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Feasibility & Site Optimization – Oncology Perspective

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Cancer as it is known to have devastating effects, large amount of research is being undertaken to understand causes and its implications. With this fact, the drug development companies across the world are pumping large amount of resources with the intention of finding effective therapies. This has led to a large number of clinical trials being conducted around the globe. With the rise in number of trials has also given an increase in hurdles surrounding them, most importantly of them being slow recruitment rate causing study delays eventually. The delays are collective ranging from site identification through site start up process and finally to study enrollment. This is where effective feasibility becomes a need which can provide several vital information that can have significant impact on operational, quality and financial aspects of a clinical study. During feasibility process there are several key factors that need to be taken into account which includes considering goals & objectives of the program, study indication, design of protocol, selecting country and site for feasibility. The key is designing a appropriate feasibility questionnaire, then planning and conducting feasibility to get the vital information for effecting planning and execution of the study. At site level too, there are numerous hurdles which have to be identified earlier in the process while selection. This not only helps sponsor/CRO to understand criticality of study to be undertaken but also helps site for them to build up in getting ready for upcoming oncology trial. This mutual understanding process between sponsor/CRO and site in the end strengthens a long lasting relationship with each other and problem of slower recruitment, quality or study delay could be effectively solved.

Drug development companies today are finding themselves in very different waters than those a decade ago. As devastating effect of cancer grows, there is an urgent need to find more effective therapies. The common diseases which were earlier thought have now become individual collection and which now can be further differentiated at molecular level. Understanding biological basis of cancer has led to development of many new treatments for cancer over a last decade. In addition, evolving concept of personalized medicine is motivating efforts in raising therapeutic index of both newer and older treatment by defining patient population who would most likely be benefited and thus reducing patients exposure to therapy that would likely to be ineffective. Under current highly competitive environment of clinical research in this therapeutic area, segmentation of oncology patient population has increased further challenges in design of clinical trials. With the rapid clinical advancement, there is a constant economic pressure on these drug companies for bringing new compounds to market more efficiently. Failure to complete the trial within a planned timeframe can lead to disastrous financial implications for any clinical development program and thereby delay the availability of new therapies to patients. In such critical scenario, knowledge remains the key to success for a clinical study and in order to obtain this information a good quality of assessment of feasibility becomes prerequisite. Feasibility is increasingly relied by clinical trial sponsors in their clinical trial planning process. Findings obtained from feasibility would provide guidance on how best a study can be designed and executed, including facilitating of subject enrollment. Trials that include properly performed feasibility would experience fewer delays and considerably reduce risk of trial closing prematurely due to lack of poor enrollment. Therefore, feasibility remains prime importance for successful conduct of trial.

Selection of right sites and its optimization is a key factor for any oncology trial as good sites starts the trial off right whereas early site challenges puts one behind schedule and over budget. Suitable resources and time allocation should be allowed and applied in order to identify open sites willing to participate and that would actively enroll patients in the trial. As per the literature, it is noted that global investigative sites today face significantly operational challenges. Nearly half of all sites engaged in a trial under enroll or are

unable to enroll single patient. Under current global pressures pharmaceutical and biotechnology companies also face the heat in not only bringing high quality products at reasonable cost but also improving site efficiency, reduce incidence of delays, mutually establishing more effective collaborative working relationships with sites. In order to benefit mutually site enhancement programs must be implemented by drug companies by taking in consideration all possible shortcomings thus improving site efficiency and outcome.

