International Journal of Clinical Trials
Milovanov SS. Int J Clin Trials. 2021 Feb;8(1):73-78
http://www.ijclinicaltrials.com
pISSN 2349-3240 | eISSN 2349-3259
DOI: https://dx.doi.org/10.18203/2349-3259.ijct20210147

Short Communication

Predicting of patient's enrollment to multicentral international clinical trials of II–III phase

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Received: 30 June 2020
Revised: 07 January 2021
Accepted: 11 January 2021

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ABSTRACT

Many international multicenter trials ending by fail due to fail to recruitment of patients. Objective was to find the integrated and simple value for the assessing the possibility of recruitment in particular sites on the feasibility stage. Design consisted of retrospective review of the selected parameters since feasibility stage to final report of studies conducting in a few sites since 2008 to 2017 year. It was also selected empirical range of the sites. Collection of data was done from the private experience of authors. The integrated and simple values for the assessment of the possibility of recruitment in particular sites on the feasibility stage were calculated. Recruitment of patient as an integrated part of site's work could be calculated as the beginning of running study on particular site which can lead to increasing of study success and could be used as an embedded value in artificial intelligence for both virtual and real studies. We titled this "calculated type of site on enrollment (CTSE)".

Keywords: Clinical trial, NAFLD, NASH

INTRODUCTION

Since 2008 up to date the cost spending to clinical trials is increased dramatically and in some trials around 100-fold times.[1-3]

Content of the cost is different and the major ones are: increased costs of clinical supplies and equipment; extended timelines of clinical trials; increased regulations, particularly at the clinical and CMC levels; monitoring complexities; patient recruitment intricacies; workforce competence; and data collection and synergy complexities.[7]

The recruitment costs consists up to 60% out of this the above items. Recruitment for the purpose of this article is the integrated value which is means both the process as well as the final figure of patients enrolled to any studies under all of the influenced factors met during the process.

Statistical analysis

To find out novel score for prediction of effectivity of future patient enrollment at individual site during the feasibility stage of clinical trial we used following statistical approaches: we observed 70 sites participating in four phase I - phase III clinical trials performed in 3 countries (Russia, Belorussia and Ukraine) during time period between 01 July 2008 and 31 Dec 2017. Numbers of enrolled patients, enrollment effectivity and etymology of 4 diseases studied are presented in Table 1.

During conducting of the studies we have chosen some enrollment success prognostic parameters to be used during the phase of feasibility and some parameters, which, on our opinion, can cumulatively represent the process of recruitment. During performance of the trials we put 70 values (number of sites in the study) in each parameter and finally data base had been formed consisting out of 1960 variables for statistical analysis.

Sperman correlation analysis (Excel 2016 standard package) has been used to elucidate relationships between all parameters. Only numeric values of parameters have been used. Further, based on the analysis of Sperman correlation, 7 parameters (patients to be planned; peoples in region; experiences of PI in clinical trial in years; number of sites in one city; peoples country; KOI leader 1=yes, 2=no; time from first contact till reply, days (time in days and time in weeks is the same parameter) have been identified to be taken for calculation of statistical regression analysis.

Table 1: Etymology of 4 diseases studied, numbers of enrolled patients and enrollment success in 4 projects of interest.

Sl no.	Nosological form (disease)	# of cities	# of sites	# of patients
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

METHODS

The following prognostic parameters have been chosen for prediction of enrollment success during the phase of feasibility:

City (number of residents in the city)

It is apparently connected to demography and distance. It was found that most of adults in Washington (US) ready to spend 30 minutes for taking medical care and about 22 miles far from the place of medical care. Over this distance the visits patients is calling difficulties. Also this authors marked differences between town and suburb residency. This definitely related with development of transport infrastructure. Our study was in cities with very different number of residents. We ranged cities participating in our 4 trials in 3 categories: <1 mln residents, 1-2 mln residents and >2 mln residents. They are given in Table 2. Definitely where the infrastructure of movement was developed the number of patients recruited to the study two time more than in cities with less developed infrastructure.

Study (complexity of the project protocol)

It means what phase and design of diseases was investigated. Design of study as a factor of poor recruitment.[12,14,33] We found that in phase III studies percentage of silence sites were 21% while in phase II studies were 33%.

