Research Article

Rate of patient's Recruitment and Recruitment Derivatives from the Perspectives of Internal factors - Protocol Study Nosology, Experience of Investigators and Potential Patient's Pool of Sites

Svyatoslav Milovanov*

Study Physician, Russia, Moscow

Annotation

The recruitment as a process found by many authors to be undergoing of many factors. There is a factors which are decreasing the recruitment and last data is reporting up to 80% trials failed due to law or even absence of recruitment on level of sites. But the factors are differently changing the recruitment. The final number of recruitment is static figure very well known, there is also known speed of recruitment which is calculating in the start of the study and these parameters along with others is quantitative evaluation of recruitment. We investigated the rate of recruitment in the light of some factors using parameters reflecting the recruitment progress of recruitment.

Materials and Methods: Retrospective analysis of data of four clinical trials II-III phases in oncology and hematology, conducted since 2007 to 2017 years. Study objectives: to investigate the study recruitment rate using different parameters and its changes along with acting of internal factors; to develop new parameters which could be sensitive for evaluation of factor's action. Statistical analysis: data had been collected from feasibility questionnaires, open statistical sources.

Results: It was determined rate of recruitment and its derivatives where was acting an internal factor.

Discussion: Recruitment been undergone the internal factors. The way of action is multidirectional and could boost the recruitment and in opposite to decrease one and knowing it is important in success of recruitment and clinical trial itself eventually.

Introduction

Factors influencing to recruitment is diverse and difficult to estimate due to highly variable [1] found more than 30 factors influencing to recruitment and much of them can ruin the trials due to fail of recruitment. The possibility to predict the recruitment based on the acting of factors is said by M. Rutger and they also found more than 30 factors acting differently to recruitment. These authors used the feasibility questionnaire to collect the data. As a rule the classification of the factors is difficulty and each author just lists the factor. To estimate the way of factors action's authors suing figures of recruitment at least at the beginning of the study M. Kabby and at the end of the study. The ratio of parameters to evaluate the internal factors from the gender and social perspectives is very rare in recruitment rate and much known is so called enrollment fraction [2-6] est the number of enrollees divided by the number of potential subjects to determine age, sex and race of patients involved to studies.

Methods and Materials

We investigated data observed by 70 clinical centers participating in phase 2-3 trials in oncology and hematology in three countries - Russia, Ukraine and Belorussia for the period from July 01, 2008 to December 31, 2017 in order to determine the factors which is influencing to recruitment, to determine the parameters and values changing under influence of this factor. The Collection of data was done out from questionnaires at the stage of searching for centers, from the results obtained at the end of the research, from open statistical sources.

We also took our classification of sites based on recruitment and speed of recruitment

- a. Silence sites-rate of recruitment - 0 patients per month;
- b. Low-recruiting - rate of recruitment by 0, 01 to 0, 19 patients per months;
- c. Middle-recruiting - by 0, 20 to 0, 89 per months;
- d. High-recruiting - by 0, 90 to 3 patients per months.

The amount of involved cities, involved sites and protocol required patients are presented in (Table 1).

Table 1: Etymology of studies, amount of cities where centers opened, amount of centers opened, number of patients to be involved according to protocol. We divided the factors associated to recruitment according to attitude to participant's human being (investigators and patients) and have got external and internal factors presented in (Table 2) & (Table 3).

S.No	Nosology	The number of cities in which centers were opened	Number of clinical centers	Study power - required number of patients (N)
1	2	3	4	5
1	Lung cancer	25	27	450
2	Colorectal cancer	19	19	340
3	Idiopathic purpura	15	15	69
4	Head and neck cancer	9	9	982
Total		68	70	1841

Table 2: Internal factors.

S.No	Internal factors
1	2
1	Disease (of protocol)
2	Experience of investigators
3	Planned (proposed) patients in stage of feasibility

Table 3: External factors.

S.No	External factors
1	2
1	Country
2	City (infrastructure)
3	Population
4	Living area
5	Density of living area (one factor as for 4)
6	Income
7	Morbidity (new cases per year)

Table 4: Parameters of protocol Nosology.

