A survey on Biostatisticians Serving in the Italian Ethics Committees

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ABSTRACT

Background: Italian ethics committees (ECs) have the responsibility for evaluating and monitoring clinical research.
Methods: An electronic survey targeted to the biostatisticians operating in the 95 ECs in Italy, was launched in November 2016. Several aspects were explored such as education, job title, training in biostatistics and experience in the evaluation of protocols within the EC.
Results: Seventy case report forms were returned (74%), and the response rate was highest for ECs located in the South (78%) and lowest in the North (51%). The biostatisticians in the respondent ECs were prevalently male, aged 50-60 years, with postgraduate education in medical specialties and statistics. The annual workload varied depending on the type of institution and geographical area, with an annual median number of protocols examined ranging from 80 in hospital ECs to 198 in university hospital ECs, and from 80 to 108, in the South and the Centre, respectively. Of these, 40% were observational study protocols. The EC biostatisticians proposed to reject 5% of protocols and to suspend with the request of clarification or amendments 10%. Only 61% and 79% of these opinions, respectively, were regarded as binding by the other EC members.
Conclusion: The biostatistician will not be able to play a significant role in the EC as long as the required skill-set remains vague and his/her opinion on a protocol is underrated.

Key words: Ethics Committee; Biostatistician; Survey; REDCap

INTRODUCTION

At the European level the Ethics Committee (EC) is defined according to the Directive 2001/20/EC of the European Parliament and of the Council as "an independent body in a Member State, consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent" [1].

Even if the European directive has been implemented differently in the European countries [2], it was intended to "harmonize the administrative provisions governing such trials by establishing a clear, transparent procedure and creating conditions conducive to effective coordination of such clinical trials in the Community by the authorities concerned" [1].

In the Italian context, up to 1998, all experimental studies had to be regulated, reviewed and approved at a national level by a Central Drug Committee (*Commissione Unica del Farmaco*). By Ministerial Decree (MD) 15/7/1997 [3] and MD 18/3/1998 [4], the responsibility for monitoring and approving clinical trials was transferred from the national level of the Ministry of Health to local ECs [5]. Unfortunately, such deregulation in Italy resulted in an overly heterogeneous evaluation of clinical studies by the local ECs and a lack of guidance from the top level, with variations in the type of functions and types of competence [6-9].

According to MD 18/3/1998, Italian EC is typically composed of two clinicians, a biostatistician, a pharmacologist, a pharmacist, the medical director (or scientific director in case of research centers), an legal expert, a general practitioner, a bioethicist, a nurse and a volunteer for the care of patients or a patient advocacy organization [4]. This choice appears as a right balance between clinicians and non-clinicians. It is worth noting that with the approval of a new Italian law about ECs, i.e., MD 12/5/2006 [10], partially modified by the MD 07/11/2008 [11], there has been more significant involvement of pharmacologists and biostatisticians [12]. For instance, before the implementation into Italian law of Directive 2001/20/EC by Legislative Decree 24/6/2003 [13] 32 biostatisticians were working in the ECs because their presence was not mandatory [14].

More recently the MD 19/04/2018 [15] established the National Coordination Center for the Territorial Ethical Committees for clinical trials on medicinal products for human use and on medical devices, with no substantial change to the composition of ECs but reducing their number in Italy, with a specific aim to expediting and reducing variation in processing of trial applications.

The new European regulation (Regulation EU N. 536/2014) remains in the background of this complicated regulatory environment, since after being issued in 2014, at the time of writing there are still no certainties as to when it will come into force in Italy.

Given the heterogeneity in the work of Italian ECs [16], a survey was carried out by the Network of Biostatisticians in the Ethics Committee (NEBICE), with the aim i) to depict the profile of biostatisticians working in the ECs, ii) to promote a connection between them by means of an internet-based network, and iii) to determine the need for targeted professional development, education programs, and training.

The present report illustrates NEBICE survey results and offers some remarks.

