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ENROLLMENT AND RETENTION IN CLINICAL TRIALS AND FACTORS INFLUENCING TO THESE PROCESSES.

[1*]Svyatoslav Milovanov, MD, PhD

[1]Study Physician, Russia, Moscow.

***Corresponding Author: Svyatoslav Milovanov, MD, PhD**
Study Physician, Russia, Moscow.

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Annotation
Enrollment and retention of patients to clinical trial is a barriers to be overcome in order to be succefful in completion of particular clinical trials of any phase. Enrollment and retention is active process and is undergone by many of the factors, influencing oppositedirectly and to managing this factors will allow to follow the main goals of the study. The factors influencing to the enrollmemt of the patients acting during the enrollment period while the factors influencing to the retention begins acting since the first patient enrolled and lasts to the last visit of the last patient. There is a factors which are decreasing the recruitment and last data is reporting up to 80% trials failed due to low or even absence of recruitment on level of sites. Additionally authors have not not defined with the term factors and barriers and this also influence to the action to prevent the fail of study. We will try to highlight as much factors and barriers as we can in order to be known it. **Materials and Methods:** Review of the publicaitons randomly found on the topic Enrollment and Retention in clinical trials as a barriers and factors influencing to these processes. **Study objectives:** to highlight Enrollment and Retention in clinical trials as a barriers and factors influencing to these processes. **Statistical analysis:** there were no statistics and only the observation of journal open sources. **Results:** It was reviewed the barriers and factors in clinical trials which are influences to the enroolment and retention of patients. First time it was suggested to split the term barriers and factors. **Discussion:** Recruitment and retention is determining by some authors as a factors and others as a barriers and in meantime the barries and factors could influence to the enrollment and retention. We did listing as much as possible factors and barriers related with retention and recruitment in order to try to find and suggest determination of the terms which will finally lead to success in particular clinical trials.

INTRODUCTION

Enrollment of patients to clinical trial is important part of any clinical trial (Fletcher B. et al., 2012). Due to fail in enrollment up to 86% of clinical trial unsuccesful (Brooks S. Et al., 2015, Huang G. Et al., 2018), and more over after the patient randomized to the trial the following keeping them active in study and then follow-up period also the challenge and being called retention of the patients and fail in this period (Robert S. 2008) also will lead to fail of the trail and the fail in retention period consist up to 15% of trails. Factors influencing to recruitment and retetnion is diverse and difficult to estimate due to highly variable (Chin Feman P. at al., 2008, McDonald A., 2006). D. Fogel (2018) found more than 30 factors influencing to recruitment and much of them can ruin the trials due to fail of recruitment. M. Rutger at al., (2017) and found more than 30 factors acting differently to recruitment. Authors seeks the way to facilitate the enrollmet (Du W et al., 2006, Rahman S., et al., 2011, Kaur G. et al, 2012). In order to falicitate the enrollment and retention based on studied factors and barriers G. Huang Et al., (2018) had grouped these factors to three ones to develop the strategy - (1) trial design and protocol development, (2) trial feasibility and site selection, and (3) communication. Kaur, G. et al (2012) to six groups - (1) trial, (2) site, (3) patient, (4) clinical team, (5) information and consent and (6) study team.

METHODS AND MATERIALS

It was done the review of the randomly found publications the topic of Enrollment and Retention in clinical trials as a barriers and factors influencing to these processes. It was grouped found factors and barriers and discussed it.

STATISTICAL ANALYSIS

No statistical analysys done.

RESULTS

Targeted recruitment of patients is the main factor in the success of clinical trials and failure in recruitment is at least 50% of unsuccessful clinical trials of II-III phases (Borfitz D, 2002, Getz, K, Woodin K., 2003, ICH GCP,

1997, 21CFR, Walters S., 2017, Rutger M. Et al., 2017, Pinto B. Et al., 2004, Cunningham, S. Et al., 2011, Huang G. Et al., 2018). The recruitment period takes up to 30% of the study time (Bachenheimer, J. Et al., 2007). The retention or to keep patients in trial in order to reach the study power and reply to investigator question is also the very hard task wich require much time and other resources (Hill A., 1951, Hill N., 2008).

