

WHAT DOESN'T WORK WITH PHASE IV STUDIES? A REAL EXPERIENCE FROM AN ETHICS COMMITTEE

F. Grigoletto, A.C. Frigo

1. INTRODUCTION

Phase IV studies are conducted in real-life conditions to expand the knowledge on the efficacy and safety of an approved drug beyond the Phase I through III (ABPI, 1993; Teehan, 1994). Moreover, post-marketing research aims at gathering information on aspects like long-term safety and activity, benefit on specific segments of the population, dose-response relationships and interactions with other drugs, economics of use, quality-of-life, and use patterns. Carried out either in hospital or general practice setting, it may be required by the Licensing Authority being the drug used within the terms of the product license. The entire post-marketing research can be distinguished in Phase IV trials and post-marketing surveillance studies (ABPI, 1993). Phase IV trials are interventional and a comparator can be employed. Post-marketing surveillance studies are non-interventional or observational and are conducted primarily to monitor safety in every day clinical practice. They are designed to detect any rare or long-term adverse effect over a larger patient population and longer time period than was possible during the pre-approval trials. They can include measures of efficacy. In contrast to Phase III trials, which usually have a randomized, controlled, double-blind design, post-marketing research requires different designs to comply with the various research questions.

Beyond the research aims over reported, for a company post-marketing research is an important commercialization tool aiming at familiarizing physicians with the new drug and designed to provide industry management with information that enables to expand the numbers and types of physicians who are using the product, to enter new markets, and to compare the product with the competitors. Post-marketing research could be shaped to meet the commercially-dependent needs, but always it should be rigorous enough to produce good science able to face peer review.

So far, relatively little has been documented about the characteristics of the post-marketing studies conducted in Italy (Venturini, 2001; Gregori, 2008). In particular, limited information is available in Italy about the proportion of observational studies among the post-marketing research, the average size of the Phase IV studies and the importance of the non-sponsored research. In order to inves-

tigate these and other features, we analysed the protocols presented to the Ethics Committee (EC) of a large size University Hospital in the decade 1999-2008.

2. MATERIAL AND METHODS

We prompted a database with the data of all the protocols presented for an evaluation to the Ethics Committee of the University Hospital of Padua (Italy) in the decade 1999-2008. The following variables were selected for our investigation: type of study (experimental, observational) and phase when experimental (I-IV), design (double-blind parallel group versus active drug, single-blind parallel group versus active drug, double-blind parallel group versus placebo, open parallel group versus active drug, open parallel group versus no treatment, cross-over, non-controlled, observational, other), sample size, sponsorship (industry, no-profit), and result of the examination by the Ethics Committee (approved, approved with conditions, returned, rejected). We decided to maintain the type and phase definition presented by the investigator, even if in some cases it was questionable. The category "other" for the design variable included very few studies with objectives related to the natural history of a disease or to the impact of decision making for transplant recipients. The category "no-profit" in the sponsorship variable was related to non sponsored research and studies promoted by public agencies (Istituto Superiore di Sanità, Agenzia Italiana del Farmaco) or private research institutions (scientific associations). The result of the examination by the Ethics Committee considered the first inspection only: the category "approved with conditions" means that the protocol, after minor changes, could be labelled as approved, while "returned" means the need of major changes for a new examination of the Committee. Details related to the study acronym and code, title and/or sponsor and investigator names, as available on the protocol, were treated as confidential and not recorded in the study database to maintain confidentiality.

All the variables were described by one-way or two-way frequency distributions, once the sample size variable, expressed also as median, was categorized. Statistical analysis was maintained at descriptive level.

3. RESULTS

The number of protocols of any type and phase included in the database for the decade 1999-2008 was 1,881 (Table 1). Out of these, the ones presented as Phase IV studies were 188 (10.0%); only two were Phase I studies while 16.2% was Phase II and 42.3% Phase III, summing up to a 68.6% of experimental studies. The 21.0% was defined "observational" research by the presenting investigator and 10.4% of the studies were not includable in the aforesaid categories. It should be noted that the observational studies here considered are to be distinguished from "observational studies" presented to the EC as: Phase IV studies:

the major difference between the two categories is that the objective of Phase IV observational studies refers always to a pharmacological treatment.