1.0 Feasibility Assessment: Role

Assessing feasibility in a correct manner can provide vital information which can have significant impact on operational and financial aspects of a clinical study. Apart from evaluation of patient enrollment potential for a site and investigators interest in study feasibility assessment can assess if a study can be done, achieved and managed based on study specific variables like timelines, design of study, inclusion-exclusion criteria, required treatment and other essential factors. For oncology trial key to success is to understand practical concerns and limitations of the trial. A good quality assessment of feasibility can provide very critical information and suitable solutions if employed effectively. A higher level feasibility assessment whether a study can be done gives first hand information on potentiality of subject enrollment defined on key inclusion/exclusion criteria, study design. Achievability by study site can be evaluated by checking site for subject enrollment potential and other information related to study like visit schedules, procedures, evaluations, quality, timelines and budget. Management of study from feasibility assessment evaluates resources and experience of potential study sites, study related costs and any additional study related information like logistics, use of central laboratories etc. By understanding challenges related to oncology trial and enhancement of feasibility information accordingly can lead to proactive strategies for efficient execution of study and thereby maximizing study outcome.

2.0 Feasibility Considerations Related To Oncology Trials

For conducting best feasibility assessment of all influences that can impact proposed clinical trial is needed and these are in the context of geographical, socio economical, clinical and epidemiological considerations given the particular indication & study protocol under investigation.

Objectives of feasibility: As feasibility can focus on series of information, key question that most sponsors seek is whether the design of the trial is appropriate for a given geographic area, has right operational plan and ensuring that trial is completed with high quality, on time and is within budgetary conditions. Also, through feasibility one can address issues which are otherwise difficult to understand by means of direct survey from PI's or databases available containing data on practice patterns.

Protocol Design: Clinical trial is generally designed based on organization's internal knowledge, inputs from KOL and experienced investigators. However, one needs to ensure that the planned design is feasible with respect to local standard of care or medical practice. Though drug development companies are turning to emerging regions and developing countries for reduced cost and timelines, the concept/protocol development is still happening in the western countries based on the standard care of practice in the western countries. Therefore, it is utmost important that feasibility of protocol design should be assessed thoroughly in these emerging and developing countries where the study is planned. This includes:

- ***Standard line of treatment:*** in a particular geographic location where proposed trial is to be conducted, investigators will not be enrolling patients into studies if trial therapy is not in tandem

with treatment currently being offered. In such cases it becomes imperative to assess this from investigators whether they will accept protocol planned line of treatment for trial.

- ***Comparator arm:*** In some oncology studies, the new treatment is compared with marketed standard available treatment. As a part of feasibility one needs to ensure that the comparator treatment which is planned as per protocol design will be available locally. If the same brand of comparator treatment which is available in western countries, is not available locally, one need to look at the feasibility of using alternative brand in those countries.

- ***Diagnostic practice:*** may vary as sites in some of the developing countries may not be following the same procedure for diagnosis as practiced in developed/western countries or as per the protocol requirements.

- ***Key Eligibility Criteria:*** should be assessed completely by posing right questions and discussing with PI to get complete assessment of those key criteria to estimate most realistic enrollment rate. The frequency of routine medical check-up/screening, diagnostic practice followed in specific country will have impact on patient eligibility as some study criteria may ask for patient's last 3 or 6 months scanned/tissue sample to be eligible for the study. These types of criteria should be accessed thoroughly to find out impact on potential patient pool at the site. The wash-out periods, current prior therapy restriction in eligibility criteria should also be assessed carefully.

- ***Study procedure:*** is one of the most important aspects of feasibility to ensure that it is feasible to conduct study as per country/site practice. Based on earlier experience with sites, it should be checked whether it is feasible to get patient compliance to planned number of protocol visits. Progression free and overall survival follow-up is one of the important endpoints assessments for most of the oncology studies. One need assess the feasibility of longer follow-up with these patients to obtain protocol related data, especially for the cancer conditions where survival is longer. Patient enrollment is usually affected by rigorous schedule, complex nature of the study and arduous evaluations in the study and all these factors can delay the enrollment and affect efficacy and safety endpoints evaluations.

Taking care of above point's optimization of study protocol thoroughly through proper consultation and planning would ease out conduct of trial. Also this will provide a vision whether study would meet its objectives and allow study sponsor to invest their time, money and patient resources for the trial. If protocol involves any specific challenges that should be resolved before start of study to avoid any surprise this might be encountered later.

Selecting Country & Projecting Enrollment: Selection of right countries/sites is of paramount importance in era of global trials.