S.no	Parameter P- value	Lung cancer	Colorectal cancer	Idiopathic purpura	Head and neck cancer
1	Type of site P4/3<0,01; 4/1<0,01 3/2<0,01	1,7+-0,1	2,58 +-0,1	1,73+-0,08	2,6+-0,17
2	Time from first contact till reply, days P 4/3<0,01; 4/2<0,01	20,37+-2,14	31,16+-3,41	28,47+-2,32	13,56+-1,13
3	Speed of recruitment P 4/3<0,01; 4/1<0,01 2/3<0.01 4/2<0,01;	0,16+-0,04	0,44+-0,06	0,07+-0,016	1,1+-0,14
4	protocol planned recruitment rate per month No differences	0,27+-0,2^{-17}	0,5	0,31+-0,67^{-18}	0,3
5	Recruitment amount final per site P 3/4<0,01; 1/4<0,01 2/3<0.01 2/4<0,01;	4,04+-1,1	11,4+-1,49	2,6+-0,36	28,67+-3,7
6	Patients to be planned per site P 1/3<0,01; 4/1<0,01 2/3<0.01 4/2<0,01;	12,74+-0,52	12,68+-0,35	6,5+-0,4	6,56+-0,37
7	Percentage of performance P 4/3<0,01; 4/1<0,01 2/3<0.01 4/2<0,01;	37,23+-10,44	96,27+-13,56	33,39+-4,26	503,33+-75,97
8	Experiences of PI in clinical trial in years	6,07+-0,06	5,7+-0,4	4,6+-0,25	6,2+-0,05
9	RATIO-Planned/maximum pats per protocol P 1/2<0,001; 1/3<0,001 1/4<0.001 2/3<0,001; 2/4<0.001	3,74+-0,15	2,82+-0,08	9,47+-0,58	0,67+-0,04
10	RATIO - time of first reply/planned patients P 1/2<0,001; 1/3<0,001 1/4<0.01 2/3<0,001; 2/4<0.01	1,68+-0,16	2,66+-0,29	6,24+-0,78	2,17+-0,2
11	1/time to reply	0,096+-0,0116	0,068+-0,006	0,055+-0,004	0,368+-0,056
12	1/planned patients	0,089+-0,004	0,085+-0,003	0,206+-0,016	0,17+-0,006

	ratio 1 ((1/time to reply)/(1/planned patients))				
	P 1/2<0,011;	1,18+-0,13	0,895+-0,09	0,36+-0,04	1,91+-0,27
	1/3<0,011				
	1/4<0.01				
	2/3<0,01;				
13	2/4<0.01				

We see that out of 13 parameters and ratio 9 has a statistical differences id est 70%.

- Analysis of the table revealed that in protocol with head and neck and colorectal cancer patient's statistically much higher sites with high speed of recruitment.
- The time of first reply by sites is very short in H&N sites compared with ITP and CRC sites. Most short period of feedback by sites from the first contact is in H&N cancer sites.
- Speed of recruitment is very high in H&N sites, then in CRC sites and most low in ITP sites.
- There are no any differences in planned speed of recruitment because all protocol planned the study with the same speed of recruitment.
- Final recruitment also has a statistical differences depends on protocol Nosology.
- Most interestingly that the ratio of planned recruitment to maximum patients per protocol has a very high statistical differences.
- Ratio the time of first reply to planned patients also has statistical differences.
- Thus clearly seeing that influence of protocol nosology to recruitment is obvious and has a different influence. Somewhere it push the speed, somewhere it slow the recruitment.

Second and third internal parameter is experience of investigators and planned recruitment by the investigator on the stage of feasibility [7-10].

According to the researcher's experience, the site was divided into three categories

- With work experience up to 4 years - beginners
- With work experience from 4.1 to 6.9 years - experienced
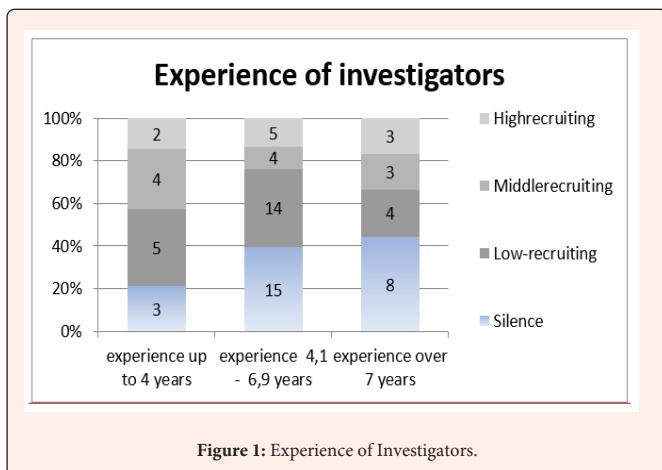- With more than 7 years of work experience - with extensive work experience

Figure 1: Experience of Investigators.