Facets of Evidence and Ethics in Clinical Research

It has been observed that clinical research can be considered ethical if the following conditions are fulfilled (even if there can be exceptions in particular circumstances): (a) social or scientific value; (b) scientific validity; (c) fair subject selection; (d) favourable risk-benefit ratio; (e) independent review; (f) informed consent; (g) respect for enrolled subjects [17,18]. More generally a trial submitted to an EC must feature, to be approved, a rigorous methodology, clinical relevance and appropriate principles of ethics directed towards patients, society and researchers (19). Notably, some ethical and methodological issues need to be handled with particular relevance by ECs, namely: the appropriateness concerning placebo use for the control group, the nature of the comparator, the equivalence or non-inferiority design hypothesis of the trial and the choice of study endpoints [20]. ECs should require systematic reviews of existing research to avoid redundant and non-inferior studies [21] and to guarantee the clinical equipoise [22]. However, there is no consensus in the bioethical community on the justification of the principle of clinical equipoise for the moral acceptability of conducting a new trial [23,24].

As stated centuries ago by Avicenna, when evaluating clinical research, we have to wonder: do I believe the data presented? Can I use the results for my patients? [25]. It is also essential that the findings of the biomedical research have public dissemination since it is ethical to share medical knowledge with colleagues and lay people [26]. In the past, there has been a substantial request for training programs from the members of the EC to appropriately deal with local needs. Many Italian local ECs are overloaded because of the high number of protocols that every year are submitted to them, even if only a small part of protocols concern innovative research, and there are many differences among the ECs in the country [19]. Heterogeneity exists in Europe regarding the number of ECs, number of EC members [27], and training

requirements. As to the latter, the following topics related to training for EC members have been proposed [28]: (a) the purpose and history of medical research, (b) the history of research ethics, (c) working together in the modern regulatory environment, (d) basic ethical principles, (e) critical appraisal of a project, (f) ethical analysis, (g) group working, (h) reaching consensus, (i) fraud and misconduct. Also, it has been noted that there are some negative aspects related to ECs, namely: extreme bureaucracy [29], late decisions and lack of interest in the decision process on genuine bioethical issues.

Ethical evaluation of a study by an EC requires on the part of at least a majority of members, a sound knowledge of Evidence-Based Medicine principles (EBM) and functional competence in biostatistical methods, since it is unethical to conduct research that is unsound, for they can improperly modify medical evidence on a particular issue, and this may ensue many ethical problems [30]. Clinicians are mainly concerned with the ethical issues related to the health of their present patient while, in addition to that, the members of the ECs need to treat and evaluate all ethical questions which arise from a study, in order to warrant the safety of a drug or treatment also for future patients [31]. Thus, the interplay between an individual level of ethics and a collective one is required and desirable. Moreover, many other ethical constraints are related to medical research: it is not ethical to deprive patients of useful treatment, as well as it is necessary to stop a trial when there is sufficient evidence of no clinical significance of treatment in order not to expose patients to useless risks.

It has been observed, in fact, that the scientific evaluation of a trial or a treatment is a necessary, but not a sufficient, condition for a sound ethical evaluation [30]. Many errors can be associated with clinical research: poor definition of the research question, of the inclusion and exclusion criteria, wrong determination of the sample size, failure of a suitable control group, failure to carry out the study objectively, failure to evaluate the results of the subjects withdrawn from the study or to comment them in the study [32,33]. Also, it has been claimed that "a valuable attribute of statisticians is their ability to ask relevant and important questions, not only about statistical issues but also about the purpose of the research" [34]. Conversely, all the other members of the EC should also have a basic knowledge of medical statistics and of the many forms of bias which may affect clinical and statistical judgment [35,36].

METHODS

The survey was launched in early November 2016, and data were collected until August 2017. An e-mail survey invitation was sent to all secretaries of the 95 Italian ECs contained in the registry of the National Monitoring Center on Clinical Research with Medicines (*Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali*) maintained by the Italian Agency of Medicines (AIFA) as updated at September 2016.

The survey was created within an electronic data capture system hosted at University of Padova and known as REDCap (Research Electronic Data Capture) [37]. REDCap is a secure, web-based application designed to support data capture for research studies, developed initially at Vanderbilt University (https://projectredcap.org).

The interested EC biostatisticians were able to access the survey anonymously via a request for use through the link (https://redcap.dctv.unipd.it/surveys/?s=X89348XXFY) contained in the survey invitation. Several aspects were explored including education, job title, training in biostatistics and personal experience in protocol evaluation within the EC.

The type of institution where the ECs observed do operate, were classified as LHA=local health authority; Hospital=local hospital; IRCCS=public or local private hospital with a research mission acknowledged by the Italian Ministry of Health; University = teaching hospital of a State or Private University.

Data were analyzed with R software version 3.2.5 [38].