The table 1 is following factors suggested by the authors which are influencing to the fail of whole study.

Table 1: Factors suggested by the authors which are influencing to fail of the study (Fogel D., 2017)

#	Factors
	Failing to demonstrate Safety
	Failing to demonstrate Efficacy
	Financial impact
	Eligibility criteria
	Patient recruitment
	Respecting the patient's concerns
	Additional costs associated with recruitment
	Poor recruitment, dropouts, and underpowered trials
	Considering the patient's financial burden
	Employing quantitative measures
	Patient time investment

After reviewing of the literature on topic of factors influencing to the recruitment and retention it was the following found.

Table 2: Deriving the factors affecting recruitment from facilitators and from barriers described in literature (Prescott et al., 1999) cited by Kaur G., (2012) with amendment by S. Milovanov.

Prescott *et al.* (1999)		
Barriers to participation in clinical trials: patient and clinician barriers		
Barriers	Classification	Factor derived
Patient barriers		
Additional demands of the randomized controlled trials (RCT) on the patient	Patient level factors	Additional trial investigations
Additional procedures, additional appointments, time pressures, venepuncture, inpatient hospital stays, discomfort from medical procedures, length of study, worry about experimentation, uncomfortable procedures, travel and travel costs, extra costs		Additional travel and extra costs
		Duration of trial and follow-up
Patient preference for a particular treatment	Patient level factors	Patients'/parents' preference for a particular treatment
Patients not wanting to change medication, not to take placebo, not to take experimental medication, not to take any medication, patient request for a specific intervention, strong patient preference for one treatment option		Patients'/parents' attitudes towards taking experimental medicine or placebo
Aversion to treatment choice by random allocation		Treatment choice by random allocation
Worry about uncertainty	Patient level factors	Patients'/parents' concerns about side effects of new drug
Efficacy of treatment on offer is unproven, distrust of hospital or medicine, fear of unknown		
Concerns about information and consent	Information and consent related factors	Amount and complexity of trial information provided
Amount of information provided to research participants, wording of information, complexity of information provided, different forms of information presentation: written /verbal/video, limited reading skills and English not being the primary language, clinicians' experience, difficulty in giving information, worry about level of information required and that information may be frightening, consent procedure barrier to recruitment	Patient level factors	Clarity in presentation of trial information
	Clinical team factors	Experience and training of clinical team seeking consent
		Social and emotional dynamics of trial discussion
		Consent rate
		Language or cultural barrier
		Difficulty in approaching

