Clinical Trial In Hospital Practice: Pharmacist's Perspective and Risk Management Reflections

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Abstract
In recent years the number of clinical trials has undergone a significant increase worldwide. In Europe the law n. UE 536/2014 represents an important turning point in the field of clinical trials of medicines. In an Italian national context characterized by profound revolutions and innovations, the hospital pharmacist plays an important role in the management of the protection of the human person, in terms of the rights, safety, dignity and well-being of the subjects enrolled in clinical trials.

Objects of work: Evaluate the clinical trials conducted and the complexity of management from the hospital pharmacist's perspective and analyse the complexity of the trials conducted.

Retrospective study was carried out at Mater Domini University Hospital in Catanzaro (Italy) during 01/01/2017- 31/12/2019. The delivery to the hospital pharmacy was recorded as index data. All clinical trials started in study period were included. In order to estimate the complexity of management, a questionnaire was developed and administrated to all authors involved to clinical trial management. The questionnaires results were calculated as average scores for individual items. The scale comprises 10 close ended, pretested, highly reliable questions. The complexity score of the trial was evaluated with Cronbach's alfa test and Pearson correlation.

In total, 94 clinical trials were started from 2017 to 2019, including 15 Therapeutic Area and 25 different Principal Investigator. In totally the Cronbach's alfa for our complexity scale is 0.807. The Pearson correlation is particularly significant ($p<0.001$) for questions related to management and risk management. In conclusion, this study provided a broad representation regarding the pharmacist's perception on role on the services provided. The pharmacist involved into clinical research study is essential for maintaining the highest standards for medication safety practices and ultimately, the quality, efficacy, and safety.
Keywords: *Clinical Trial, Research Pharmacist, Clinical risk management, Hospital Pharmacist, Cronbach's alfa Pharmacy Management.*

1. Introduction

In recent years the number of clinical trials has undergone a significant increase worldwide [1]. Clinical research is fundamental in determining the state of the art in medicine. Clinical studies are in fact the founding tool of evidence-based medicine, that is of contemporary medicine tout court. Today Clinical trial requires specialized training, not only in pharmacology but also in data management, patient education, statistic sciences. The team involved in clinical research includes physicians, pharmacists, nurses, biomedical engineers; each bring different skills to the research effort.

In Europe the law n. UE 536/2014 represents an important turning point in the field of clinical trials of medicines. In an Italian national context characterized by profound revolutions and innovations, the hospital pharmacist plays an important role in the management of the protection of the human person, in terms of the rights, safety, dignity and well-being of the subjects enrolled in clinical trials.

Clinical research protocols continue to increase in complexity and often require the perspective of specialists in the development process [2].

Objects of work: Evaluate the clinical trials conducted and the complexity of management from the hospital pharmacist's perspective and analyse the complexity of the trials conducted.

2. Methods and procedures

Retrospective study was carried out at Mater Domini University Hospital in Catanzaro (Italy) during 01/01/2017- 31/12/2019. The delivery to the hospital pharmacy was recorded as index data. All clinical trials started in study period were included.

Through a record linkage method, between the paper register in use and the computer database created ad hoc, intensive monitoring of the clinical trials launched and conducted was carried out. Characteristics analysed were Investigator Operating Unit, experimentation area, personnel involved, phase and type of processes, protocol and object of the study (device number, device, and integrator), number of transits or preparations, storage method of the clinical supplies. Data were presented as mean ± standard deviation (SD). The significance of difference in mean values was assessed by Student's test, where p-value<0.05 were considered to be statistically significant.

In order to estimate the complexity of management, a questionnaire was developed (Table 1). The items were related to awareness, motivation and knowledge of the characteristics of drug management. The questionnaire wanted to investigate everything related to the principles of risk management during the pharmaceutical supply process, the quality aspects of the operations of the pharmaceutical supply chain and the principles established by good clinical practices (GDP). The perceptual analysis was also conducted through the items aimed at detecting the perception of the experimental activity carried out by hospital pharmacist involved in the management of clinical trials.

The questionnaire was administered for each clinical study. All authors, independently of each other, responded to the survey. The characteristics of the enrolled pharmacist were comparable with the characteristics of all Italian hospital pharmacist in the study period. The results of the questionnaire were calculated as average scores for individual items.