- Less sites/countries can cause enrollment delays and many sites/countries can raise costs without sufficient return on investment. Optimal number of good countries should be selected to ensure completion of enrollment on time based on epidemiology of type of cancer specific for that country and quality that country can offer considering trial environment as well as budgetary aspects. As enrollment rates differs depending on country involved, the important factor plays a critical role in selection of country includes *cancer indication incidence and prevalence* perspective

as this varies considerably by geographic area (e.g.: In USA, prostate cancer is the most common type of cancer in male. In Asia, Taiwan has the highest incidence rates of Breast cancer cases followed by Singapore and Philippines. The most common type of cancer cases and deaths are from Prostate, Lung& Bronchus and Stomach in Latin America and Caribbean). Countries where low incidence and prevalence could also be selected if necessary as referral practice can transfer patients to tertiary centers of expertise where enrollment rates may be in comparison with geographical region/country having higher incidence and prevalence.

- Presence of competing trial is another important factor in country/site selection as many good sites may feel uncomfortable to open multiple studies in same indication and setting. If multiple studies do also open up, one or more study may enroll poorly. Therefore it is necessary to assess whether site for any competitive study for common indication like breast cancer and it's needed to ensure that these shouldn't be overlapping and affecting enrollment rate. Therefore, knowing the site and its capability becomes very important.

- In order to plan a clinical trial an accurate projection of enrollment is required as some of the sites may overestimate enrollment rate. However, one can make use of their experiences of working in those countries, sites and in indications to estimate realistic enrollment rate. Also, some sites lack appropriate data sources that can allow them to quantify patient populations that may be available to participate. Sites earlier participation in prior trials in same indication and setting can provide an accurate projection rate. However, this too can be variable due to changes over time in standards line of treatment, specific eligibility criteria and competitive trial environment. For estimating the affect of these factors thorough understanding of therapeutic area as well as current and planned trial environment is required. Studies published earlier can be a useful source for estimating enrollment as these reports can generally provide number of sites participating in trial and overall trial enrollment period but don't provide months required to enroll patients and report factors such as increase in number of sites, countries participating during course of the trial etc. But, the

  data gathered from previous studies can give a useful lower range for potential enrollment. As far as estimating patient enrollment rate is concerned, detailed feasibility assessment needs to be done by discussing with PI or experienced sub-investigator at sites to avoid any surprises during conduct of trial. A thorough, properly planned feasibility with PI/Site will help to avoid the phenomenon related to *"Lasagna's Law"*

Investigational Site Selection: Though country selection is an important criterion for oncology trial, best predictor for success of trial is choice of investigative sites. Performance on patient enrollment and the quality of data obtained from previous trials is a useful indicator on investigative site under question. As in oncology trials a significant proportion of sites fail to enroll patients and this is known to be foremost challenge for oncology clinical trials.

- PI willingness and commitment towards managing clinical trials have to be checked properly. Sites which might be having good patient pool, but if PI & site staffs are very busy in managing these patients and not having enough time to look into study, then these sites are not appropriate that can be considered for the study. Hence sites/PI's having high willingness and interests are good options to consider even if they have less experience in conducting clinical trials. This willingness or enthusiasm among investigators can be assessed by conducting personal interviews with

investigators where critical information on their previous experience on study therapy if done earlier can be revealed. Also, what are the safety issues, role of new treatment/diagnostic procedure would play over existing ones, local availability of comparator product can be known through direct discussion which may not be possible through questionnaires. In person discussion with PI/Site staff can help to get detailed feedback for gathering relevant information to tackle feasibility question. This information obtained could be useful in designing of protocol for companies that are new to market and lacks bigger market research capabilities. The experience of site too needs to be assessed for its sufficient availability of staff that is trained on GCP as well as on study protocol. The availability of dedicated CRC is very important for successful conduct of oncology study that is required to be completed with quality and timeline.

- Getting estimate about site budget and PI grant is one of the key points to be discussed during the feasibility to avoid any kind of delays in finalizing site contract when the sponsor wants to finally go ahead with that site.