RESULTS

The investigation covered 95 ECs in Italy, and 70 questionnaires were returned, yielding a 74% response rate. The response rate varied by geographical location (Northern, Center and Southern Italy), with a 78% compliance for ECs in the South versus 51% for those located in the North, and by type of institution in which the examined ECs operate.

The biostatisticians in the respondent ECs were prevalently male (n=41,59%), between 50 and 60 years of age (n=30, 43%) and 39 were not affiliated with the facility in which the EC operates. For 42 of them (60%), the highest academic degree was Ph.D. or postgraduate specialty (46 academic degrees, overall). Among Ph.D. fields, the most common was epidemiology (43%). Among postgraduate specialties, the most frequent was in health/medicine (69%) followed by specialty in statistics (see Table 1). This distribution exhibits geographical variation, being statistics the most common specialty in the North and health/medicine the most common specialty in the South.

The self-reported best level of statistical training, relevant to EC activity (i.e. descriptive, inferential and medical statistics, clinical epidemiology, …) was mainly achieved through short courses, from 27% to 47% (depending on the topic) and courses in specialty programs, from 15% to 25%, whereas courses in Ph.D. programs contributed to a lower extent (from 9% to 18%). The practical knowledge of statistics was measured by the frequency with which the EC biostatistician analyses data (categorized as always, never,

TABLE 1. Distribution of PhD or post-graduate specialty as highest academic degree, obtained by the EC biostatistician by type of institution in which the EC operates.

		LHA		Hospital		IRCCS		University		Total	
		N	%	N	%	N	%	N	%	N	%
Specialty	Statistics			2	13.3	3	33.3	3	60.0	8	25.0
	Medical/Health	3	100.0	13	86.7	4	44.0	2	40.0	22	68.8
	Epidemiology					2	22.2			2	6.3
PhD	Statistics	1	50.0	1	25.0	2	40.0	1	33.3	5	35.7
	Medical/Health					2	40.0	1	33.3	3	21.4
	Epidemiology	1	50.0	3	75.0	1	20.0	1	33.3	6	42.9

Legend: LHA Local Health Authority; IRCCS Research Clinical Institute

TABLE 2. Practical knowledge in data analysis by type of data and geographical location of the EC (15 missing answers).

		North		Centre		South		Total	%
		N	%	N	%	N	%		
Analysis of non-biomedical data	always	10	35.7	2	16.7	7	43.8	19	33.9
	sometimes	9	32.1	3	25.0	5	31.3	17	30.4
	never	9	32.1	7	58.3	4	25.0	20	35.7
Analysis of data from experimental studies	always	15	53.6	7	63.6	12	75.0	34	61.8
	sometimes	12	42.9	4	36.4	4	25.0	20	36.4
	never	1	3.6					1	1.8
Analysis of data from epidemiological/observational studies	always	20	71.4	9	75.0	15	93.8	44	78.6
	sometimes	7	25.0	3	25.0	1	6.3	11	19.6
	never	1	3.6					1	1.8
Analysis of other biomedical data	always	8	29.6	6	50.0	9	56.3	23	41.8
	sometimes	14	51.9	5	41.7	5	31.3	24	43.6
	never	5	18.5	1	8.3	2	12.5	8	14.6

sometimes). Its distribution by type of data and geographical location of the EC is shown in Table 2.

Concerning the scientific activity, the median number of publications of the EC biostatistician, in the last five years on indexed journals, ranged from 4 to 46, for hospitals and university ECs, respectively. Regardless of the institution and the geographical location of the ECs, 76% of biostatisticians declared to be involved in research activities and 70% in teaching activities.

The annual workload for the EC members varied by the type of institution and geographical area. The median number of examined protocols per year ranged from 80 in hospital ECs to 198 in university ECs, and from 80 to 108, in the South and the Centre, respectively. About 40% of these protocols concerned observational studies.

As for the evaluation of protocols, the study design and objectives, together with statistical issues were identified as the most relevant aspects to be taken into account. The handling of missing data and economic aspects were regarded as less important (see Table 3, panel A). When asked to rank the principal motivations for a protocol rejection, an unethical treatment or aspects related to the sample size were given high importance (Table 3, panel B). Sample size calculation equally influenced protocol suspension and rejection (Table 3, panels B-C).

