Methodological aspects of observational studies discussed by Ethics Committees: a multicentre, cooperative survey

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Summary
The Italian Medicines Agency (AIFA) has recently introduced a set of rules on the classification, planning and conduction of observational studies in pharmacological research. Even though the AIFA rules are aimed mainly at studies involving drugs, they are expected to make an important contribution to improving the quality assurance of all observational studies, which is often still inadequate despite the fact that much biomedical research is observational.
The aim of this study was to depict the quality of the observational study protocols presented to some Italian ethics committees (ECs) and to provide a basic framework for evaluating the effectiveness of the AIFA rules, introduced in March 2008.
To this end, a survey of six ECs was conducted. A total of 364 protocols presented as observational before March 2008 were examined by two trained and independent reviewers, not EC members at any of the participating centres. The overall quality of the protocols was very similar to that reported in other papers, both international and national. Although the main aspects of the studies were clearly defined in several cases, particularly in the multicentre studies, there emerged a fairly high percentage of protocols that, on post-hoc comparison, were found not to comply with the AIFA rules in spite of the fact that these rules summarize indications that are widely agreed and accepted.

KEY WORDS: *epidemiological studies, ethics committee, observational studies, quality.*

Introduction

Observational studies are the most common type of epidemiological and clinical research, constituting a primary source of evidence for the development of medical research. Yet they do not rank at the top of the sources of evidence in terms of quality: indeed, depending on the classification adopted, their quality level is ranked, at most, as II-2 (1) or class B (2). However, it is difficult to dispute that, in terms of frequency, they account for a large proportion of the research studies published in the medical literature. In view of this, considerable efforts have been made to propose a common methodological setting for conducting and evaluating such studies (3-5): the most significant initiative at international level is the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statement (6),

whereas in Italy the debate in the epidemiological community in the period 2004-2006 (7-9) and SISMEC's most recent position paper (10) are among the points of reference for investigators. The Italian Medicines Agency (AIFA) recently made an important contribution to the standardization and quality assurance of observational studies in pharmacological research by developing and issuing a set of rules for the proper classification, planning and conducting of observational studies (Guideline Observational Studies - AIFA 2008 http://oss-sper-clin.agenziafarmaco.it/normativa). In addition, the AIFA document sets out specific requirements regarding the submission of study protocols to ethics committees (ECs), a step considered mandatory in certain cases. The most important indications included in the rules are that each observational study *must* be based on a strict protocol, in which the following *must* be specified: the aim and design of the study, the rationale of the research, the class of the study according to the AIFA classification, the sample size, the information expected to be gathered, the resources required, both in terms of health care professionals and of general economic resources, the modality of patient participation, and the level of information provided to patients. In addition, for all studies, the study protocol must be formally presented to the relevant EC, while in the case of prospective cohort studies, it must also be formally evaluated and approved by the EC. It is important to note that these requirements are explicitly referred to, in the AIFA rules, as a *minimum set* of requirements and that single ECs have the faculty to impose, via an internal regulatory system, more strict requirements, for example making it necessary for formal approval to be obtained for any kind of observational study and not only for prospective cohort studies. In actual fact, this is what was already happening in several ECs, where the requirements of the AIFA rules were already incorporated in internal regulations.

Even though the AIFA rules are aimed mainly at studies involving drugs, they are expected to have a great impact on the overall quality of observational studies in Italy. Indeed, producing a complete protocol for any observational study and, within it, a precise statement on the sample size required for the completion of the research is currently neither common practice nor a requirement always observed in the protocols submitted to ECs. In addition, the requirement of formal disclosure of the study to the relevant EC will make it possible to arrive at a precise estimate of the studies actually being conducted in the country. Nevertheless, it has to be pointed out that, some anecdotal reports apart, very little detailed information is available on the quality of past protocols, examined by ECs before the introduction of the AIFA rules.

The aim of this study was to depict, from a methodological point of view, the quality of observational study protocols presented to and discussed by some Italian ECs and to provide a basic framework for evaluating the effectiveness of the AIFA rules, introduced in March 2008 (11). It did not set out to evaluate the appropriateness of the definition of the studies as "observational" and therefore no formal post-hoc assessment was done in this sense.

