Enrolment Compliance and Study Data

PEER REVIEWED

The current concept of clinical trial conduct is a balance between benefits from treatment (efficacy) and risks that this treatment may have (risk), which is defined as a "risk-based monitoring" approach. This approach combines a thorough assessment of factors that have the potential to influence safety of study subjects and integrity of study data, with a centralised review of patients' data[1]. However, being a standard practice of clinical trials, the regulations do not give a definite answer how to conduct this monitoring. It is recommended to design a study-specific monitoring plan tailored to specific risks of a particular trial[1]. Such a plan includes factors that are critical for the study conduct.

There are several factors in a successful clinical trial, but we consider two of them to be key – enrolment within the projected timelines and collection of reliable data. The estimation of the accrual period of a clinical trial has dramatic practical, scientific, and economic consequences[2]. The major players in the estimation of the accrual period are the feasibility group and project management. The fact that a study has enrolled patients within the expected timelines does not automatically mean success. To produce quality and scientifically valid data, the study population has to be consistent with the protocol criteria, and those already enrolled should be followed up for a minimal required time period to meet the study endpoints[3].

The preferred approach to statistical analysis is intent-to-treat (ITT) analysis, which includes all enrolled patients in the groups to which they were assigned, regardless of their adherence with the entry criteria, compliance with the protocol requirements (protocol deviations), premature withdrawal, and availability for a follow-up [4]. ITT is considered the standard statistical approach in randomised clinical trials. The wide acceptance of the approach is due to its main advantage: as the data are analysed, exactly as randomised, no bias or confounding – either from known or unknown sources – is likely to occur. Disadvantages of the ITT analysis are: inclusion of ineligible patients (e.g. enrolled by mistake), patients who were discontinued prior to the initiation of study treatment, patients with treatment non-compliance, and those who had been lost to follow-up data and thus the study endpoints were evaluated with a significant degree of approximation. To eliminate these issues, a per-protocol (PP) analysis is used. It guarantees relatively clean data for the analysis, but sacrifices the above-mentioned property of the ITT approach – bias due to selective exclusion of patients from the analysis becomes a concern. Even considering that FDA recommends use of ITT as the primary statistical analysis, the situations of a significant difference of ITT vs PP groups may make interpretation of study results less obvious. If, for example, a significant number of patients with violation of inclusion and/or exclusion criteria is enrolled, and they will be excluded from the PP analysis, a study could be insufficiently powered to demonstrate a statistically significant difference between treatment groups, and it will subsequently raise a question as to whether the correct population had been chosen for the study[5]. In addition, in non-inferiority trials, PP statistical analysis plays a more important role [6].

As stated, one of the major components of a "homogenous" ITT population is enrolment of patients who fit the protocol inclusion and exclusion criteria. Herein, we discuss the role of the medical monitor in the process of enrolment of eligible patients.

The primary responsibility in enrolling only eligible patients lies with the investigator. The main reasons for enrolment of ineligible patients are misinterpretation of the study protocol requirements, "overuse" of medical judgement vs the protocol criteria, and substitution of key screening procedures due to unavailability of the ones required by the protocol, as well as the human factor, or mistakes. To minimise the chance of erroneous enrolment, the industry-wide accepted practice is review of patient eligibility prior to randomisation, which is done either by a CRO, or a sponsoring company medical monitor. Based on our experience, we highly recommend using a pre-randomisation eligibility review and approval procedure, and such an approach ensures enrolment of 98-100% of compliant patients. One may ask – why not always 100%? This is mostly due to the study sites providing incomplete information. We do not consider intentional sending of wrong, or fraudulent information – this is a topic for a separate talk – but situations when investigators underestimate a patient's condition or laboratory data.

Our standard approach is to develop a study-specific eligibility checklist, which includes the key inclusion and exclusion criteria, and equally important – a detailed step-by-step procedure, which indicates the exact steps, responsible persons, communication pathways and timelines, but still is not too long and does not take too much time to fill in. Such a procedure is normally a part of the study-specific medical monitoring plan, and all members of the clinical team, as well as the study sites, receive comprehensive training in this procedure.

It is obvious that the contents of the eligibility checklist will vary depending on the therapeutic area, screening procedures, and design of the study protocol. It is important to take into account that a protocol can have up to several dozen inclusion and exclusion criteria, all having equal importance for the decision, as if a subject does not meet a single criterion, s/he is considered not eligible and should be a screen failure. However, the difference exists and is determined by the objectivity of assessment and complexity of these criteria. We can distinguish the following groups of eligibility criteria:

1. Objective criteria, which could be easily verified and confirmed with applicable administrative, clinical, and laboratory data: demographics (age and gender), criteria related to the disease under study (clinical signs, pathology/histology diagnosis), various laboratory and additional data (e.g. radiology), and laboratory parameters.
2. Subjective criteria that frequently include a statement about an investigator's clinical judgement, most typically include wording such as "medical or psychiatric condition that, in the opinion of the investigator, would make study drug administration hazardous".
3. Historical criteria – medical history, previous and concomitant

medications. Quality of this data depends on the availability of information at the time of screening, and there might be situations when additional, disqualifying information is discovered after the patient had already started study treatment.