TABLE 1
All studies presented to the Ethics Committee by year and Phase (percentages)

Year	Number of protocols	Phase				Observational	Other	Total
		I	II	III	IV			
1999	147	0.7	9.5	61.2	20.4	5.5	2.7	100.0
2000	160	0.6	17.5	55.6	11.3	6.9	8.1	100.0
2001	140	0.0	16.4	49.3	16.4	9.3	8.6	100.0
2002	161	0.0	16.2	52.8	4.3	7.5	19.2	100.0
2003	199	0.0	19.6	40.2	8.0	16.1	16.1	100.0
2004	214	0.0	18.7	35.5	7.9	16.4	21.5	100.0
2005	234	0.0	15.4	35.5	8.1	36.3	4.7	100.0
2006	197	0.0	15.7	38.1	8.6	33.5	4.1	100.0
2007	201	0.0	15.4	34.8	10.5	31.3	8.0	100.0
2008	228	0.0	16.2	34.2	8.8	30.7	10.1	100.0
All yrs	1,881	0.1	16.2	42.3	10.0	21.0	10.4	100.0

During the decade, we observed that while the frequencies of Phase II and Phase IV studies were rather stable around their decade average percentages (Table 1), Phase III studies were regularly decreasing from 61.2% in 1999 to 34.2% in 2008 and, on the contrary, observational studies were increasing from an average percentage equal to 9.5 in the first half of the decade to three times (29.7%) in the second half. About 80% of the full set of studies was research organized on multicenter basis.

Table 2 reports the frequency distribution of the Phase IV studies according to the design. About three fourths of the studies (73.9%) were controlled clinical trials (CT), 48.4% had an active drug as comparator and 16.0% a placebo. Only 8.5% of the Phase IV research was presented as observational. If we relate the sponsorship to the design within the Phase IV studies (Table 3), the percentages of industry and no-profit research were similar for the different designs. Among the 188 Phase IV studies, 143 (76.1%) were sponsored by the industry. This percentage was higher than that related to the entire sponsored research (Table 4) relevant to all the studies of any phase and type (1,267 studies out of 1,881, which is 67.4%). In the framework of industry-sponsored research (Table 4), the percentage of Phase IV studies was 11.3% compared to 53.8% of Phase III studies and 16.5% of Phase II studies.

TABLE 2
Phase IV studies presented to the Ethics Committee by design

Design	Number of studies	%
Double-blind parallel group vs active drug	33	17.5
Single-blind parallel group vs active drug	5	2.7
Double-blind parallel group vs placebo	30	16.0
Open parallel group vs active drug	53	28.2
Open parallel group vs no treatment	4	2.1
Cross-over	14	7.4
Non controlled	30	16.0
Observational	16	8.5
Other	3	1.6
Total	188	100.0

TABLE 3
Phase IV studies by design and sponsorship (percentages)

Design	Sponsorship	
	Industry (n=143)	No-profit † (n=45)
Controlled clinical trials	73.4	75.6
Non-controlled clinical trials	16.8	13.3
Observational	8.4	8.9
Other	1.4	2.2
Total	100.0	100.0

† This category includes non sponsored studies or sponsored by public and private research institutions.

TABLE 4
All studies presented to the Ethics Committee by phase and sponsorship (percentages)

Phase	Sponsorship	
	Industry (n=1,267)	No-profit (n=614)
I	0.2	0.0
II	16.5	15.6
III	53.8	18.4
IV	11.3	7.3
Observational	14.0	35.4
Other	4.2	23.3
Total	100.0	100.0

† This category includes no-profit research and studies sponsored by public and private research institutions.

Table 5 shows the distributions of sample size for Phase II-IV and observational studies: the two lowest size categories reported higher frequencies in Phase IV studies than in Phase III and the opposite for the highest, this inducing median sample size value of 200 and 360 patients respectively. Phase IV studies showed lower sample sizes also than observational studies, where the median was equal to 557 patients.