The scale comprises 10 close ended, pretested, highly reliable questions [3]. The complexity score of the trial was evaluated with Cronbach's alfa test [4] and Pearson correlation.

Cronbach's alpha is the most widely used tool in measuring multiple items in a conceptual study [5]

Mathematically calculated through the formula: $\propto = \frac{k}{k-1}\left(1 - \frac{1}{S_T^2}\sum_{i=1}^{k} S_i^2\right)$

k is the number of items, S2i is the variance of ith item and s2i is the variance of the total score formed by summing all items [5-6]. The internal reliability for the individual subscales of the questionnaire was guaranteed using Cronbach's value coefficient. To improve internal consistency, one question has been omitted. We also determined the correlation between the final score and each item of the scale. All tests were carried out from a bilateral approach, considering p<0.05 as statistically significant.

The statistical analysis was performed using the programme SPSS 19.0 for Windows.

3. Results

In total, 94 clinical trials were started from 2017 to 2019, including 15 Therapeutic Area and 25 different Principal Investigator. Based on our research, over 90% of the supplies in the clinical trial are infusion drugs, the rest of the products are tablets. The characteristics of clinical trial are summarized in table 1. Digestive pathophysiology and Oncology are the main medical speciality of clinical trials in study period. Most clinical trials mainly consist of monoclonal antibodies (65%).

The authors, all females and mean age 46.67±9.61 years, independently of each other, responded to questionnaire (Table 2).The items roughly divided into those on the performance (question 1 through 3), management organization (question 4 through 7), and activity (question 8 through 10). Mean of Items was 4.383, range 0.646, variance 0.039 (Table 3).

In totally the Cronbach's alfa for our complexity scale is 0.807.

The average management-related questions have a range between 4.27 (Item 7) and 4.54 (Item 4) (Table 4). The value of Cronbach's alfa increase (Δ=+0.991%) if item 1 is deleted, while the value decrease when item 7 (Δ=-5.20%) (Table 5). The Pearson correlation is particularly significant ($p<0.001$) for questions related to management and risk management (Table 6).

4. Discussion

The range of Cronbach's alfa normally is between 0 and 1: One if the items are all the same and Zero if none is related to another [7]. George and Mallery had provided the rules of thumb. If alpha value is >0.9=Excellent; >0.8=Good, >0.7=Acceptable, etc. The mean found in our study was 43.83±14.09, with variance deviation of 12.41 and 0.12 respectively. The result of the reliability measure was good. Alpha value of 0.807 shows that all items in our survey were consistent and reliable to assess the attitude and perception of hospital pharmacist [8]. Cronbach's value for the internal reliability obtained for the individual subscales in the questionnaire was 0.573 and 0.758 respectively for performance and management. however, our study also has limitations. First of all the small size of the questionnaires analysed, which could lead to bias in the results, although they have shown validity.

The European Directive 2001/20/EC specifies that every member of a trial team should have the appropriate education, training and experience [9]. The design, coordination and analysis of data in clinical trials require a multi-professional team-work, which includes principal investigator, sub-investigator, clinical research associates, clinical and research pharmacist, data manager, study coordinator, clinical research associate, research nurse [10].

Daily activities, carried out by the hospital pharmacist, include dispensing research drugs, randomization, record keeping and inventory management, studies logistics. The introduction of clinical pharmacist in medical equip can give general positive results helping physician achieve results more rationally.

The pharmacist is able to:

- identify areas of potential safety risks such as inappropriate labelling, storage, or dispensation requirements and can proactively create mechanisms to mitigate risks;
- critically evaluate protocols and documents [11].

The pharmacist can also have a dramatic impact on the risk management of research studies, which can result in improved medication safety for studies subjects [12].

In addition to routine activity (dispensing research drugs, randomization, record keeping, and inventory management, regularly meets with investigators, site coordinators, study monitors, etc) pharmacist play a role in clinical research organization due to knowledge of statistical, pharmacology, toxicology, pharmacovigilance, pharmacoeconomic analysis [13-15].