		patents for consent
Clinician barriers		
Time constraints	Clinical team factors	Clinical workload
Time pressures from usual clinical practice, time demands of recruitment and follow-up		
Staffing and training	Clinical team factors	Research experience of clinical team
Lack of trained staff, no additional support, lack of research experience in clinicians, lack of available support staff		Availability of designated research team
		Availability of research staff out of hours
		Presence of designated research nurse/practitioner
Rewards and recognition	Clinical team factors	Clinician attitude to involving patients in research
Economic incentives		
Impact on doctor patient relationship fear of Adverse effect on doctor-patient relationship, perceived conflict in their role as clinicians and researchers	Clinical team factors	Clinician attitude to involving patients in research
Concern for patients		
Concern about treatment toxicity, side effects, burden of trial for patients including travel distance and costs, reluctance to recruit severely ill patients		
Problems in complying with the protocol	Clinical team factor	Clinician preference for a particular treatment
	Trial level factor	Study protocol compared to clinical practice
Campbell *et al. (2007)*		
Hypothesis of factors tested for association with recruitment success		
Trials with complex trial design do not recruit as well as simple trials	Trial level factor	Trial design
Less well-funded trials do not recruit well	Trial level factor	Funding
Trials without dedicated trial management expertise do not recruit as well as those with trial management expertise	Trial level factor	Trial management
Trial with multidisciplinary input recruit better than those that do not have this input	Trial level factor	Previous feasibility assessment
Trials with consumer involvement recruit better than those that do not	Trial level factor	Previous feasibility assessment
Trials that have a successful pilot phase recruit better than those that do not have a pilot phase	Trial level factor	Previous feasibility assessment
		Previous pilot trial
Trials that have dedicated paid local coordinators recruit better than those that do not		Trial management
Cancer trials recruit better than non cancer trials	Trial level factor	Being a drug/cancer trial
Drug trials recruit better than non-drug trials		Being a drug/cancer trial
Trials funded through a response-mode funding have different recruitment rates to those funded through a commissioned process	Trial level factor	Funding
Reasons for delays in recruitment to the included cohort of trials		
Problems with central staff, local research staff, internal problems (for example, staff)	Site level factor	Number of trained staff
	Clinical team factor	Motivation of clinical team
Local clinical arrangements, merging/reorganization of trusts, major relocation of services, department policies	Site level factor	Local clinical arrangements
Funding issues	Trial level factor	Funding
Delays in ethical clearance	Trial level factor	Information available from the Chief Investigator
Research and Development (R&D) delays, time delay since grant application		
Delays in supply of drug/placebo	Trial level factor	Information available from the Chief Investigator
Adverse publicity about medical research, external problem (for example, publicity)	Trial level factor	Publicity by the trial team
		External publicity
Setting up general practitioner (GP) practices took longer than anticipated	Site level factor	Time to open up site

Simultaneous other local research projects, competing research, conflict with other trials	Site level factor	Competing local research projects
Delays due to changes in data legislation, changes in technology	Site level factor	Lack of pilot/feasibility assessment
Fewer eligible than expected, smaller percentage agreeing to participate, recruitment targets too ambitious	Trial level factor	Lack of pilot/feasibility assessment
	Site level factor	Recruitment target
Absence of perceived clinical equipoise	Trial level factor	Clinical equipoise
Issues with procedures/interventions, trial process too demanding	Patient level factor	Additional trial investigations
Complexity of trial design, trial methodology considered too complex	Trial level factor	Trial design
Conflicting workload pressures, long waiting lists, additional theatre time required	Clinical team factor	Clinical workload
Language/written English difficulties	Patient level factor	Language or cultural barrier
Treatment preferences	Patient level factor	Patients'/parents' preference for a particular treatment
	Clinical team factor	Clinician preference for particular treatment
Research not considered as priority	Clinical team factor	Perceived importance of research generally in clinical practice
		Perceived importance of the particular research question
No local access to intervention	Patient level factor	Intervention available only in the trial
Case studies of trials: common factors in the successes of part B trials		
Facilitator	*Classification*	*Factor derived*
Important/interesting research question, topic important, urgent need for research, important question, timely and managed to roll several questions into one study	Clinical team factor	Perceived importance of the particular research question
Good design/good protocol, pragmatic study	Trial level factor	Trial design
		Study protocol compared to clinical practice
Clinicians keen to recruit to trial	Clinical team factor	Motivation of clinical team
		Clinician attitude to involving patients in research
Drugs already tested, so easy to explain to patients	Patient level factor	Familiarity with experimental treatment
Did not demand extra effort from patients, Impact on practice running and costs minimized, minimizing work for health professionals	Patient level factor	Additional trial demands
No competing trials for those centers/patients	Site level factor	Competing local research projects
Drugs not available outside the trial	Patient level factor	Intervention available only in the trial
Excellent trial management, trial units helpful, caring, annual meetings for all concerned, role of trial steering group	Trial level factor	Trial management
Good planning and organization by Clinical Trials Support Unit (CTSU), CTSU responsive, efficient, central organization of many aspects of research		
Good communication between trial team and clinicians, flexibility of trial teams	Study team factor	Communication and coordination among study team members at site
Good public relations/feedback/updates	Trial level factor	Trial publicity
Good funding, National Health Service (NHS) funding	Trial level factor	Funding
Trial run by good team/infrastructure, Principal Investigator (PI) well respected, PIs worked hard to keep collaborators on board, trial team communicative, responsive and alert to problems. Communication within team, between team and collaborating clinicians	Study team factors	Motivation of the study team at site
	Clinical team factor	Research experience of PI and study team members at site
Good trial team, good research assistants		Communication and coordination among study