Material and Methods

A survey was conducted on the ECs of six participating centres: "Azienda per i Servizi Sanitari n. 2 – Isontina" in Gorizia, "Azienda Ospedaliero Unversitaria – Santa Maria della Misericordia" in Udine, Azienda Ospedaliera in Padua, Azienda Ospedaliero-Universitaria "Ospedali Riuniti" in Ancona, Azienda Policlinico Umberto I in Rome, AUSL Latina. The centres differ from one another not only as regards the size and main activities of the hospital hosting the EC, but also as regards the workload of the EC (Table 1). Protocols submitted as observational studies to the EC of each participating centre were reviewed. Protocols were considered consecutively from the start to the end of the study period, which was from 2000 to 2007 overall, but varied in each participating centre for logistical reasons: 2000-2006 in Udine, 2005-2007 in Gorizia, 2005-2007 in Rome, 2006-2007 in Latina, 2004-2007 in Ancona, 2000-2005 in Padua.

Two trained and independent reviewers, not members of any of the ECs of the participating centres, examined the protocols of the studies presented as observational and thus selected for this research. They performed data extraction using a standardized form in MS Access 2003, which can be downloaded from this journal's website. The criteria applied for

Table 1. Main characteristics of the hospitals participating in the study.

EC	Type of hospital	Number of hospitalizations				Number of protocols reviewed by the EC[1]			
		2004	2005	2006	2007	2004	2005	2006	2007
Ancona	A.O.	40786	39307	38725	38701	135	151	145	145
Gorizia	A.T.	–	19745	19606	19336	6	7	5	8
Padua	A.O.	58620	57128	54939	52768	112	234	197	201
Rome	A.O.	75677	76954	71512	63233	200	220	240	250
Latina	A.T.	39752	40748	56278	50772	–	75	80	89
Udine	A.O.	32762	32423	32872	–	54	35	45	–

Abbreviations and symbols: A.T. = *azienda territoriale* (community hospital); A.O. = *azienda ospedaliera* (hospital). - = data not available. In Udine, the hospital's EC was merged in 2007 with that of the University hospital, and thus the data for that year are no longer comparable with those of the current survey. The 2006 data for Rome were revised by the administrative offices after the nomination of an external auditor. The 2006 and 2007 data for Latina include day hospitals.
[1] Both interventional and observational studies are included.

the collection of information, using this form, were kept as generic as possible in order to ensure that most of the information available in the protocol on all its main aspects, namely type of study, rationale, design, sample size and statistical analysis, patient consent form (see Table 2), was retained. Studies were indicated as involving "drug evaluation" only if the involvement of a drug in the study did not simply mean the use of a generic class (like "antibiotics") and only if the evaluation of the drug used was included in the primary endpoints of the study. In addition, it has been specified whenever the different aspects of the protocols fulfilled requirements included in the AIFA rules, thereby making it easier to evaluate the protocols in the light of these new rules. Details of the study acronym and code, title and/or sponsor, as reported in the protocol, were treated as confidential and not recorded in the study database to maintain confidentiality.

The information extracted by the reviewers was then evaluated by them and also by a third reviewer in order to produce a final version of the database suitable for data analysis purposes.

The statistical analysis was kept descriptive and performed using the R System version 2.7.0 (12).

Results

A total of 364 protocols were reviewed and form the database for the present study. The six participating centres contributed the following number of protocols: Padua, 114 (31%); Ancona, 97 (27%); Gorizia, 21 (6%); Rome, 51 (14%); Latina, 10 (3%); and Udine, 71 (19%).

As regards the study types, five protocols were submitted as observational studies to the relevant ECs by the study investigators but were explicitly defined, in the study protocols, as phase II (2), phase III (1) or generically as "experimental" studies (2). Thirty-two protocols (9%) were defined observational but lacked any study protocol or any further information as regards their classification. For the remaining protocols (90%), details on the study type were available, as shown in Table 3. Of the 327 studies remaining after the exclusion of the ones mentioned above, 271 (83%) studies were multicentre and of these 52 (19%) were also multinational.