A pharmacist should be included on the Scientific Review Committee (SRC) to:

- provide expertise in the area of medication use (included the safe and effective use of investigational drugs) [16];
- evaluate a trial's scientific merit and feasibility in the areas of drug supply management, applicability and requirements for an IND application, administration and dosing strategy, applicability of additional regulatory requirements (e.g. Risk Evaluation and Mitigation Strategy programs), medication safety strategies, and research support staff [4];
- review the appropriateness of drug information, accuracy and completeness of the informed consent describing the pharmacological effects and anticipated risks and benefits, and the process for reporting adverse reactions [17];
- ensures that the study drug is stored appropriately in a secure area and separated by protocol, as several active studies may utilize the same drug that is separated from non-investigational drug supply [13,14];

- conduct a proactive risk assessment to identify safety concerns that may result in medication errors should encourage the sponsor to make methodological adjustments in the protocol development and design process to avoid similar safety risks on future studies [14].

The pharmacist play an important role in risk management (identification, assessment, and prioritization of risks) and in the coordinated and economical application of resources to minimize, monitor, and control the occurrence of negative events [18].

5. Conclusion

In conclusion, this study provided a broad representation regarding the pharmacist's perception on role on the services provided. Further studies should be conducted in order to view the global perspective both nationally and internationally. The pharmacist, obviously, thanks to his skills, plays the fundamental role of management of the supply of drugs in the studio (supply, inventory, storage and maintenance of blinding). The pharmacists also ensure that the study drug is stored appropriately [10]. The pharmacist involved into clinical research study is essential for maintaining the highest standards for medication safety practices and ultimately, the quality, efficacy, and safety. The pharmacist has the potential to serve as a consultant during protocol development or review, support the implementation of the protocol at an institution, and provide continuous compliance or audit support. Ultimately, the pharmacist's background and training in the safe and effective use of medications naturally translates into the clinical research environment and allows investigators to more confidently and competently conduct clinical studies [18-20]. In addition, the pharmacist is able to prevent errors [8,21] that pose a threat to patient safety [22].

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Table 1. Clinical Trial Characteristics.

Phase		N(98)	% (100%)
	I	1	1.02
	II	20	20.41
	III	69	70.41
	IV	8	8.16
Blinding			
	Open label	20	20.41
	Single-Blind	46	46.94
	Double Blind	32	32.65
Medical speciality			
	Digestive pathophysiology	22	23.40
	Oncology	20	21.28
	Cardiology	10	10.64
	Internal Medicine	8	8.51
	Urology	8	8.51
	Metabolic Disease	6	6.38
	Pneumology	4	4.26
	Rheumatlogy	4	4.26
	Others	11	11.70

ATC CODE of the drug involved in the clinical trial			
	L	28	28,57
	O	26	26,53
	N	11	11,22
	C	10	10,20
	G	8	8,16
	A	6	6,12
	U	4	4,08
	R	3	3,06
	S	2	2,04
	N/A	12	12,24

N/A: Not Available.

Table 2. Questionnaire.

Category	N	Question
Performance	1	The research protocol is clearly and well-structured
	2	Medical specialty involved in the study represents an expanding therapeutic area
	3	The object of clinical trial is an innovative drug
Management Organization	4	Storage conditions of clinical supplies require special attention
	5	Clinical supplies are delivered frequently
	6	Preparation and administration of the dose are managed univocally and sequentially
	7	Need for special conditioning material (in-line filter, light resistant bags, etc.)
Activity	8	Clinical trial management is demanding
	9	Multidisciplinary team is involved in the study
	10	The training carried out by institutional channels (Sponsor, CRA,) has provided adequate training to team members

Table 3. Statistical analysis summary

	Mean	Min	Max	Range	Max/min	Variance	N. of Items
Mean of Items	4.383	3.918	4.565	0.646	1.165	0.039	10
Variance of Items	0.343	0.102	0.564	0.462	5.540	0.019	10
Covariace between Items	0.101	-0.023	0.434	0.457	-18.738	0.006	10

Table 4. Value of Items.

	Mean	standard deviation	Variance
Item 1	4.5646	0.31896	0.10069
Item 2	4.3878	0.58951	0.34397
Item 3	4.5136	0.64424	0.41081
Item 4	4.5408	0.68450	0.46375
Item 5	4.4898	0.44440	0.19547
Item 6	4.3741	0.61718	0.37702
Item 7	4.2755	0.75075	0.55788
Item 8	4.2449	0.53417	0.28243
Item 9	4.5170	0.48605	0.23384
Item 10	3.9184	0.65638	0.42644

Table 5. Statistically analysis if item is eliminated.