Although an EC decision on a research protocol is made by consensus, a question on the individual opinion of the EC biostatistician was included in the survey. The proportion of protocols that were not approved by the EC biostatistician did not appear to depend on the type of institution in which the EC was set and the affiliation of the principal investigator, except for the suspension of protocols in university ECs (Table 4).

Overall, the biostatistician proposed to reject 5% of the protocols and to suspend with the request for clarification or amendments 10%. About 61% and 79% of these opinions, respectively, were regarded as binding by the other EC members in reaching a decision. It is worth noting that EC biostatisticians older than 45 years (n=30, 29 missing answers) were taken into greater consideration when proposing to reject a protocol.

In evaluating a protocol, 58% of EC biostatisticians declared to consult supplementary material (i.e., textbooks, online databases). This proportion was higher in the North (70%) and lower in the South (33%). As to the time spent, 40% of protocols were examined in 16-30 minutes, but variability exists between the different types of institutions that host the EC (Table 5).

Concerning the implementation of training, education and information programs for EC biostatistician, 18 declared that their EC did not provide for continuing education opportunities, never promoted courses on

TABLE 3. Frequency of ranks attributed by the EC biostatistician to some aspects in the evaluation of a protocol (panel A) and in a protocol rejection (panel B) or suspension (panel C). (1=maximum relevance, 10=minimum relevance).

A PROTOCOL EVALUATION	Rank (%)									
	1	2	3	4	5	6	7	8	9	10
Rationale	34.7	8.2	12.2	4.1	4.1	4.1	12.2	8.2	2.0	10.2
Study Objectives	42.9	16.5	2.0	2.0	2.0	2.0	2.0	6.1	14.3	10.2
Study Design	44.9	10.2	6.1	2.0	2.0	0.0	0.0	6.1	4.1	24.6
Sample Size calculation	38.8	8.2	8.2	2.0	4.1	0.0	6.1	4.1	12.2	16.3
Statistical analysis of primary endpoints	34.7	8.2	8.2	6.1	2.0	6.1	0.0	10.2	6.1	18.4
Statistical analysis of secondary endpoints	14.3	8.2	14.3	8.2	10.2	12.1	8.2	4.1	6.1	14.3
Treatment of missing data	10.4	16.8	6.2	12.5	6.2	12.5	6.2	18.8	6.2	4.2
Informed Consent	24.5	12.2	6.1	4.1	8.2	6.1	10.2	8.2	4.1	16.3
Insurance Issues	20.3	14.3	6.1	4.1	8.2	6.1	8.2	4.1	10.2	18.4
Economic issues	12.2	10.2	18.4	4.1	8.2	10.2	10.2	4.1	10.2	12.2
B PROTOCOL REJECTION	**Rank (%)**									
	1	2	3	4	5	6	7	8	9	10
Rationale	7.0	18.5	9.3	11.6	11.6	14.0	4.7	14.0	9.3	0.0
Study Objectives	25.0	27.2	11.4	2.3	2.3	2.3	4.5	6.8	18.2	0.0
Study Design	20.9	34.9	11.6	2.3	0.0	0.0	4.7	9.3	16.3	0.0
Unethical Treatment	26.7	9.8	4.9	4.9	9.8	4.9	9.8	12.1	17.1	0.0
Sample Size	27.5	17.5	10.0	0.0	5.0	2.5	5.0	15.0	17.5	0.0
Statistical Analysis	20.9	18.5	7.0	11.6	2.3	4.7	16.3	4.7	14.0	0.0
Informed Consent	11.9	11.9	7.2	19.0	11.9	7.1	7.1	4.9	19.0	0.0
Insurance	14.3	9.5	4.8	11.9	11.9	4.8	7.1	9.5	26.2	0.0
C PROTOCOL SUSPENSION	**Rank (%)**									
	1	2	3	4	5	6	7	8	9	10
Rationale	3.0	22.8	12.9	7.9	9.9	7.9	7.9	12.9	14.8	0.0
Study Objectives	20.2	28.2	15.2	2.0	0.0	5.1	2.0	5.1	22.2	0.0
Study Design	32.6	17.8	12.9	3.0	0.0	0.0	3.0	12.9	17.8	0.0
Unethical Treatment	20.8	7.9	5.0	10.9	10.9	0.0	10.9	15.8	17.8	0.0
Sample Size	29.0	22.0	10.0	5.0	0.0	0.0	5.0	7.0	22.0	0.0
Statistical Analysis	24.2	19.2	14.1	5.1	7.1	2.0	0.0	7.1	21.2	0.0
Informed Consent	22.2	10.1	20.2	8.1	10.1	5.1	2.0	2.0	20.2	0.0
Insurance	15.0	15.0	8.0	8.0	13.0	3.0	5.0	10.0	23.0	0.0

research methodology (n=20) but regularly informed on regulatory aspects (n=24).

