% of respondents).

Economic impact of potential reforms

Data provided by AICRO members yielded an estimated weighted average cost per trial executed in Italy of 434'000 Euros (direct patient-related costs), and of 578-867'000 Euros (overall trial costs).

Accordingly, an optimised insurance

TABLE 4

TRIAL SITE DESIRABILITY INDEX (9 COUNTRY COMPARISON)*

	GERMANY VS. ITALY	NL VS. ITALY	UK VS. ITALY	FRANCE VS. ITALY	BELGIUM VS. ITALY	SPAIN VS. ITALY	AUSTRIA VS. ITALY	CH VS. ITALY
DIFF (MEAN)	3.12	1.21	1.08	1.07	0.94	0.27	-0.10	-0.61
PAIRED T STAT	18.1148	5.0461	4.7247	6.4430	3.7856	5.3599	-0.3654	-2.2048
SIGNIFICANCE	Yes	Yes	Yes	Yes	Yes	No	No	Yes
	249	222	242	244	219	250	194	194

ANOVA	Num	2239
	Adj R-sq.	0.1728
	F	59.44
	Prob > F	0.0000

* Legend: Test for difference between Italy and comparator countries (From highest to lower Mean Difference) ;
1 = Most desirable country; 9 = Least desirable countries

scheme would yield an estimated 824 million Euros of incremental trial investments over three years (direct patient-related costs) or 1.1-1.65 billion Euros (total trial costs) depending on whether patient-related costs are computed at 50% or 75% of total costs) (Table 5).

Particularly relevant is the potential impact of a unique and binding clinical trial authorization (CTA), estimated at 1.1 billion Euros in incremental trial investment over three years (direct patient-related costs), or 1.4-2.1 billion Euros when considering total trial costs (Table 5). These figures highlight the extent to which market participants desire streamlined trial authorization, and the degree to which they are ready to vote with their budgets if trial approval processes were rationalised.

DISCUSSION

Previous findings indicate that the regulatory environment, including policies governing research activities and clinical trials, influence industry's localisation [5]. Similarly, it is established that a collaborative relationship between public administration, research and industry is conducive to BioPharma investments, whose high-risk business model benefits from a welcoming "national system of innovation". [8]

The results of our study are aligned with this notion. However, our survey substantially expands on this, as it provides novel and potentially relevant information on trial investment decisions. The SAT-EU survey has for the first time gathered direct evidence on the extent to which the regulatory environment has failed to bear fruit in Italy. Moreover, our research revealed the extent to which Italy stands to benefit by making desirable changes. The vast majority of countries actively involved in clinical trials were represented in the survey, while most respondents were key decision-makers in their organisations, i.e., the people in charge of making trial investment decisions. Given the survey's size, the variety of domains explored, the number of countries and organisations involved, and the prevalence of senior decision-makers, our results may provide relevant insight into 'real world' trial investment decisions [6].

The SAT-EU study indicates that Italy scores quite low on all four levels tested, namely on availability of trial-related information (10th in a 12 country ranking), on predictability and speed of ECs/IRBs (12th out of 12), on availability of required equipment (9th/12). Most importantly, Italy ranked only 7th out of 9 on overall desirability as a place to conduct clinical trial. Indeed, such a low score assigned by highly placed market participants holding the keys to trial investment decisions, is dismal for a country with a long and respected scientific tradition. Participants commented that the Italian ethics and contracting process are so laborious

TABLE 5A

POTENTIAL IMPACT OF A EU LEVEL TRIAL INSURANCE FOR MULTICENTRIC TRIALS (N=253)

ADDITIONAL TRIAL SITES (RANGE) (SAT-EU) (1)	ADDITIONAL TRIALS SITES (1)	% OF 253 RESPONDENTS OPTING FOR EACH ADDITIONAL TRIALS CATEGORY (SAT-EU) (1)	NR OF ITALIAN TRIALS POTENTIALLY IMPACTED PER YEAR OUT OF UNIVERSE OF 404 TRIALS (2)	ADDITIONAL INVESTMENT PER TRIAL (EUROS) (3)	INDICATIVE MARKET IMPACT (1 YEAR, MILLION EUROS)	INDICATIVE MARKET IMPACT (3 YEARS, MILLION EUROS)
1-2	1.5	17.8%	72	650,570	47	140
3-4	3.5	14.6%	59	1,517.996	90	269
5-6	5.5	13.0%	53	2,385.422	126	377
NOTHING WILL CHANGE	0	40.3%	163	0	0	0
NOT SURE	0.5	14.2%	58	216,857	12	37
		100%	**404**		**275**	**824**

(1) Data from SAT-EU Study, BMJ Open 2013 [6]
(2) AIFA data: 404 out of 697 trials in Italy are multicentre international trials [1]
(3) AICRO Estimates: Cost per trial of 433,713 Euros