TABLE 5
*Phase II through IV and observational studies by size and phase (percentages)**

Sample size	Phase			
	II (n=305)	III (n=792)	IV (n=188)	Observational (n=378)
≤ 100	66.6	23.7	37.8	38.4
100 ÷ 300	17.4	25.1	30.3	17.2
300 ÷ 600	12.8	21.3	13.8	10.3
600 ÷ 1,000	1.6	11.2	7.5	10.8
1,000 ÷ 3,000	1.6	12.3	5.8	15.1
> 3,000	0.0	6.4	4.8	8.2
Total	100.0	100.0	100.0	100.0
Median sample size	80	360	200	557

* Two Phase I studies and 196 studies with phase variable classified as "other" are omitted.

Sample size variable showed similar distributions for industry-sponsored and no-profit studies. Within the Phase IV studies, Table 6 shows that observational studies reported highest frequencies in the highest size categories (median sample size = 1,000 patients), and higher than the frequencies of non-controlled CT (where the median sample size was 360 patients) and controlled CT (where the median sample size was 176).

TABLE 6
Phase IV studies by size and design (percentages)

Sample size	Design			
	Controlled CT (n=139)	Non-controlled CT (n=30)	Observational (n=16)	Other† (n=3)
≤ 100	37.8	40.8	25.0	66.7
100 ÷ 300	37.8	7.4	18.7	33.3
300 ÷ 600	14.8	18.5	6.3	0.0
600 ÷ 1,000	5.2	18.5	12.5	0.0
1,000 ÷ 3,000	2.2	11.1	12.5	0.0
> 3,000	2.2	3.7	25.0	0.0
Total	100.0	100.0	100.0	100.0
Median sample size	176	360	1,000	90

† This category includes only 3 studies aiming at investigating the natural history of a disease or subjects genotyping.

The results of the first examination performed by the EC are reported in Table 7: the large majority of the protocols were approved or approved with conditions, this meaning that the compliance of the minor changes requested could be examined by the secretary office with the possible supervision of some member of the Committee.

TABLE 7
Phase IV studies by result of the EC examination and sponsorship (percentages)

Result of the EC examination	Sponsorship	
	Industry (n=143)	No-profit† (n=45)
Approved	52.1	61.4
Approved with conditions	43.0	31.8
Returned	0.7	4.5
Rejected	4.2	2.3
Total	100.0	100.0

† This category includes no-profit research and studies sponsored by public and private research institutions.

4. DISCUSSION

Adequate information on the post-approval clinical research in Italy is not available and very few the papers describe the characteristics of clinical research protocols submitted to Italian local Ethics Committees (Venturini, 2001; Gregori, 2008). To comply with this need, we analyzed 1,881 protocols presented to the Ethics Committee of the University Hospital of Padua in the decade 1999-2008. We explored some features of the post-approval research represented by 188 Phase IV studies. The definition of a clinical study as Phase IV is an easy matter, it depending on the clear fact that the drug under study was approved or not approved for the investigated disease. Trickier can be the distinction between clinical trial and observational study: in the latter case the investigated drug has to be administered independently on the inclusion of the patient in the study. To qualify as observational a study, our Ethics Committee ascertained in all cases that this condition was fulfilled.

The frequency of post-approval research was rather modest in the framework

of the entire clinical research (10.0%). Moreover, the largest percentage of post-approval research was represented by Phase III-like controlled CT (Table 2). The most part of post-marketing research pursued the goal of learning more about not only the safety but also the efficacy of the drug after it has been approved, as the percentages of controlled and non controlled CT raised up to 89.9%. The “real-world” generally reported by the literature, referring to the focus of Phase IV research for the new medicines uses, probably was not so “real” in the setting of the reported experimental studies. The post-marketing surveillance is left to a modest 8.9% of the observational studies. Our results do not support the frequent assertion “*the basic design of most Phase IV studies is naturalistic and observational*” (Teehan, 1994). Interesting to note, 16.0% of the post-approval research was represented by double-blind parallel group studies with placebo as comparator, a design definitely more appropriate for Phase III studies.