		team members at site
Team worked hard at how to explain the study to patients		Communication and coordination between study team at site and Clinical Trials Unit (CTU)
		Research experience of clinical team
		Communication skills of clinical team
Role of research nurse	Clinical team factor	Presence of designated research nurse/practitioner
Study included everybody	Trial level factor	Patient inclusion criteria
Toerien *et al* (2009)		
Study design, number of arms, control: active/placebo	Trial level factor	Trial design
Single/multicenter	Trial level factor	Trial design
Intervention: drug/surgery/allied/others	Trial level factor	Being a drug/cancer/surgical/-----trial
Funding source	Trial level factor	Funding
Caldwell *et al* .(2010)		
Recruitment strategies		
Novel trial designs	Trial level factor	Trial design
Recruiter differences	Information and consent related factors	Experience and training of doctors clinical team seeking consent
		Senior doctors and nurses seeking consent
Financial incentives for patients/participants	Information and consent related factors	Monetary incentives for clinical research
Methods of providing information	Information and consent related factors	Amount and complexity of information provided
	Patient level factor	Clarity in presentation of trial information
		Consent rate
Treweek *et al* .(2010)		
Recruitment strategies		
Design changes	Trial level factor	Trial design
Modification to the consent form or process	Patient level factor	Consent rate
Modification to the approach made to potential participants	Information and consent related factors	Amount and complexity of information provided
		Clarity in presentation of trial information
		Senior doctors and nurses seeking consent
Financial incentives for patients/participants	Information and consent related factors	Monetary incentives for clinical research
Modification to the training given to recruiters	Information and consent related factors	Experience and training of clinical team seeking consent
Greater contact between trial coordinator and trial sites	Trial level factor	Trial management

There is clear that factor could be a barriers and could ease the recruitment and retention.

J. Mapstone, (2007) presented barriers influencing to recruitment (table 3)
Table 3.

Table 3: Barriers to participation in a randomised controlled trial.

#	Clinician based	Patient based
	Time constraints	Additional procedures and appointments for patient
	Lack of staff and training	Additional travel problems and cost for patient
	Worry about the impact on doctor-patient relationship	Patient preferences for a particular treatment (or no treatment)
	Concern for patients	Worry about uncertainty of treatment or trials
	Loss of professional autonomy	Patient concerns about information and consent
	Difficulty with the consent procedure	Protocol causing problem with recruitment
	Lack of rewards and recognition	Clinician concerns about information provision to patients

Also authors in order to predict the enrollment quite frequently using the term predictors applying to factors and barriers.

M. Rutger et al., (2017) used 59 predictors of sites which were at the end of recruitment is met their predicted enrolment goal mentioned before start the recruitment in the feasibility questionnaire. The 59 candidate predictors was categorized into seven categories: (1) general center characteristics, (2) staff availability, (3) clinical trial experience, (4) patient pool characteristics, (5) potential/perceived enrollment challenges, (6) recruitment plan and strategies, and (7) contract execution and protocol approval.
Breakdown presented in table 4.
Table 4.

Table 4: List of candidate predictors Abbreviations: PI = Principal Investigator, ICH = International Conference of Harmonization, GCP = Good Clinical Practice, ACS = Acute Coronary Syndrome, T2D = Type 2 Diabetes.