The analysis reveals a picture of double the percentage of silent sites (43%) in centers with more than 7 years of Principal Investigator experience. This fact can be interpreted as a high activity in the search of patients by beginners who are earning a reputation for themselves, but this percentage of activity goes into low recruiting. The number of highly recruited sites is approximately the same in all groups [12-15]. Statistical parameters of expirience of investigators presented in (Table 5).

Table 5: Parameters in depends of experience of Investigator.

S.no	Parameter, P-values	Experience of investigators, years X±m		
		experience up to 4 years	experience 4,1 - 6,9 years	experience over 7 years
1.	Type of site	2,36+-0,26	1,97+-0,16	2,06+-0,27
2.	Time from first contact till reply, days P 1/2<0,01; 2/3<0,01;	28,71+-4,61	18,11+-2,23	33,39+-7,58
3.	Recruitment period days	884+-48,96	795,61+-22,69	768,44+-27,19
4.	Speed of recruitment	0,32+-0,11	0,29+-0,1	0,44+-0,18
5.	protocol planned recruitment rate per month P 1/2<0,01; 2/3<0,01;	0,42+-0,03	0,28+-0,01	0,4+-0,03
6.	Recruitment amount final per site	8,79+-2,93	7,68+-2,48	11,5+-4,8
7.	Patients to be planned per site	10,07+-1,25	11,08+-0,79	10+-0,96
8.	Percentage of performance	87,08+-30,46	90,12+-40,13	178,98+-94,01
9.	Experiences of PI in clinical trial in years	2,5+-0,43	5,87+-0,05	7,78+-0,34
10	Time (in days) after activation till first screened patient P 1/2<0,01;	132,14+-31,3	54,39+-13,41	79,22+-29,64
11	RATIO-Planned/maximum pats per protocol P 2/3<0,01;	5,48+-1,05	4,65+-0,67	2,73+-0,29
12	RATIO - time of first reply/ planned patients	4,65+-1,55	1,95+-0,27	3,89+-1,07
13.	1/time to reply	0,06+-0,01	0,11+-0,03	0,17+-0,07
14.	1/planned patients	0,14+-0,03	0,11+-0,01	0,14+-0,02
15.	ratio 1 ((1/time to reply)/(1/planned patients))	0,67+-0,2	1,1+-0,19	1,13+-0,36

We see that out of 15 parameters and ratio 4 has a statistical differences id est 27%.

Analysis of the table 5 revealed that experience of investigator has a few parameters with statistical differences in values of these parameters.

- The time of first reply is statistically longer in group with less than 4 years experience.
- Speed of recruitment has no statistical differences.
- There is statistical differences in planned speed of recruitment – little - experienced and high-experienced planned higher rate compared to middle-experienced.
- Final recruitment did not have the statistical differences.
- Time after activation of site till first screening is statistically substantially longer in small-experienced group compared to other two groups.
- Ratio the time of first reply to planned patients also has no a statistical differences.
- Ratio planned proposed recruitment to number of patients per protocol has a

statistical differences smaller in high experienced group.

Thus clearly seeing that there is an influence of experience investigator recruitment.

Third Internal Factor Is Proposed Recruitment or Target Recruitment.

For the purpose of unification and to compare the results we divided the sites depends on proposed recruitment based on speed of recruitment –

Silence sites – rate of recruitment - 0 patients per month;

Low-recruiting - rate of recruitment by 0, 01 to 0, 19 patients per months;

Middle-recruiting - by 0, 20 to 0, 89 per months;

- ➢ High-recruiting - by 0, 90 to 3 patients per months.
- ➢ We've got that in target recruitment there is only two groups –
- ➢ Middle-recruiting - by 0,20 to 0.89 per months;
- ➢ High-recruiting - by 0,90 to 3 patients per months.

And this is clear because sites have to show their capability to recruit patients and if sites could not do the recruitment so such sites do not involve to the study and not filling-out the feasibility questionnaire Statistical values presented in (Table 6).