Surprisingly, within the Phase IV studies, the distributions of industry-sponsored and no-profit research had quite similar percentages of controlled clinical trials (Table 3). Among the industry-sponsored studies, the frequency ratio between Phase IV and Phase III studies was about 1 to 5, while the same ratio was 1 to 2.5 for the no-profit research (Table 4). As expected, no-profit research was more devoted to observational research or to studies related to diagnostic problems than to experimental studies.

In our opinion the major surprise from the present investigation concerns the size of the populations investigated. Dealing with Phase IV studies, the current literature without exceptions recalls the “large-scale” characteristic of the Phase IV studies, often related to the need of estimating the frequency of rare or very rare adverse events. Examining the distribution of the studies by sample size (Table 5), we realize that the percentages of Phase IV studies corresponding to the lowest size categories were higher than the corresponding categories of the Phase III studies, and the opposite for the highest categories. Actually the median sample size was equal to 200 patients for the Phase IV studies and to 360 patients for the Phase III studies. Controlled and non controlled clinical Phase IV trials were distributed towards lower sample size values than observational Phase IV studies (Table 6), being the relevant sample size median value equal to 176, 360 and 1,000 patients respectively. This sustains the similarity here already cited of the Phase IV CT to the Phase III CT.

As the result of the first examinations of the study projects by the EC is concerned, most of the protocols were approved or approved with conditions, these implying minor changes to the protocols, without striking differences between industry-sponsored and no-profit research (Table 7). The lower percentage of approved protocols for industry-sponsored studies can be due in part to insurance problems, heavier to be satisfied by profit companies.

There is a widespread belief that post-marketing research is tough to perform because of the difficult equilibrium between scientific and commercially-dependent needs. Actually this balance is often hard to preserve in the face of varying regulatory and commercial situations. In our opinion the major difficulty raises when the research is organized in a real-world setting because the scientific

value of the studies can be definitely compromised in many ways but mainly by biased selection of the investigated population. This explains in part why most of the post-approval research is Phase III like. In any case, the Ethics Committees must be on the alert to sponsors who look for recruitment of large numbers of patients without posing valid scientific objectives.

*Department of Environmental Medicine
and Public Health, School of Medicine
University of Padua*

F. GRIGOLETTO
A. C. FRIGO

REFERENCES

- ABPI (Association of the British Pharmaceutical Industry, 1993), *Guidelines for Phase IV Clinical trials*, <http://www.abpi.org.uk/>
- D. GREGORI, P. BERCHIALLA, F. CARLE, A. C. FRIGO, M. S. V. DOTTI, G. CAPPARONI, S. FAVILLI, A. R. VESTRI, M. G. TRONCON, S. BOLOGNINI, F. GRIGOLETTO (2008), *Methodological Aspects of the Observational Studies Discussed in the Ethics Committee: a Multicenter, Cooperative Survey*, "BioMedical Statistics and Clinical Epidemiology", 2(2), 127-135.
- M. TEEHAN (1994) (*prepared by*), *Guidelines for Phase IV Clinical Trials*, "Canadian Journal of Psychiatry", 39, 629-630.
- F. VENTURINI, C. ALBERTI, M. P. ALBERTI, G. SCROCCARO (2001), *Clinical trials in Italy: focus on the protocols submitted to the Ethics Committees*, "Journal of Clinical Pharmacy and Therapeutics", 26(2), 103-110.

SUMMARY

What doesn't work with Phase IV studies? A real experience from an Ethics Committee

Phase IV studies are conducted in real-life conditions to expand the knowledge on the efficacy and safety of an approved drug. Carried out either in hospital or general practice setting, they can be distinguished in Phase IV trials and post-marketing surveillance studies. Limited information is available in Italy about their characteristics as the proportion of observational studies, the average size and the importance of the non-sponsored research. In order to investigate these and other features, we analysed 1,881 protocols presented to the Ethics Committee of a large size University Hospital in the decade 1999-2008. Out of the 188 (10%) Phase IV studies, about three fourths were controlled clinical trials, 48.4% had an active drug and 16.0% a placebo as comparator; only 8.5% was presented as observational. Most of the Phase IV studies could be classifiable as Phase IIIb. The median sample size value was 200 patients, while the Phase III studies reported a median of 360 patients, this contradicting the "large-scale" characteristic of the Phase IV studies reported in the literature.