- Clear understanding about site EC/IRB requirement is also an essential factor during site selection process. Even though, a site has excellent data quality and enrollment potential, lengthy IRB timeline can make site less desirable for its inclusiveness. Some IRB's may not approve the study with placebo arm and if study in question has placebo arm then such sites would not be appropriate.

- Site infrastructure like local diagnostic laboratory or imaging equipments like CT scan, MRI, SPECT etc. required for study purpose need to be assessed carefully ensuring feasibility of study conduct. Facilities for study medications storage and study related documents need to be checked. The space and facilities available for CRA for during routine monitoring activities should be verified.

- If the sites are away from major cities i.e. in town, one needs to look into site accessibility, making sure the transportation of cold chain drug shipment or lab sample shipment within specific time period.

***Regulatory Aspect*:** assessment of country health authority requirement for approval and conduct of the study should be understood clearly before selecting the specific country on the list. One needs to get better understanding of country health authority approval process, timelines & documents requirements. The process and timelines for drug import license, export license of lab samples are the key aspects of feasibility assessment. As regulatory timelines differ from country to country, consideration of this cause is important for planning a trial. Countries which have sufficiently long regulatory timelines would make them less preferable for studies of shorter timelines. During conduct of feasibility treatment option which is widely available that could be approved or reimbursable by health authority in country under selection for study need to be assessed.

Relationship Building: Maintaining rapport with sites and investigators is important for successful flow of study. This can be done by having one-on one meeting suited to their needs. During this interactive meeting there should be a chance to ask questions, giving feedback, discussion of protocol and any suggestions they might have. This process would create rapport and make investigators being a part of the trial. Also, one can provide objectives and goals about the trial which is to be conducted. Having small group discussions with site staff is useful in understanding their needs and concerns related to study.

Offering newer investigators chance to ask questions can help them understand nature of trial and incorporate their suggestions if practical. This practice would certainly build good rapport with site and PI's facilitating smooth flow of study opening doors to any study in future.