#	Predictors
General center characteristics (GCC)	
	Indicates whether the center has access to electronic medical records (0 = no, 1 = yes).
	Indicates whether a high-speed Internet connection is available at the center (0 = no, 1 = yes).
	Indicates whether the center has access to a patient database (0 = no, 1 = yes).
	Indicates whether the center is responsible for the long-term follow-up of patients in this trial (0 = no, 1 = yes).
	Indicates whether the PI is routinely involved in follow-up visits with study patients (0 = no, 1 = yes).
	Indicates whether the PI's specialty corresponds to the research area (here, cardiology/diabetes). (0 = no, 1 = yes).
	The region in which a center is located. Similar to Desai et al.(2012) each site is classified into one of the following regions: Asia Pacific, China, Eastern Europe and Russia, India, Latin and South America, North America (United States and Canada), Western Europe.
	Indicates whether the center can be considered a clinical setting (0 = no, 1 = yes). Percentages: 88.5, 11.5.
	Indicates whether the center can be considered a clinical research center (0 = no, 1 = yes).
	Indicates whether the center can be considered a government-run medical facility (0 = no, 1 = yes).
	Indicates whether the center can be considered a group practice (0 = no, 1 = yes).
	Indicates whether the center can be considered a medical hospital (0 = no, 1 = yes)..
	Indicates whether the center can be considered a private practice (0 = no, 1 = yes). Percentages: 75.2, 24.8.
	Indicates whether the center can be considered a site management organization (0 = no, 1 = yes).
	Indicates whether the center can be considered a cardiology specialist center (0 = no, 1 = yes).
	Indicates whether the center can be considered a teaching hospital (0 = no, 1 = yes).
Staff availability (SA)	
	Indicates whether a registered dietician/nutritionist is available (1 = yes, 0 = no)..
	Indicates whether an endocrinologist is available (1 = yes, 0 = no
	Indicates whether a pharmacologist is available (1 = yes, 0 = no).
	Indicates whether a phlebotomist is available (1 = yes, 0 = no).
	Indicates whether a radiologist is available (1 = yes, 0 = no). Percentages: 58.5, 41.5.
	Indicates whether a recruitment specialist is available (0 = no, 1 = yes).
	Indicates whether a research nurse is available (0 = no, 1 = yes).
	Indicates whether a study coordinator is available (0 = no, 1 = yes).
	Indicates whether a sub-investigator is available (0 = no, 1 = yes).
Clinical trial experience (CTE)	
	Indicates whether the center has ever been audited by a regulatory agency or health authority (0 = no, 1 = yes).
	The department's experience (number of trials in the past three years) with clinical trials conducted according to ICH and GCP Guidelines.
	The department's experience (in number of trials) with clinical trials conducted in this disease area.