Country (number of inhabitants, size of patient population, number of clinical trials simultaneously conducting in the country)

As a parameter, it has a significant role as regulatory but also as a pool of patients and a number of studies simultaneously conducting in the country. We investigated three countries – Russia, Belorussia and Ukraine. Number of studies for these countries in 2007–2017 year was less than 1000 per year with the people over 200 mln living in this area compared with Israel for example where number of studies are over 40000 per year with 8 mln people.

Nosology (disease under investigation)

It means the exactly investigating diseases. We investigated oncological studies and one study was in thrombocytopenia.

Table 2: Dependence of enrollment effectivity on number of the city residents

Number of city residents (mln)	Enrollment effectivity of sites involved in the study (%)				
	Silent sites	Low-recruiting sites	Middle-recruiting sites	High-recruiting sites	Total
<1	52	42	6	0	100
1-2	11	44	33	12	100
>2	40	22	14	24	100

Time (in days)

It includes time from the ethics approval to the first enrollment by first contact with sites in days and weeks created by us as an important parameter for evaluating of site. Time is mentioned from ethics approval to first recruit.[21]

Time period (in days)

We also took time period (in days) from the site activation till the first screened patient.

Patients to be planned

It is the enrollment plan predicted by the PI at the stage of feasibility. It means the estimated number of patients which evaluating by investigator on feasibility stages. Using this same approach it was found the less enrollment than expected was the reasons for fail of more than 2000 studies.[8] In the meantime reaching the expected number of patient is lead to successful completion of trial.[30] This also more expecting in areas with large population and we found the same for the parameter "number of people in the region".

Year of data record

This non-specific parameter in our opinion could play the role on massive database.

Level of life

The parameter denotes the average salary for the area where the site is located. In dollars in region per month means the average salary for the area of site location. The financial aspects has a connection to recruitment (and has an important role in influence to recruitment in both ways – negative and positive.[2,9,16,21,26,27]

The PI as local key opinion lead. Parameter is the investigator "key opinion leader" on our opinion has an impact recruitment.

Two parameters "incidence of cases of the disease of interest per 1000 inhabitants" and "number of newly diagnosed cases of diseases (total) per year in the country" is connected ones and they more or less evidently shows necessity to mention at least during our investigation.

Parameters representing final enrollment success used retrospectively after completion of the study: "level of enrollment success" - is parameter we received by empirical approach based on final recruitment rate; parameter "recruitment period (in weeks) – the time period between the site activation and the last patient enrolled in the site' and the same in days is obviously needed one and we means that this is actual period when recruitment was going on; parameter "maximum patients per protocol" – minimum number of patients to be enrolled to reach statistical significance is statistical figure of patients to proof the study points; parameter "number of inclusion/exclusion criteria in the protocol" is very frequently mentioning one by many authors; parameter "site number"- exactly number of site out other sites set to this particular site in this particular study is means the exactly number of site setting to particular site in particular study; parameter "activated (1=yes, 2=no)" was the site initiated or not means the site was initiated or not and it also could be named sleepy sites.

Same as criterion 2 parameter "duration of recruitment period from activation till last pt (weeks)" is time specific for each site and that why could have a worth for us. [11,17]

Only one parameter "level of enrollment success" is the exceptionally synthetic parameter calculated after the studies had been completed.

We have assigned to the sites four levels of enrollment: level of enrollment 1 is high recruited site, appointed range 3; level of enrollment 2 is middle recruited sites, appointed range 2; level of enrollment 3 is law recruited sites, appointed range 1; and level of enrollment 4 is non-recruited sites, appointed range 0.

RESULTS

Based on this parameters we built regression formula based the standard statistic package of Excel 2016.

Regression formula is given by:

$$\begin{aligned}\text{Type of site} = 4.55 + {} & (-0.015 \times (\text{Parameter A})) \\ & + (6.95 \times 10 - 8 \times (\text{Parameter B})) \\ & + (-0.06 \times (\text{Parameter C})) \\ & + (0.03 \times (\text{Parameter D})) \\ & + (-5.24 \times 10 - 9(\text{Parameter E})) \\ & + (0.8 \times (\text{Parameter F})) \\ & + (-0.018 \times (\text{Parameter G}))\end{aligned}$$

Where parameter A: patients to be planned by PI; parameter B: people in city where site will be opened; parameter C: experience of principal investigator in clinical trials in years; parameter D: number of sites in one city; parameter E: people in country where study will be conducted; parameter F: is the PI the key opinion leader – 1, or not – 2; and parameter G: time (in days) after first sent questionnaire to site and first reply. To check the prognostic reliability of the formula we analyzed the performance of the formula on the following studies.