Table.6

S.no	Parameter, p-value	Parameters values depends on target recruitment X±m	
		1- 0,20 до 0,89 middle patient recruitment potential per month	2 - 0,90 and more high patient recruitment potential
1.	Type of site	2,29+-0,23	1,96+-0,14
2.	Time from first contact till reply, days	21,63+-3,9	25,48+-3,33
3.	Recruitment period days	803,83+-30,21	807,59+-21,9
4.	Speed of recruitment	0,49+-0,16	0,25+-0,07
5.	protocol planned recruitment rate per month	0,35+-0,02	0,33+-0,01
6.	Recruitment amount final per site	12,92+-4,04	6,78+-1,95
7.	planned duration of recruitment initially, months	13,88+-1,09	12,91+-0,65
8.	Targetproposed recruitment rate P 1/2<0,01	0,69+-0,04	1,42+-0,09
9.	Patients to be planned per site P 1/2<0,01	9,29+-0,83	19,87+-2,41
10.	Percentage of performance P 1/2<0,01	114,34+-32,17	37,06+-8,72
11.	Experiences of PI in clinical trial in years	5,96+-0,4	5,54+-0,31
12.	Time (in days) after activation till first screened patient	109,58+-27,41	58,98+-12,16
13.	Amount of sites in one city P 1/2<0,01	1,13+-0,12	1,57+-0,14
14.	SQUARE REGION, km2 P 1/2<0,05	512,46+-131,09	885,16+-115,42
15.	RATIO-target (planned) recruitment/ maximum pats per protocol P 1/2<0,01	3,58+-0,66	6,5+-0,56
16.	RATIO - time of first reply/planned patients	2,88+-0,56	1,91+-0,3
17.	1/time to reply	0,15+-0,05	0,1+-0,02
18.	1/planned patients P 1/2<0,01	0,14+-0,02	0,07+-0
19.	ratio 1 ((1/time to reply)/(1/planned patients))	1,9+-0,9	2,22+-0,85

We see that out of 19 parameters and ratio 7 has a statistical differences id est 37%.

Analysis of table revealed that there is no statistical difference in time of first feedback and duration of recruitment period.

It showed clear relation that due to perform the planned recruitment is not a motivation or statistically not significant.

There are no any differences in planned speed of recruitment.

- ➢ Final recruitment also has no a statistical differences but means two times more in middle-recruiting potential sites.
- ➢ Percentage of performance is statistically higher in middle recruiting sites (three times more than to group of high potential recruiting which clearly show that target recruitment is high motivational factor for middle-recruiting sites.
- ➢ Most interestingly that the ratio of planned recruitment to maximum patients per protocol has a very high statistical differences and two timeless in the middle recruiting sites.
- ➢ Experience of investigator the same for two groups.
- ➢ Ratio the time of first reply to planned patients also has no statistical differences.

Thus target recruitment has an influence to final recruitment and the less figure planned the more patients will be recruited.

Cumulative figure of investigated of three parameters presented below in (Figures 2, 3, 4 & 5).
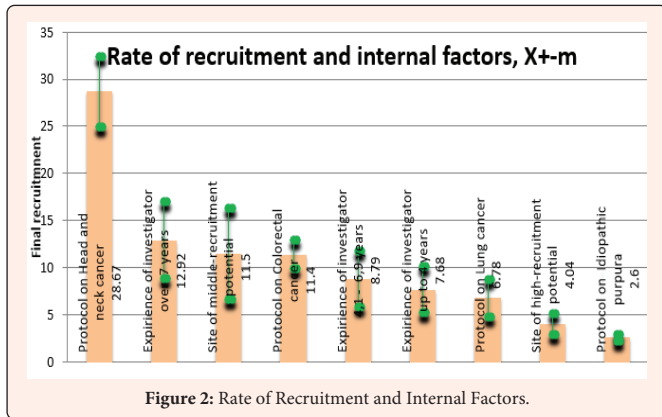
Citation: M Svyatoslav (2021) Rate of patient's Recruitment and Recruitment Derivatives from the Perspectives of Internal factors - Protocol Study Nosology, Experience of Investigators and Potential Patient's Pool of Sites. Corpus J Clin Trials 2: 1007

Page 4/6

Figure 2: Rate of Recruitment and Internal Factors.

