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Research Article

PREDICTING OF ENROLLMENT AS A PART OF RISK-BASED MANAGEMENT OF CLINICAL TRIALS

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Abstract

Risk-based management (RBM) for clinical trials is tool which has been developed to address the many threats to clinical trials. The mostly actions in any RBM plan is applying to efficacy of IMP and safety and well-being of patients when enrollment start being based on the convince that feasibility done on high quality level and selected sites will give enough enrollment. The failure in recruitment is also the risk wich must be avoided and addressed in case of appearing. Absence of recruitment in clinical trials reached 80% which lead to failures of clinical trials and this cause the many other influence to the patients. It means that RBM must be applied already on the feasibility phase in order to avoid the bad enrollment. We developed the tool for objective decision whether the site would enroll the patients and this could be included to the risk-based management plan of any clinical trials..

Materials and methods: It has been analyzed an enrollment rates and related parameters of three clinical trials II-III phases in oncology and one clinical triali in hematology, conducted since 2007 to 2017 years.

Study objectives: to investigate the study recruitment rate of sites using different parameters and to make the prediction of rate on padticualr site and compare it with rhe risks listed in regulatory documents ruling the risk evaluation for the next action and corrective plan.

Statistical analysis: data had been collected from feasibility questionnaires, open statistical sources and the descritpive, correlative statistics has been applied.

Results: It was determined prediction of recruitment on particular site and possible risks which could be raised with retaled to this prediction.

Discussion: Recruitment of patients is crucial factor for success of clinical trials and many of trial is failed to reach the target recruitment. The possible reasons is laying on feasibility and following selection of sites. The risk to include the non-recruiting sites is very high and could be evaluated as a major or sometime as critical therefore the prediction of site recruitment must in RBM plan.

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INTRODUCTION

An obligatory stage before starting a clinical trial is to conduct a study of the capabilities of clinical centers to implement the protocol - feasibility (Kibby M., 2011). The same author talks about the flexibility of the concept of feasibility from sponsor to sponsor.

Poorly conducted feasibility study is a barrier to patient recruitment (Parke J, 2022) and undergones the study to risk to be failure. Risks which might be raised during the clinical trial is accepted by clinical trials stakeholders and graduated accordingly (Risk classification guide, 2022). The number of failed studies due to insufficient enrollment of patients reaches 80% (Fletcher B at al., 2012) and the poore feaibility is one of the reasons for this failures (Parke J, 2022). As enrolment must be calcualted before the stafrt of recruitment (ICH GCP E6(R1) Step 4 version dated 9 November 2016) therefore there is a simple calcualtion (Bachenheimer J. At al., 2007). It is still actual to develop the mathmatical approach to predict the enrollment right after the feasibility in order to evaulate the risks for clincal trial .

METHODS AND MATERIALS

The material of the study was the pro- and retrospective results of observation for 4 clinical studies:

1. Head and neck cancer - III phase - (EudraCT - 2010-019952-35)
2. Lung cancer - (EudraCT - 2011-001084-42)
3. Colorectal cancer - (EudraCT - 2006-004214-41)
4. Idiopathic purpura. - (EudraCT - 2009-014842-28).

All observed clinical trials were completed successfully in patient recruitment.

Patient recruitment results and recruitment-related data were obtained from clinical centers in Russia, Ukraine, and Belarus (RUB), and the main recruitment results for all clinical centers.

We also took our classification of sites (Types) based on recruitment and speed of final recruitment

- Type 1. Silence sites – rate of recruitment - 0 patients per month;
- Type 2. Low-recruiting - rate of recruitment by 0,01 to 0,19 patients per months;
- Type 3. Middle-recruiting - by 0,20 to 0,89 per months;

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- Type 4. High-recruiting - by 0,90 to 3 patients per months.

Parameters we took to investigate the undergone of recruitment is following:

1. Type of site (based on final recruitment)
2. Time from first contact of site to first reply
3. Duration of recruitment in days
4. Speed of recruitment
5. Target recruitment (proposed or planned by investigator in the beginning of the study)
6. Target speed of recruitment
7. Percentage of performance of target recruitment
8. Expirience of investigator

RATIO of parameters like

9. Target recruitment to study population (maximum figure of patients to be recruited by the protocol)
10. Time of first reply to target recruitment
11. 1 to time of reply
12. 1 to target recruitment
13. Ratio of 1 to time of reply to ratio 1 to target recruitment

STATISTICAL ANALYSIS

Following done:

- Calcuation of mean and error, moda and mediana for choosen parameteres (more than 1960),
- Dispersion analysis
- Pirson and Sperman correlation
- Calculation of Student t-criterium

RESULTS:

We investigated the sites which proposed the recruitment and afteward after completion the enrollment did not enroll the patients (Table 1).