3.0 Starting Feasibility:

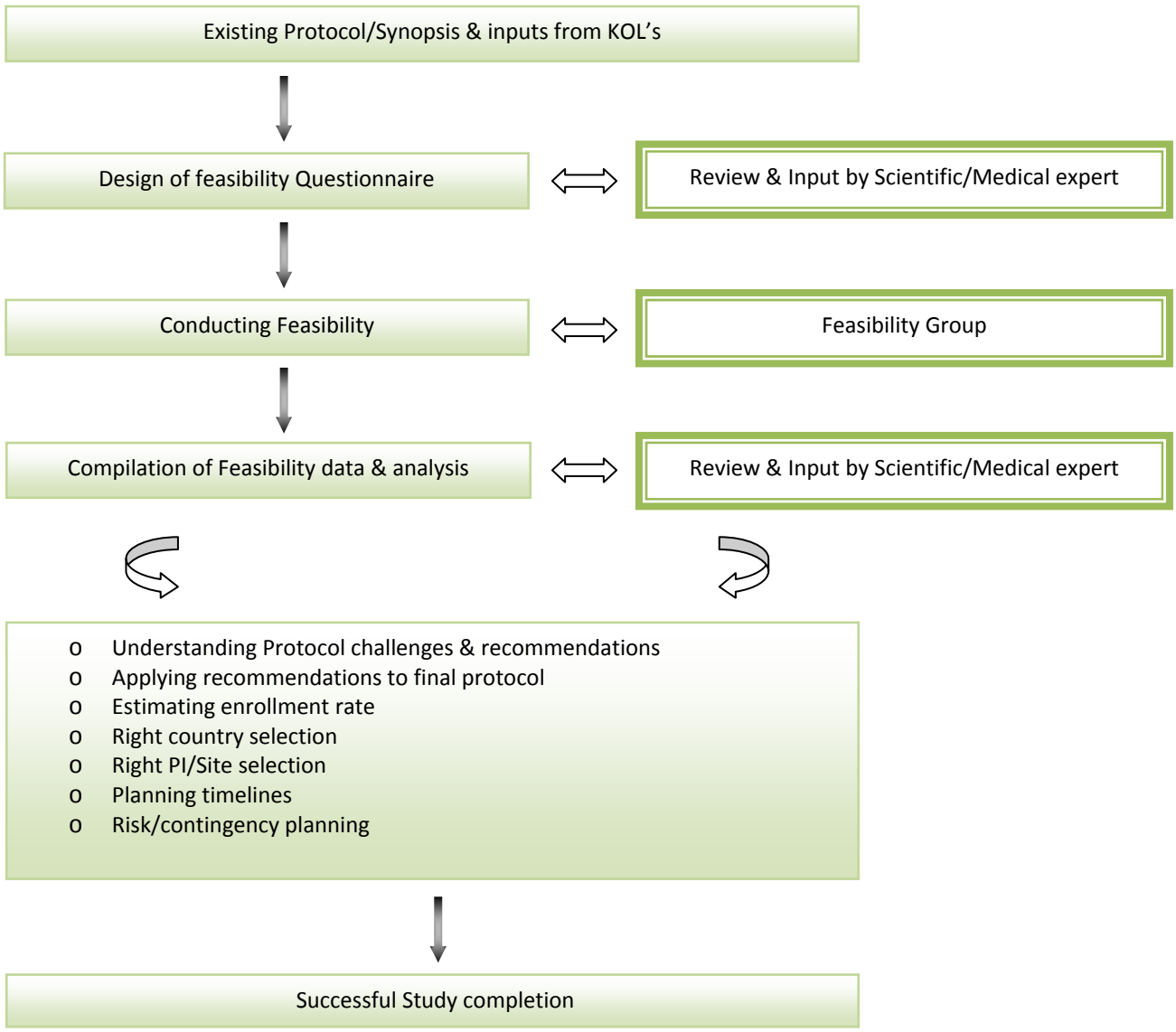
Considerations on challenges to be encountered can provide a useful guidance in design of feasibility questionnaire. Designing good feasibility questionnaire is the key which requires complete knowledge of data to be collected during feasibility assessment process. The feasibility questionnaire is most important tool to collect information from potential sites. Therefore, it is essential to design it well thereby ensuring that questions are related to the study in question and takes care of any issue that can arise during the course of the trial. A typical questionnaire would give answers related to:

- Standard of care available at the site and whether it matches study protocol.
- Adaptability of trial design & procedure to local practice standard.
- Number of patients can be enrolled on the study and retention of patients
- Ethics committee timelines, documents needed and other issues that need to be considered.
- Adequacy and availability of site staff.
- Experience of the site in handling such type of study and kind of study handled earlier.
- Equipment and other facilities available at the site like PET, CT or MRI scans.
- Patient reimbursement issues and their care during course of the study.
- Treatment available to patients on inpatient or outpatient basis.
- Follow up care issues after the study is completed.
- PI/site expectation about budget

The important information needs to be correctly evaluated and optimized so that important decisions can be made for planning and execution of the trial. For global trials, if English is language of choice, vocabulary and sentence structure has to be kept simple and specific, this is important if English is not investigator's native language as it will help to avoid any misunderstandings and reduce any time delays. If needed, usage of words like 'recruitment' and 'enrolment' should be avoided while obtaining enrollment numbers and instead 'number of patients available to be screened' or 'number of patients available to be dosed/randomized' should be used to avoid any ambiguity. Person involved in conducting feasibility assessments should have adequate knowledge in target oncology disease and have understanding of information requested in questionnaire. Also, the individuals carrying out feasibility assessment must be assisted by scientific/medical expert for discussion of any queries towards the study. In addition, a good rapport with the oncology specialist and having one on one meeting or telephonic conversation at start of feasibility assessment can play a vital role in feasibility process. Use of control group will help in refining feasibility instrument (questionnaire) and would result in questions to be asked which are precise and easy to answer and provide useful information. Clinical staff needs to spend more time and effort in contacting the sites by multiple phone calls, emails and faxes to ensure they return the forms promptly thereby avoiding unnecessary delay for start of study. Enough time must be allocated to sites after sending a feasibility questionnaire and complete protocol for their review so that investigators can respond to it precisely. The direct discussion with PI/site is always helpful to get complete clarity on their responses. Feasibility data must be effectively analyzed and any signs or questions asked were misunderstood or misinterpreted must be checked, and if any such issue going back to sites for more information can avoid