Clearly is seeing that in study where was acting the factor of head and neck cancer has a high rate of recruitment and in opposite the idiopathic purpura has minimum rate.
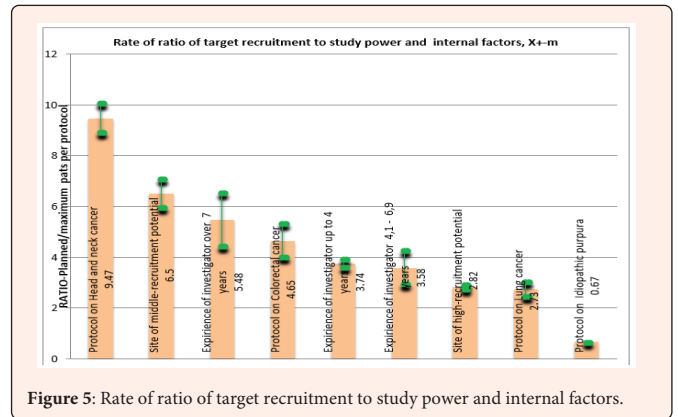

Figure 3: Time of First Feedback and Internal Factors.

Figure is show that time of feedback as an activity of site is fast in trials where acting the head and neck cancer and slow with factor of experienced investigator. Also fast feedback observed by site with trials of lung cancer and by investigator with middle experienced investigator.

Figure 4: Performance of target recruitment and internal factors (please refer to table above).

(Figure 3) show that performance if very high in where was factor of head and neck cancer. The performance of around 100% shown with factors of middle-recruiting potential sites and colorectal cancer (Figure 5).

Figure 5: Rate of ratio of target recruitment to study power and internal factors.

Figure shows that this ratio is very sensitive during acting of internal factors and nosology acting in increasing way whiles the hematology in decreasing way. The percentage of changed parameter and ratio of internal factors presented to (Figure 6)
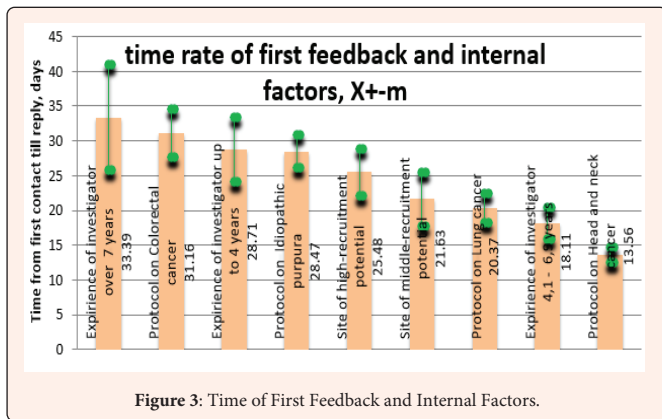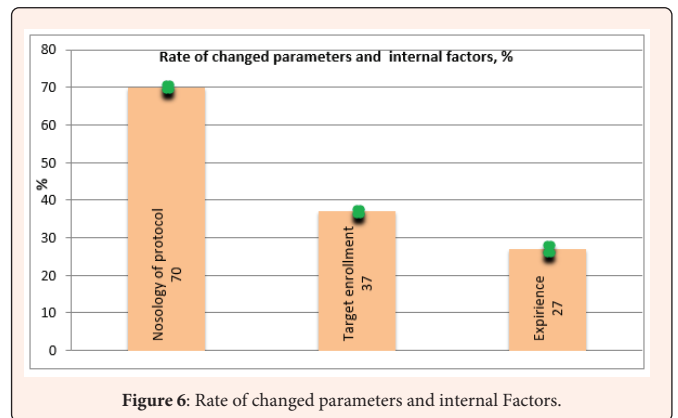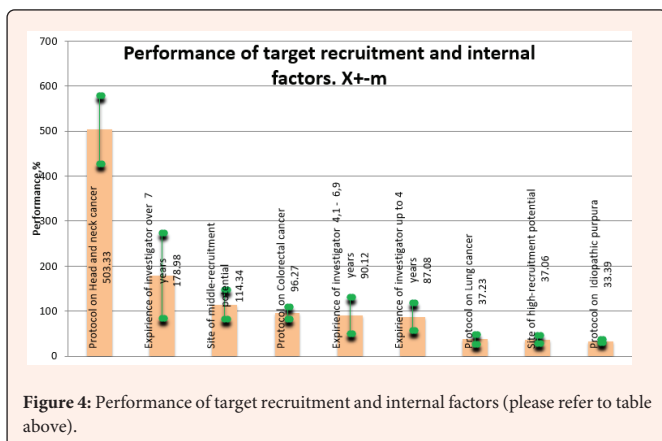

Figure 6: Rate of changed parameters and internal Factors.