TABLE 5B

POTENTIAL IMPACT OF A UNIQUE AND BINDING CLINICAL TRIAL AUTHORIZATION (CTA) FOR MULTICENTRIC TRIALS (N=253)

ADDITIONAL TRIAL SITES (RANGE) (SAT-EU) (1)	ADDITIONAL TRIALS SITES (1)	% OF 253 RESPONDENTS OPTING FOR EACH ADDITIONAL TRIALS CATEGORY (SAT-EU) (1)	NR OF ITALIAN TRIALS POTENTIALLY IMPACTED PER YEAR OUT OF UNIVERSE OF 404 TRIALS (2)	ADDITIONAL INVESTMENT PER TRIAL (EUROS) (3)	INDICATIVE MARKET IMPACT (1 YEAR, MILLION EUROS)	INDICATIVE MARKET IMPACT (3 YEARS, MILLION EUROS)
1-2	1.5	17.0%	69	650,569	45	134
3-4	3.5	20.6%	83	1,517.995	126	378
5-6	5.5	18.6%	75	2,385.421	179	537
NOTHING WILL CHANGE	0	26.5%	107	0	0	0
NOT SURE	0.5	17.4%	70	216,856	15	46
		100%	**404**		**365**	**1.096**

(1) Data from SAT-EU Study, BMJ Open 2013 [6]
(2) AIFA data: 404 out of 697 trials in Italy are multicentre international trials [1]
(3) AICRO Estimates: Cost per trial of 433,713 Euros

and slow that by the time an Italian site is set up, an international multicentre trial may have already completed enrolment in other countries. Numerous participants also commented that while they would like to include Italy in their multicenter trials, they often do not do so, because it is just too difficult and time consuming.

Our study is also the first to estimate the potential economic impact of reforms (e.g., European insurance, unique and binding trial authorization / centralisation of ECs) aimed at increasing investments in clinical trials in Italy. This is relevant for Italian researchers and policy makers. Particularly important is the estimated impact of a unique and binding

clinical trial authorization (CTA), as repeatedly recommended [9,10]. This figure is hard to ignore at 365 million Euros/year, or 1.1 billion Euros in incremental trial investment over the course of three years in direct patient costs.

Interestingly, encouraging experiments are ongoing at the regional level. Tuscany has approved regulations aimed at centralising ECs, standardising contracts, and introducing clinical trial units in regional hospitals. Since 1998 Umbria has a centralized ethics committee for the whole region. More recently at the national level, the 8th of February 2013 decree has stated that the number of ECs should be reduced to 1 EC per million inhabitants. This would translate into a 75% reduction in the number of ECs in Italy, from the 243 committees in 2012 to just 61.

It is noteworthy that in most Italian regions the multitude of ECs continue to exact a few million Euros via protocol review fees, while discouraging investment worth hundreds of millions of Euros instead. Similarly, a contract that is re-negotiated ten times to include ten hospitals in the same region benefits no one. Also, not making critical information easily available to prospective trial investors would seem inexplicable in today's information era. Accordingly, results of our survey provide direct and objective support to current efforts to reduce the number of ECs, and further recommend that attention be paid to making ECs' functioning more efficiently by training and accrediting EC members, such as has been done in the Netherlands. [11]. Given that the pan-European SAT-EU survey has shown that pool of eligible patients, speed of approvals, and web-based visibility of trial units are significantly more important than costs or government financial incentives, Italy would also benefit from standardized contracting on at least regional, if not national level, and from greater web exposure of clinical trial units.

As is well established in economics, the increase in investment would typically have multiplier effects, and therefore benefit not only Italian researchers, hospitals, and patients, but also a series of directly and indirectly associated industries, from specialised clinical research and information technology organizations, to mass service providers such as those catering to hospitality and travel.

Our study has some limitations. First, estimates of Italian trial costs were derived from a sample of CROs. Despite the fact that some of the most prominent CROs doing trials in Italy were involved, and that the data provided were validated by their relevant association, our sample may not necessarily be representative of all CROs. Second, the SAT-EU survey was conducted in 2011-2012, before recent regional and national legislation. How these changes will effectively be put into action, and how they could possibly influence trial location will be observed in the future.

CONCLUSIONS

Our study demonstrates that Italy's governance of clinical innovation is suboptimal, and not competitive with major European countries. By limiting the number of clinical trials that include Italian sites, it fails to benefit researchers, patients, hospitals, and more generally Italian competitiveness in BioPharma innovation. Bureaucratic procedures are penalizing Italy's recognized high scientific standards in medicine and clinical research. Implementation of streamlined legislation governing clinical trials, reduction in the number of ECs, standardisation of contracts, and improvement of trials management through adequate clinical trials units, can bring more clinical research to Italy. We hope this data encourages industry and academic medical societies to join forces to support recent reforms and demand further changes both at the national and regional level.

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