any pitfalls or delay for start of the study. Imparting goodwill with the site in question can give a long lasting relationship for future studies.

Schematic Representation of Feasibility Process



4.0 Building Site for the study

Sites today face many challenges in conducting clinical trial. These hurdles could be operational, administrative, regulatory and other delays which could prolong the start of the study. This is grave for any kind of study where timelines are important even more crucial for oncology trials where giving new treatment could be beneficial when older treatments are not working and patients are highly stressed due to nature of the disease itself. Moreover in today's economic scenario cost of clinical trials has made a significant impact on sites decision in going ahead with studies. In selecting any site, there are several factors that should be taken in account like past trial performance, number of patients recruited earlier for the indication, time availability for conduct of study, number of staff and their qualifications, number of

current trials conducted, geographic location, use of local or central IRB, cost, audit history, quality of data and site's overall past assessments.

Timely success of any clinical study can be affected by three major segments of clinical trial process which includes pre-study, active study duration and close-out phase. Optimization of sites in above areas can result in more cost efficient, smooth route of entire clinical trial. Building up of site optimization process which can address today's economic and quality challenges in clinical trial involves important tasks that includes protocol evaluation & its relationship to site performance, determining performance strategy for site with its effective solution, implementation of solution and follow-up after completion of study.

There are several reasons that most impacts site performance and their willingness to participate in clinical trial. Some of these reasons are having inadequate study information (about trial and study compound), unavailability of sufficient numbers of eligible participants, payment issues and enrollment support. Another area that leads to site dissatisfaction is working with Electronic data capture (EDC) systems. As capable sites may be handling many studies so a study which has complex process of entering information in a system than other similar study where the process of entering data is easier and not time consuming, in such case site would focus on easier EDC system study. [1, 2]

Sites should be provided with essential tools that can maximize study participation performance, thereby reducing costs and time for enrollment. Proper education and training imparted to sites as well as participating subject can enhance compliance and integrity of the study. Following up regularly with sites during the trial ensures that study procedure is correctly conducted, drug supplies are being adequately met and other logistic issues are taken care of. This aids in reducing compliance and any kind of regulatory issues that might arise or likely to arise. Continuous communication of study status to sponsor helps to incorporate any necessary study change which then could yield a more positive study outcome.

Subject enrollment is a key challenge in large number of oncology trials and selection of sites is another important task for any enrollment strategy. Selection of site for cancer trial must be such that at the end of feasibility, there is sure confidence that each site selected will enroll and perform as per required quality. Multitude of reasons have been documented why available patients are not enrolling in a trial and these have intertwined matrix of factors that includes geographic location, socioeconomic status of patients, participating sites/institutions, amount of investigator grants, availability of research staff, protocol complexity, difficulty in data collection tools, patient visit schedules, reimbursements/standards of care, patients inaccessibility to study sites, fear of informed consent forms and various other reasons.[1,2]

Protocol complexity is another major hurdle where sites cannot reach desired enrollment numbers. Tough protocol can also present a problem for its approval from regulatory bodies of the country where study is likely to be held and also from internal IRB's or Central IRB's. If a specific aspect of protocol is presenting problems for the site, investigator should be able to discuss with the sponsors representative in the beginning itself. Viable concerns regarding protocol by investigators must be addressed by sponsor and provisions must be made to accommodate concerns of particular site or country. At sponsor level, if protocol is built bearing patient in mind, more compliant study population can be obtained. During protocol development stage it's necessary to keep oneself in patient's position and ask questions to self related to study procedure, visit schedule, dosage regimen, diagnostic treatment that could hinder patient's willingness to enroll and comply with study requirements. Study materials should also be designed keeping patient perspective in mind that can yield better regulatory and ethical clearance.