Short Discussion

Authors [5] mentioning that out of 80% of patients have a good will to participate in study but only 10% of them is actually participated and from other side 33% of sites and principal investigators cannot enroll even a single patients to the study (Thomson med stat report, 2004) and only these two factors is heading to fail up to 76% of clinical trials of II and III phases.1[3] is saying on 80% of screen failure rate for mostly of the clinical studies. We named these two factors as internal factors and also specified them to three factors – protocol nosology, target recruitment (the same also proposed recruitment, target enrollment) and experience of investigators. We found that rate of recruitment and their derivatives has a statistical significance and based on number of the changes we ranged the importance of the each internal factors. The most important internal factors confirmed the nosology of protocol. Therefore, either we have to find out the way to manage these two factors proactively or to manage other 24% of successful recruitment in order to boost them. To managing we have to have a figures and parameters. We used parameters obviously needed to evaluate the recruitment like number of patients to be enrolled and finally enrolled. Authors [10] using the ratio of parameters like enrollment fraction and we also created the ratio of parameters and found that some ratio is much sensitive to evaluate the internal factors.

Reference

1. A L´opezJaimes, S Zapotecas Martinez, CA Coello Coello (2009) An Introduction to Multi objective Optimization Techniques // Nova Science Publishers, Inc, pp: 1-26.

2. AM McDonald, RC Knight, MK Campbell, VA Entwistle, AM Grant (2006) what influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies, Trials 7: 9.

3. B Fletcher, A Gheorghe, D Moore, S Wilson, S Damery, (2012) Improving the recruitment activity of clinicians in randomized controlled trials: a systematic review, BMJ Open 6;2(1):e000496.

4. Du W, Gadgeel SM, Simon MS (2006) Predictors of enrollment in lung cancer clinical trials. Cancer 106: 420-425.

5. Joan F, Bachenheimer and Bonnie A. Brescia, (2007) Reinventing Patient Recruitment: Revolutionary Ideas for Clinical Trial Success, Gower Publishing, Surrey, UK.

6. LC Lovato, K Hill, S Hertert, DB Hunninghake, JL Probstfield, (1997) Recruitment for controlled clinical trials: literature summary and annotated bibliography, Control Clin Trials l8(4): 328-357.

7. LM Friedman, CD Furberg, DL DeMets, (2010) Fundamentals of Clinical Trials, fourth ed, Springer.

8. MN Fouad, JY Lee, PJ Catalano, TM Vogt, SY Zafar, (2013) Enrollment of patients with lung and colorectal cancers onto clinical trials, J. Oncol. Pract. 9 (2): e40-e47.

9. Murthy VH, Krumholz HM, Gross CP (2004) Participation in cancer clinical trials: Race-, sex-, and age-based disparities. JAMA 291(22): 2720-2726.

10. Myles PS, Williamson E, Oakley J et al. (2014) Ethical and scientific considerations for patient enrollment into concurrent clinical trials. Trials 15: 470.

11. Nass SJ, Moses HL, Mendelsohjn J eds (2010) A National Cancer Clinical Trials System for the 21st Century. Washington, DC, National Academies Press.

12. P Chin Feman, LT Nguyen, MT Quilty, CE Kerr, BH Nam LA (2008) Effectiveness of recruitment in clinical trials: an analysis of methods used in a trial for irritable bowel syndrome patients, Contemp Clin Trials 29(2): 241-251.

13. Robert S. Bienkowski and Norman M. Goldfarb. Screen Failures in Clinical Trials: Financial Roulette or the Cost of Doing Business? // Journal of clinical research best practices 4:7.

14. S Rahman, AA Majumder, SF Shaban, N Rahman, M Ahmed, KB Abdulrahman, (2011) Physician participation in clinical research and trials: issues and approaches, Adv Med Educ Pract 2: 85-93.

15. Stewart JH, Bertoni AG, Staten JL, Participation in surgical oncology clinical trials: Gender-, race/ethnicity-, and age-based disparities. Ann SurgOncol 14(12): 3328-3334.

Citation: M Svyatoslav (2021) Rate of patient's Recruitment and Recruitment Derivatives from the Perspectives of Internal factors - Protocol Study Nosology, Experience of Investigators and Potential Patient's Pool of Sites. Corpus J Clin Trials 2: 1007

Page 6/6