When asked whether his/her skills and experience fit the position of EC biostatistician (on a 0 -100 scale), the median self-perceived adequacy was good, ranging from 70 for LHA ECs to 90 for hospital ECs.

DISCUSSION

Italian ECs have the responsibility for evaluating and monitoring clinical studies in human subjects, with the ultimate goal to promote high ethical standards in research for health [19, 39].

The NEBICE study was intended to provide an outline of the characteristics and activities carried out by the biostatisticians in the Italian ECs, to identify the best strategies to promote methodological rigor and ethical behavior. Although the survey was not aimed at an evaluation of quality and workload of ECs, it offered an intriguing insight into the operation of the clinical trial regulations in Italy, and a perspective which is different, albeit complementary, from that recorded by AIFA in its annual Bulletin (http://www.aifa.gov.it/en/content/bulletin-clinical-trials-drugs-italy).

To our knowledge, NEBICE is the study which involves the highest number of Italian ECs.

In our investigation, we mainly focused on the ethical

TABLE 4. Median and interquartile range of the distribution of protocols not approved by the biostatistician (%), by type of institution in which the EC operates and opinion. *: principal investigator affiliated with the same institution of the EC.

	LHA	Hospital	IRCCS	University
Rejection *	5 (1-20)	5(5-10)	10(1-10)	5(0-10)
Rejection	5(3-20)	5(3-7.5)	5(0-10)	5(0-10)
Suspension*	30(9-50)	10(10-30)	20(10-30)	5(0-40)
Suspension	20(10-50)	15(3.7-30)	15(10-25)	20(5-45)

TABLE 5. Median and interquartile range of the distribution of protocols evaluated by the biostatistician (%), by type of institution in which the EC operates and time spent in the evaluation.

	LHA	Hospital	IRCCS	University
15 min (%)	5(0-10)	0 (0-12.5)	10 (5-18.7)	0 (0-10)
15 -30 min (%)	20 (10-70)	35 (13.7-48.7)	30 (12.5-57.5)	50 (45-70)
31 -60 min (%)	10 (10-45)	50 (10-60)	35 (19.5-50)	30 (10-40)
61 -120 min (%)	20 (7-50)	5(0-20)	6 (0.5-25.5)	5 (0-20)
>120 min (%)	5 (0-15)	0(0-6.2)	0(0-5)	0 (0-5)

and methodological issues that a biostatistician in an EC may ordinarily encounter. We observed that the role of the biostatistician in the Italian ECs is multifaceted. Only a few of them have a Ph.D. degree while the most part has postgraduate education in medical specialties. Also, it is quite remarkable that other EC members do not hold in enough regard the contrary opinion of the biostatistician.

The biostatistician will not play a significant role in the EC as long as the requirements that an individual has to fulfill to be a biostatistician in an EC remain vague and, his/her opinion is not binding for the judgment of approval or refusal of a protocol.

This fact may also entail severe ethical problems, as a valid quantitative approach to research is a requirement for complete ethical evaluation of a protocol.

More generally, there is a lack of understanding of the intimate connection between biostatistics and ethics. Biostatistics must not be conceived as a value-free science since the ethical consequences of making a statistically wrong decision have to be taken into account [40,41].

The evaluation of a research protocol involves many biostatistical issues which present some intricate ethical counterparts. Given that there is such a strict relationship between ethics and methodology in ECs, the role of the biostatistician should be enriched with more comprehensive and interdisciplinary training to be capable of acting in response to the new challenges of the innovations in the biomedical sciences.

It is fundamental to pinpoint the mandatory competencies that the biostatistician of ECs should have, to guarantee standardization, fairness, and rigor in protocol evaluation, ultimately increasing the level of competence as new challenges, and new study designs arise [42-44]. Professional certification through organizations that establish credible and robust certification systems, incorporating requirements of the continuance of certification (i.e., to ensure that a certificate holder continues to learn and stay up to date in the practice field) might accomplish this task. Nevertheless, the need for professional certification of biostatisticians is still a matter of debate in the Italian scientific community.

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