Table 1: *Distribution of site types before and after CT*

No	Types	Before the start of enrollment	After completion of ernollment
1	2	3	4
	Type 1	0	26 (37%)
	Type 2	0	5 (7%)
	Type 3	36 (51%)	22 (31%)
	Type 4	34 (49%)	16 (23%)

Table 2: *Enrollment before start and after completion.*

No	Recruitment of patients planned expected and not recruited (A)	Recruitment of patients planned and recruited (Б)	Number of recruited estimated and above estimated (C)
	249 (26 sites)	480(44sites)	622 (44 sites)
TOTAL A+B	729		
Percent complete			85%

Thus, it can be seen that more than 44% of sites do not recruit patients as expected at the beginning of the study. The authors (Brooks S. Et al., 2015) provids data up to 80% of sites after the start of the study do not recruit patients. And again we investigated only successful study on recruitment of the patients at the end.

Then we took the total number of patients which were propsed to be recruited before the start of enrollment and after completion of enrollment (Table 2).

It can be seen that it was supposed to recruit 107 (15%) more patients initially

Then we analyzed the sites which were activated and did not enroll the patients (Table 3) and whole time spent of recruitment (Table 4) speed of recruitment (Table 5, 6),

Table 3: *Number of centers activated but not recruiting patients*

	Nozology	Number of centers selected for the study	Number of activated centers that did not recruit patients
1	2	3	5
1	Head and neck cancer	9	3 (33%)
3	Lungs' cancer	27	3 (11%)
2	colorectal cancer	19	2 (11%)
4	Idiopathic purpura	15	3 (20%)
TOTAL		**70**	**11 (16%)**

It can be seen that the target time to recruit patients increased up to 4.5 times. The countries of Russia, Ukraine and Belarus accounted for up to 57% of recruited patients.

Estimated recruitment speed is shown below (Table 6).

So it is clerly seeing that the rate of recruitment of patients in international multicenter clinical trials revealed a significant difference (by 100%) between the target rate of recruitment and the actual one, which was multidirectional.

SHORT DISCUSSION.

Feasibility study is a prediction of future research (Lievre M. At al., 2001) and one of the main objectives of the feasibility study is to show that the study clinical centers (sites) have a pool of patients required by the protocol (Lievre M. At al., 2001). The recruitment of patients and the success of the entire study depend on the quality of the feasibility (Parke J, 2022), and to date, the number of successful studies is much less than unsuccessful ones (Kelsey M., 2011). Currently, up to 80% of clinical trials of all phases fail (Hwang T.J at al., 2016, Crowther M., 2013).

Our study shows that only 56% sites is recruiting the patients out of all selected sites in the study which were succesfull in recruitment at the end and 37% of sites do not recruiting any patients since they showed that they has the patients on the feasibility stage. The determination of the rate of recruitment of patients by clinical centers is also fixed by

Table 4: *Time spent on recruitment.*

	Nosology	Number of cities	Quantity centers	Actual recruited patients world-wide	Final recruitment time, months %) and increase compared to the target	Final patient enrollment (%) in Russia, Ukraine and Belarus
1	2	3	4	6	5	6
1	Head and neck cancer	8	9	982	26 (108%)	258 (33%)
2	Lungs' cancer	23	27	385	26 (216%)	109 (22%)
3	colorectal cancer	13	19	483	26 (216%)	216 (48%)
4	Idiopathic purpura	15	15	69	39 (300%)	39 (57%)
TOTAL		**59**	**70**	**1919**	**117 (205%)**	**622 (32%)**

Table 5: *Ratio of patient recruitment rates*

	Nosology	Estimated (targeted) patient recruitment rate	Actual patient recruitment rate, months	Actual patient recruitment rate, months, in % of the target
1	2	3	4	5
1	Head and neck cancer	**0,65**	1,1	200%
2	Lungs' cancer	**1,3**	0,15	12
3	colorectal cancer	**0,5**	0,43	86
4	Idiopathic purpura	**0,35**	0,06	20

Table 6: *Estimated recruitment speed*

	Nosology	Estimated (targeted) patient recruitment rate	Estimated rate of recruitment of patients, months (% of the target)
1	2	6	3
1	Head and neck cancer	**0,65**	0,2 (31%)
2	Lungs' cancer	**1,3**	1,06 (81%)
3	colorectal cancer	**0,5**	1,05 (210%)
4	Idiopathic purpura	**0,35**	0,7 (200%)

international rules (clause 5.18.4 of ICH GCP E6(R1) Step 4 version dated 9 November 2016) and should be determined at the beginning of the study. However, there is no generally accepted classification of centers according to recruitment speed. We proposed the fours types of the sites based on speed of recruitment which could be used in future to evaluate the sites. Recruitment of patients in clinical trials according to protocol requirements is an important component of the successful clinical trial of any phase and if the recruitment of patients does not occur on time, then this entails an increase in clinical centers, an increase in efforts to recruit patients and an increase in the period of recruitment of patients (Probstfield JL 1987, Petrovitch H et al., 1991). Our analysis revealed that increasing of the recruitment time raised up to 4 times compare to the target time and spees of rectuitment appeared slow down more than 100%. It means that neither of three parameters of recruitment – time, speed and number did not comply with the protocol requirement. Risk based management rules (Risk classification guide, 2022) is evaluating the non-compliance in recrutment as a minor or major risk for the study. In order to predict the enrollment on particular site and to decrease of the risks of non-compliance there is a simple calculation (Bachenheimer J., 2007, Woodin K. at al., 2003) and we proposed to use the mathematical formula by Dr. S. Milovanov (2021).

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