Objectives and goals of the study have to be clearly defined so as to be effectively included in protocol and CRF. [1, 2, 3]

Budgetary concerns can also be a hindrance for sites willingness to participate in a clinical trial. Budget should be determined by assessing protocol complexity as well as difficulty level in areas of patient identification, patient motivation for participating in study, patient availability at sites/investigator level fulfilling goals of enrollment which could otherwise affect enrollment and retention. It has to be made sure that sites are adequately funded for enrollment activities that are essential for success of enrollment. Estimating average number of anticipated screen failure rate would eventually help in establishing a standard reimbursement program for sites. These budget considerations would keep site motivated throughout duration of study thereby providing have maximum output for patient processing. Improving upon the contract and budget negotiation process, appropriate start-up timelines, and monitoring quality would expedite the impeded process of the trial. [1, 2, 3]

Geographic location of site has greater impact with regards to timelines, language translations, packaging requirements, custom clearance and variability in time zones. These factors are critical for site selection and in understanding requirements of each country. [3]

Effective communication strategies between sponsor/CRO and sites have to be followed from start to end of trial. The incorporation of various media tools like webcasts, telecons, reporting mechanisms will elevate in maintaining motivation level thereby giving optimal performance by the site. Also, effective communication system model is needed between site staff and subject for ensuring better patient compliance, increasing level of trust in patient and making him aware what is expected of him before consent form is signed. [3]

Sites must also be improvised in terms by understanding local and country specific regulatory environment, meeting principal investigators obligations, training of study coordinator and other research staff involved in the study, setting up adequate storage facility for study supplies and data storage places and finally marketing of study sites for complete conduct of the trial. [1, 2]

Post study evaluation should be carried out to assess performance by site; this can be done by predesigned site feedback program. Delivering constructive feedback to site would relatively enhance their performance for maintaining high level data quality and thus raise their motivation. If site is average site, helping them to overcome challenges that can be encountered during the study would help sponsor by having highly motivated and quality site to work on any future studies. This post study evaluation process that is usually forgotten would provide an opportunity in determining success of medical affairs, data management, statistics and clinical operations in conducting the trial as well as to examine sites for quality of data, compliance, enrollment and retention. [3]

Overall, sponsor/CRO should provide in person training over webinars or independent learning. Onsite training is most preferable for concerns on Protocol, EDC, CRF, and any amendments. Training at investigator meeting would be a good idea for initial protocol, ICF, study drug, GCP and SAEs. Sponsors/ CRO managing oncology clinical trial should focus on all possible efforts towards building on lasting relationship which could benefit them mutually. Sites must be strategically geared up making them ready for conducting a global oncology trial.

5.0 Conclusion

The innovation of oncology clinical research is offering greater promise of new cancer treatments and also creating added complexity in conduct of oncology studies. Performing feasibility in this ever growing therapeutic area is crucial and an important planning step. Good quality of feasibility assessment of oncology study does provide useful information on practicality, restrictions in oncology trial and complete understanding of these challenges to ensure successful planning and execution of oncology trials. A great deal of planning and approach is required while optimization of protocol design, decisions to be taken on enrollment rates, selection of country thus ultimately selection of right sites for the trial. The correct selection would then be well within timelines and budget without causing major delays and raising overhead costs. For successful conduct of the trial it is imperative to consider these issues early in development and working with experienced feasibility group capable of analyzing a planned program, offering relevant recommendations and answering relevant questions, thus maximizing study outcome. Sites must be optimized thoroughly to achieve desired performance. Sponsor/CRO must collaborate with sites giving all practical solutions for successful conduct of an oncology trial. Ways must be explored such that sponsor/CRO and sites can work cohesively towards improving efficiency and increasing productivity.

References

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