	The PI's experience (in years) with clinical trials conducted according to ICH and GCP Guidelines.
	The study coordinator's experience (in years) with clinical trials conducted according to ICH and GCP Guidelines.
	The sub-investigator's experience (in years) with clinical trials conducted according to ICH and GCP Guidelines. Categories: None, less than 1 year, 1–4 years, 4–7 years, or greater than 7 years. Equals 0 if no sub-investigator is present.
Patient pool characteristics(PPC)	
	What proportion of your patients live within approximately 10 km (6 miles) distance from your clinic
	The number of ACS patients with newly diagnosed T2D the center treated during the past 12 months, divided by 100.
	Do you expect the procedures or assessments required to be a challenge with respect to enrollment? Please rate from 1 to 5 (with number 1 being the most challenging). Treated as continuous.
	Do you expect the importation issues to be a challenge with respect to enrollment? Please rate from 1 to 5 (with number 1 being the most challenging). Treated as continuous.
	Do you expect in- and exclusion criteria to be a challenge with respect to enrollment? Please rate from 1 to 5 (with number 1 being the most challenging
	Do you expect the study medication to be a challenge with respect to enrollment? Please rate from 1 to 5 (with number 1 being the most challenging). Treated as continuous.
	Do you expect medication reimbursement issues to be a challenge with respect to enrollment? Please rate from 1 to 5 (with number 1 being the most challenging). Treated as continuous.
	Do you expect the patient population to be a challenge with respect to enrollment? Please rate from 1 to 5 (with number 1 being the most challenging). Treated as continuous.
	Do you expect regulatory authority issues to be a challenge with respect to enrollment? Please rate from 1 to 5 (with number 1 being the most challenging). Treated as continuous.
	Do you expect a lack of sufficient staff resources to be a challenge with respect to enrollment? Please rate from 1 to 5 (with number 1 being the most challenging). Treated as continuous.
	Do you expect the visit frequency and/or study duration to be a challenge with respect to enrollment? Please rate from 1 to 5 (with number 1 being the most challenging). Treated as continuous.
	Indicates whether the center has concerns about the investigational medicinal product (0 = no, 1 = yes).
	Indicates whether other, possibly competing trials are currently running/planned on the center. Categories: “No”, “Yes, but we can still meet the enrollment goal for this study”, “Yes, and it may impact our ability to meet the enrollment goal for this study”.
	The expected proportion of screen failures.
Recruitment plan and strategies (RPS)	
	The planned/target number of enrolled subjects.
	The planned length (in months) of the follow-up period.
	Indicates whether the center has stated to be both willing and capable of providing additional support to assist with chart review to identify patients for the study (0 = no, 1 = yes).
	Indicates whether the center has stated to be both willing and capable of providing materials or services to promote the study to referral physicians/other departments (0 = no, 1 = yes).
	Indicates whether the center has stated to be both willing and capable of to keep regular contact between visits (0 = no, 1 = yes).
	Indicates whether the center has stated to be both willing and capable of providing community follow-up and visit reminder emails, cards and phone calls (0 = no, 1 = yes).
	Indicates whether the center has stated to be both willing and capable of maintaining contact with the patients' other caregivers, particularly primary care physicians (0 = no, 1 = yes).
	Indicates whether the center has stated to be both willing and capable of providing personal thank you letters to patients (0 = no, 1 = yes).
	Indicates whether the center has stated to be both willing and capable of utilizing alternate contact information for patients, including that of family and friends, to assist in maintaining patient contact (0 = no, 1 = yes).
	Indicates whether the center has stated to be both willing and capable of providing study-pertinent items to patients at milestone visits (i.e. diabetes recipes, exercise guides, etc.) (0 = no, 1 = yes).
	Indicates whether the center has stated to be both willing and capable of creating a study community website for patients to view news and articles related to their condition (0 = no, 1 = yes).
	Indicates whether the center has stated to be both willing and capable of providing periodic webcasts for patients (0 = no, 1 = yes).
Contract execution and protocol approval (CEPA)	
	The total number of days required from submission of essential study documents to obtain final protocol approval from all of the site's required committees combined. Categories: 1 to 10, 11 to 20, 21 to 30, 31 to 60, Greater than 60.
	Indicates whether it usually takes the center more than 30 days to execute a contract and budget (0 = yes or unknown, 1 = no).

Thus, there is no single approach to the classification of factors, as well as in terminology. The authors also note that the factors influence in different directions.

SHORT DISCUSSION

It is clearly shown that factors could be a barriers if they decrease the recruitment and fail retention, facilitators if they improve these processes, predictors by the future prespective of success of trials and facotrs itself. Definitely the qualitative description of the factors is depends of the aim of publication of particuar authors and not limited by the presented factors above – some authors (Wolf L., 2007) single out the influence of factors on the site and outside the site (macro and micro influence of factors) and the effect of some factors throughout the recruitment of patients and some at a certain period of recruitment (Terheyden, J et al., 2021)

Friebel T. et al., (2004) distinguish between passive patient recruitment and active patient recruitment, while Miller D. Et al., (2010), proposed automation of patient recruitment, and screening.

And fo course factors affecting patient recruitment attract the attention of authors primarily in terms of success in recruiting patients and predicting success (Fogel D., 2017), but factors can also be parameters characterizing sites (Kibby M. 2011). Such ambiguity of factors influenced the proposed numerous classifications of factors. It is not clear the basis for definition of terminology and need to be investigated in futher additionally.

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