Clinical trial of ulcerative colitis II-III phases

We took 14 sites initially planned for the study since 2018 year. This study finished in third part of 2020. The results of this analysis are present in Table 3.

Table 3: Calculated type of site on enrollment (CTSE) in independent ulcerative colitis II-III phases study: number of patients recruited in each site.

CTS-E	City	Recrui-tment	Scree-ning	Initiation (1–yes)
0.6	Moscow	0	0	1
1.7	SaintPetersburg	0	0	1
2	Omsk	5	9	1
2.1	Ekaterinburg	26	68	1
2.26	Omsk	0	0	0
2.29	SaintPetersburg	3	12	1
2.37	SaintPetersburg	2	4	0
2.49	Moscow	0	0	1
2.88	Penza	0	0	0
2.9	Ulyanovsk	1	3	1
3.05	SaintPetersburg	0	0	0
3.05	SaintPetersburg	0	0	0
3.11	Kazan	0	0	0
3.16	Tula	0	0	0

Using quantitative measures for better outcome of events (like clinical trials for example) is evidently and quite investigated.[1,38] Not all factors are equally important that

why scientists developed mathematical framework is approaching to compare different parameters in the beginning. Recruitment as a beginning of any study and as an important part of it is attracting the attention very much.[6] The breakdown of parameters also different and could be split depends on trial's outcomes, study phase, cost-related and many others.[6,13]

Fogel mentioned that there were missed the researches of formula for possible rate recruitment depending on distance from site and he pointed that absence of such researchers for other factors is crucial sometimes for recruitment and retention.[13]

It was reviewed literatures on this matter for past 30 years and emphasized that cost of phase III is cost not only the phase III funds but all of the previous trials.[13] According to his study the reasons of trial failure to two large group– due to efficacy and safety, but he emphasized that recruitment is one of the reason. It was emphasized that failing to recruit needed and calculated number of patients to prove the efficacy and safety of IMP is long–existing problem.[29] Number of trails failed due to recruitment is up to 40%.[15,22,31] The absolute figure of this fail is 48000 patients enrolled to 20% of trials failed in recruitment [19] out of 2-4% patients enrolling to oncology trials overall from all population of oncological patients.[23] It was a lung and colorectal cancer with equal distribution on male and female on six different insurance in USA. Authors noticed the correlation in medical specialty and enrollment: medical oncologist more likely recruiting the late stages of cancer (69%) while surgeons earlier. Also authors found that to recruit 20 patients was spent 4000 hours. So we see the importance of the time and correlations. Therefore recruitment is an important part of progress of study at any phase. Site as a place to where a patients must come is influencing to recruitment very much and depend on this influence the recruitment could met or could not met set up goals of study. Fail of recruitment on site level is poor recruitment, high dropouts and sometime underpowered trials. From the beginning of the study on site there is a big problematic gap between the anticipated enrollment and real eligible patients (Bennette et al and Dickson et al).[12,33] A lot of sources found that numerous of sites in any studies failed to meet enrollment, or failed to enroll any subject at all.[3,4,28,37] The reasons for such results is very different: implementation of a clearly defined "system" of recruitment, engagement of other staff, time from ethics approval to first recruit, the provision of a dedicated trial coordinator.[20] Also revealed that many sites in many clinical trial is without patient at all on all duration of study (silence sites) or law-recruiting sites which is not expected based on feasibility data collected before initiation of sites.[34]

So the necessity to find the way for decreasing the cost of clinical trials is highly demanded.

CONCLUSION

We developed integrated value of possible recruitment in particular site based on some parameters which influence to enrollment. We titled this calculated type of site on enrollment (CTSE). This integrated value allowed us to predict the recruitment for the following: if we have CTSE in the range >2.49 so it is highly predictable that we can have the huge number of patients in site; if we have CTSE in the range >2.0 to ≤2.49 then we will have a middle activities on recruitment on site; if we have CTSE in the range=1.49 to ≤2.0 this will be the law level of recruitment activities and; CTSE less than 1.49–non-recruited site.

We also see accomplished formula as a part of artificial intelligence in future. As of now it is not cancel the obliged management of evaluation of site by responsible staff.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Milovanov SS. Predicting of patient's enrollment to multicentral international clinical trials of II–III phase. Int J Clin Trials 2021;8(1):73-8.