The main aspects of the study protocols, where known, are detailed in Table 4. A total of 214 studies (65% of the 327 studies considered in this survey) were sponsored (Table 5). Table 6 details the presence/absence of sponsors according to study design, and in the same way stratifies the data on whether or not the studies set out to evaluate a precise drug. Such studies represented (20%) of all the protocols. Twenty-five percent (53/214) of the sponsored studies involved drugs.

Discussion

The overall quality of the study protocols examined in our survey was very similar to that reported in oth-

Table 2. Description of the main elements evaluated in the review of the protocols.

	Description
Study organization	
Principal investigator	Details of the study's principal investigator
Sponsor	Clear indication of the presence/absence of study sponsors and details
CRO	Clear indication of whether the study was conducted by a clinical research organization (CRO) and details
Multicentre	If the study was a multicentre study, clear indication of this
Multinational	If the study was a multinational study, clear indication of this
Introduction and rationale	
Detailed rationale	Presence of a detailed rationale of the study
Bibliography	Presence of a set of references in the study protocol
Objectives	
Objectives	Clear, concise description of the study objectives
Primary endpoints	Precise indication of the primary endpoints of the study
Secondary endpoints	Precise indication of the secondary endpoints of the study
Design	
Design classification	The classification of the study as given in the study protocol
Study details	Details on the study design
Drugs involved	Specification of any drugs involved and adherence to usual regime (no intervention)
Flow chart	The presence of a flow chart in the study protocol to describe forms/examinations administered
Patient selection criteria	
Inclusion criteria	Clear specification of patient inclusion criteria
Exclusion criteria	Clear specification of patient exclusion criteria
Informed consent in inclusion criteria	Whether informed consent was explicitly included in the set of inclusion criteria
Sample size details	
Sample size	Presence of a statement regarding the number of people expected to be enrolled
Formal assessment of sample size	Presence of a formal rationale for the proposed sample size
Statistical analysis	
Data management	Presence of a detailed account of the data management method
Statistical analysis	Presence of a detailed account of the planned statistical analysis method
Informed consent	
Informed consent	Presence of an informed consent form
Privacy	Details of data treatment measures taken to protect privacy
Doctor-to-doctor letter	Presence of a letter for patients' GPs informing them about the conducting of the study
Case report form	
CRF included	Inclusion of a full case report form (CRF) in the protocol
Key aspects	
Protocol	Presence of a protocol

Table 3. Distribution of study types by setting (mono- or multicentre setting). Numbers are column percentages.

Type of study	Mono-centre	Multicentre		Overall
		Italian	Multinational	
	N=56	N=219	N=52	N=327
Prospective cohort	41	55	58	53
Retrospective cohort	5	8	10	8
Case control	20	7	0	8
Registry	0	3	10	3
Ecological	2	1	0	1
Cross-sectional	5	17	8	14
Diagnostic	0	1	0	1
Genetic	6	1	2	2
Pharmaco-economic	2	0	0	1
Observational[1]	20	7	13	10
Overall[2]	17	67	16	100

[1] Generic observational studies not otherwise classifiable.
[2] Row percentages.

er papers evaluating experimental studies (13, 14). The number of studies lacking any kind of protocol in our survey was around one-third that recorded in similar situations (14). Although the main aspects of the protocols were well defined in some studies and in particular in multinational, multicentre studies, the post-hoc comparison revealed a fairly high percentage of protocols that did not comply with the AIFA rules (15), which really only reiterate existing common requirements, already widely agreed upon (16). The setting of the study was specified in only 73% of the protocols, and only in about half of the aetiological (mostly case-control) studies. Study hypotheses, inclusion/exclusion criteria and a detailed rationale of the study were not given in about one fourth/one third of the studies. In particular, although the AIFA rules are quite precise in the case of prospective cohort studies, requiring that all aspects be fully specified, about 30% of such studies failed to furnish all the details needed to meet the AIFA requirements; the EC is thus obliged to reject such protocols or at least to request further information (Table 4). This makes the overall evaluation of the study cumbersome for the EC and it is the main reason for the high rate of requests for additional information (17).