		Item	Mean of the scale if the element is eliminated	Variance of the scale if the element is eliminated	Crohnbach's alpha if the element is eliminated
Performance	1	The research protocol is clearly and well-structured	4.362	0.039	0.815
	2	Medical specialty involved in the study represents an expanding therapeutic area	4.382	0.044	0.779
	3	The object of clinical trial is an innovative drug	4.368	0.041	0.786
Management Organization	4	Storage conditions of clinical supplies require special attention	4.365	0.040	0.765
	5	Clinical supplies are delivered frequently	4.371	0.042	0.794
	6	Preparation and administration of the dose are managed univocally and sequentially	4.384	0.044	0.790
	7	Need for special conditioning material (in-line filter, light resistant bags, etc.)	4.395	0.042	0.767
Activity	8	Clinical trial management is demanding	4.398	0.041	0.797
	9	Multidisciplinary team is involved in the study	4.368	0.041	0.806
	10	The training carried out by institutional channels (Sponsor, CRA,) has provided adequate training to team members	4.434	0.014	0.795

Table 6. Pearson correlation analysis

		Item1	Item2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item10
Item 1	Pearson Correlation	1	.298**	.046	.025	.187	.144	-.097	.054	.004	.381**
	Sig. (2-tailed)		.003	.654	.811	.066	.158	.344	.597	.969	.000
	N	98	98	98	98	98	98	98	98	98	98
Item 2	Pearson Correlation	.298**	1	.532**	.327**	.326**	.441**	.382**	.175	.277**	.379**
	Sig. (2-tailed)	.003		.000	.001	.001	.000	.000	.084	.006	.000

	N	98	98	98	98	98	98	98	98	98	98
Item 3	Pearson Correlation	.046	.532**	1	.397**	.237*	.336**	.349**	.107	.233*	.452**
	Sig. (2-tailed)	.654	.000		.000	.019	.001	.000	.296	.021	.000
	N	98	98	98	98	98	98	98	98	98	98
Item 4	Pearson Correlation	.025	.327**	.397**	1	.355**	.321**	.844**	,480**	.401**	.255*
	Sig. (2-tailed)	.811	.001	.000		.000	.001	.000	.000	.000	.011
	N	98	98	98	98	98	98	98	98	98	98
Item 5	Pearson Correlation	.187	.326**	.237*	.355**	1	.273**	.422**	.281**	.274**	.182
	Sig. (2-tailed)	.066	.001	.019	.000		.007	.000	.005	.006	.073
	N	98	98	98	98	98	98	98	98	98	98
Item 6	Pearson Correlation	.144	.441**	.336**	.321**	.273**	1	.361**	.213*	.200*	.345**
	Sig. (2-tailed)	.158	.000	.001	.001	.007		.000	.036	.048	.001
	N	98	98	98	98	98	98	98	98	98	98
Item 7	Pearson Correlation	-.097	.382**	.349**	.844**	.422**	.361**	1	.504**	.346**	.209*
	Sig. (2-tailed)	.344	.000	.000	.000	.000	.000		.000	.000	.039
	N	98	98	98	98	98	98	98	98	98	98
Item 8	Pearson Correlation	.054	.175	.107	.480**	.281**	.213*	.504**	1	.015	.355**
	Sig. (2-tailed)	.597	.084	.296	.000	.005	.036	.000		.886	.000
	N	98	98	98	98	98	98	98	98	98	98
Item 9	Pearson Correlation	.004	.277**	.233*	.401**	.274**	.200*	.346**	.015	1	-.014
	Sig. (2-tailed)	.969	.006	.021	.000	.006	.048	.000	.886		.895
	N	98	98	98	98	98	98	98	98	98	98
Item 10	Pearson Correlation	.381**	.379**	.452**	.255*	.182	.345**	.209*	.355**	-.014	1
	Sig. (2-tailed)	.000	.000	.000	.011	.073	.001	.039	.000	.895	
	N	98	98	98	98	98	98	98	98	98	98

**. The correlation is significant at the 0.01 level (2-tailed).

*. The correlation is significant at the 0.05 level (2-tailed).

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