Furthermore, although the sample size planned for the study was indicated in the vast majority of the protocols (83%), it was very rarely (38%) based on a formal assessment or reasoning, even though this aspect is still a major pillar of current research guidelines (18,19,6). Whether this indicates that medical investigators lack adequate training in the working out of sample sizes for observational studies (things are clearer in the case of randomized trials) or rather points to an unavailability of technical biostatistical support is still something to be investigated. This second hypothesis would be in line with the fact, also outlined in this report but still being recognized in the literature, that sponsored trials are generally better quality investigations compared to ones that arise from the investigators' spontaneous initiative. This is a trend mainly seen with prospective (and perhaps costly) studies but also with genetic investigations, a high percentage of which are sponsored studies. This prompts two main considerations: the first, in general, is that spontaneous trials sometimes focus on topics that are less attractive to private industries, on account of their limited marketing potential; nevertheless such studies could have a great impact on the public health system, making the need to provide effective methodological support for them one of paramount strategic importance. Second, the fact that sponsored studies, in spite of their generally higher quality, can be flawed in some regards makes scrupu-

Table 4. Information contained in study protocol by main types of study. Information required by the AIFA rules is highlighted in grey. Numbers are column percentages.

	Type of study										
	Prospective cohort	Retrospective cohort	Case control	Registry	Ecological	Cross-sectional	Diagnostic	Genetic	Pharmaco-economic	Observational[1]	Overall
	N=173	N=25	N=26	N=11	N=3	N=45	N=3	N=6	N=2	N=33	N=327
Study organization											
Principal investigator	83	96	100	91	100	89	100	83	0	97	87
Sponsor	69	60	50	82	0	78	33	83	50	48	65
Clinical research organization (CRO)	18	28	8	36	33	20	0	0	0	15	18
Multicentre	87	88	58	100	67	93	100	50	50	67	83
Multinational	14	20	0	45	0	9	0	17	0	21	15
Introduction and rationale											
Detailed rationale	83	60	73	82	100	78	33	67	100	94	80
Bibliography	82	92	92	82	67	82	33	83	100	94	84
Objectives											
Objectives	95	100	100	100	100	100	100	100	100	100	98
Primary endpoints	40	40	8	36	0	31	0	67	50	18	34
Secondary endpoints	31	32	4	27	0	27	0	0	50	15	26
Design											
Design classification	78	80	54	91	100	47	100	50	100	100	75
Study details	95	100	100	100	100	100	100	100	100	64	94
Drugs involved	24	20	4	36	0	7	33	0	0	36	20
Flow chart	31	12	12	18	0	22	33	40	50	15	24
Patient inclusion criteria											
Inclusion criteria	97	96	85	91	100	89	100	80	100	85	93
Exclusion criteria	80	84	65	64	33	64	100	60	50	48	73
Informed consent as inclusion criterion	68	40	50	73	33	67	100	60	100	52	63
Sample size											
Sample size	87	80	96	73	67	98	100	60	100	79	87
Formal assessment of sample size	45	80	27	36	0	16	67	20	50	15	38
Statistical analysis											
Statistical treatment of data	73	52	58	64	100	80	33	60	100	58	69
Informed consent											
Informed consent	86	76	85	82	33	93	100	100	0	76	84
Privacy	75	68	54	73	33	89	100	80	0	73	74
Doctor-to-doctor letter	25	16	38	9	0	33	33	60	50	9	25
Case Report Form											
CRF included	53	52	38	45	67	53	67	40	0	55	52
Overall[2]	53	8	8	3	0	14	0	2	0	10	100

[1] Generic observational studies not otherwise classifiable.
[2] Row percentages.

Table 5. Information contained in study protocol by presence/absence of a sponsor. Information required by the AIFA rules is highlighted in grey. Numbers are column percentages.

	Sponsor N=214	No sponsor N=113	Overall N=327
Study organization			
Principal investigator	82	92	87
Clinical research organization (CRO)	26	10	18
Multicentre	86	80	83
Multinational	22	8	15
Introduction and rationale			
Detailed rationale	79	81	80
Bibliography	81	87	84
Objectives			
Objectives	98	99	98
Primary endpoints	33	35	34
Secondary endpoints	26	26	26
Design			
Design classification	94	56	75
Study details	91	97	94
Drugs involved	25	15	20
Flow chart	30	18	24
Patient inclusion criteria			
Inclusion criteria	94	92	93
Exclusion criteria	75	71	73
Informed consent as inclusion criterion	70	56	63
Sample size			
Sample size	87	87	87
Formal assessment of sample size	41	35	38
Statistical analysis			
Statistical treatment of data	71	67	69
Informed consent			
Informed consent	86	82	84
Privacy	78	80	74
Doctor-to-doctor letter	26	24	25
Case Report Form			
CRF included	55	49	52
Overall[1]	65	35	100

[1] Row percentages.

lous EC review of these studies an absolute priority, in particular in the case of genetic investigations where the subject matter is highly sensitive.

From the patient's perspective, it is not reassuring that 30% of the study protocols did not include any statement on privacy and 20% did not make provision for patients to give their informed consent to participate in the study, even prospective cohort studies where this aspect is seen as mandatory (20).

If we try to summarize these findings in relation to the AIFA rules, we could say that the rules might be expected to impact on the quality of 30-40% of the

Table 6. Type of studies by presence/absence of a sponsor or of a specific drug involved. Numbers are column percentages.

	Sponsor		Specific Drugs involved		Overall
Type of study	Yes	No	Yes	No	
	N=214	N=113	N=67	N=260	N=327
Prospective cohort	56	48	61	51	53
Retrospective cohort	7	8	9	8	8
Case control	6	12	1	10	8
Registry	4	2	6	3	3
Ecological	0	3	0	1	1
Cross-sectional	16	9	4	16	14
Diagnostic	0	2	1	1	1
Genetic	2	0	0	2	2
Pharmaco-economic	0	1	0	1	1
Observational	7	15	18	4	10
Overall[1]	65	35	21	79	100

[1] Row percentages.

study protocols related to observational research. This may be taken as proof that the AIFA rules represent an answer to an existing need for quality protocols; furthermore, these figures can be also taken as a benchmark for evaluating the effectiveness of the AIFA intervention, once a period of, say, two years has elapsed following the EC's implementation of the new rules.

Study limitations

First of all, the selection of the ECs participating in this study was not based on statistical criteria but only on voluntary decisions, making the extraction of proper inferences impossible. Nevertheless, the sample thus obtained was a fairly balanced mix of ECs from very small (e.g. Gorizia hospital) and from larger centres (like Padua and Rome).

Also, the study did not follow up the submissions of the protocols to the relevant ECs. Indeed, an EC's evaluation process might have made provision for re-examination of the protocol once the investigators had provided additional information, or perhaps have allowed re-submission in a different form (as in the case of experimental studies improperly presented as observational); it might also have ended in formal rejection, should the study protocol have ultimately been deemed scientifically or ethically inadequate. This important information was not collected in the present study, for logistical reasons (in most cases, EC meeting notes were not stored together with the protocols), but also for methodological reasons. Indeed, the decision reached by the EC is determined not only by the quality of the protocol, but also by the specific setting of the EC itself and by the cultural and psychological dynamics among the EC members (21). The inclusion of follow ups of this kind would have resulted in an uncontrolled increase of variability; in the view of the authors, this is an aspect that should be addressed through proper, ad hoc investigations in settings more controlled than this paper's simple survey setting. Other authors, too, have found that interactive dynamics between members can influence the final decision, as can differences in workload, affecting the level of attention of the people involved in the discussion (22).

In addition, the studies evaluated in this survey were all submitted to the ECs in a period that coincided with the development (and partial overlapping) of several regulatory acts. Thus, some of the unsatisfactory behaviours that emerged might be attributable to the fact that this was a post-hoc analysis of studies that were perhaps submitted at a time when certain

requirements were considered less pressing. Nevertheless, it should be noted that the main international guidelines were all available at the beginning of our study window.

Concluding remarks

This survey shows that, 20-40% of observational studies are not up to the required standard with regard to some or all of the methodological aspects considered. These studies constitute the basic framework of action for the AIFA rules. In the view of the authors, these findings may be taken as a benchmark for assessing the effectiveness of the introduction of the AIFA rules in terms of quality of observational research and information for the patient, the latter currently dangerously absent in a significant proportion of the protocols examined.

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