When elaborating a study-specific eligibility checklist, objective criteria should be recorded in a precise manner, rather than simply checking a "yes/no" checkbox: complete diagnosis, laboratory values (with normal ranges!), ECG or cardiac ultrasound parameters, etc. In some situations, especially those involving pathological and immunohistochemistry diagnosis, it may be reasonable to make the corresponding report a part of the eligibility package. Even if inclusion criteria are obvious and seem straightforward, for example, solid tumours' protocols usually have a requirement of at least one measurable lesion per RECIST 1.1 criteria, or revised response criteria for malignant lymphomas in lymphoma trials. There may still be a mistake in characteristics of nodal and extra-nodal lesions (different axes are used for defining if the lesion is measurable), besides which, patients may be stratified in accordance with the number or/and location of nodal and extra-nodal lesions, which also require verification.

A typical workflow of eligibility verification at PSI includes the following steps:

1. After completion of all screening procedures, the site will provide completed eligibility review checklist and copies of local screening laboratory and other reports, if applicable, to the PSI Medical Monitor at Study Code_MedicalMonitor@psi-cro.com. Such an email domain includes all medical monitors assigned to the study, project manager, senior clinical research associates (CRAs), and the project coordinator.
2. The PSI medical monitor will review the documents to ensure the patient meets all inclusion and does not meet any exclusion criteria.
3. If the PSI MM considers that additional data are necessary to confirm a patient's eligibility, or the submitted documents require clarification, s/he will contact the site as soon as possible and ask for clarification, or request additional data.
4. The timelines for eligibility review and confirmation are established on a study-by-study basis, but typically will not exceed 48 hours. It could be done on an expedited basis (within 1–2 hours), if requested by the study site in a case of an urgent randomisation, but it will require a perfectly prepared eligibility package and availability of the site team for resolution of medical monitor's queries, if necessary.
5. Once the PSI medical monitor confirms the patient's eligibility, s/he will sign the appropriate section of the eligibility review checklist and send to the study site and/or the clinical team for randomisation processing.
6. Original eligibility checklist with investigator's signature, and a copy of the checklist with medical monitor's signature and approval are filed in the on-site site file. All correspondence with the site, PSI clinical team, and the sponsor is filed by the responsible member of the PSI team in the appropriate section of the project master file.

Our experience of eligibility review in 30 Phase II-III randomised clinical trials within the last five years allowed us to identify the following categories of mistakes made by clinical investigators.

1. Incorrect assessment of the previous treatment of the disease under study; most typically in oncology trials it will be miscalculation of previous lines of chemotherapy, incorrect understanding of refractory disease definition, and the previous treatment of the disease that does not fit the protocol criteria.

In a Phase III study of Diffuse Large B-Cell Lymphoma, patients who progressed within 12 weeks after completion of the first line of chemotherapy were not allowed to enter the study, as well as those considered to have primary refractory disease. A patient was receiving the first line chemotherapy and was diagnosed with stable disease at re-staging after the 4th cycle. Due to that, he was switched to another regimen. Progression of lymphoma was revealed significantly after 12 weeks after initiation of the first line of chemotherapy. The investigator considered the patient eligible, based on more than 12 weeks from start of therapy to progression. However, the patient was rejected by the medical monitor, based on the primary refractory condition, which is defined as no response to the initial therapy, and includes not only progression of disease, but also stable disease[7]. And actually, lack of objective response led to administration of the second line of chemotherapy.

2. Use of unallowed previous, or concomitant medications.

The majority of study protocols have at least one medication-based exclusion criterion. It could be exclusion of certain medications (e.g. prior pemetrexed may be not allowed in NSCLC study), or a group pf drugs (e.g. prior and concomitant 5-HT3 receptors antagonists in study of chemotherapy-induced nausea and vomiting (CINV)), or exclusion is based on metabolic pathways (e.g. inhibitors of CYP3A4 or CYP2D6 enzymes). Obviously, tracking the last category of prohibited medications is more complicated and, to make it easier, as much as possible a comprehensive list of medications under question should be either included in the study protocol as an appendix, or provided to study sites as a separate document. Another matter to consider is that previous therapies for the disease under study are easier to identify and handle, as these medications are normally thoroughly tracked, and a mistake may occur as a result of an oversight. A typical example – in Phase II NSCLC study topoisomerase I inhibitors were not allowed prior to randomisation and while on study. The eligibility review form indicated that the patient had recently received topotecan, and this patient was not enrolled. A more complex situation is with concomitant medications. Needless to say, almost 100% of patients enrolled in oncology clinical trials use concomitant medications. The study sites should be instructed to methodically and accurately collect information about all concomitant medications used by the study subject within the protocol-specified timelines; for example, during the past 30 or 60 days. Particular attention should be paid to dietary supplements and over-the-counter medications, as sometimes patients do not mention them, especially when these are common medications to treat allergy or common cold signs.

3. Screening procedures performed not in accordance with the protocol.

From our experience, radiology assessments are the most frequently violated or misinterpreted at the screening stage. They include: incorrect radiology modality, performing procedure without contrasting in situations where the contrast is required, incomplete scanning, and misinterpretation of the lesions' dimensions.

4. Overuse of medical judgement, especially with the criteria that do not foresee any possible deviations.

There are a number of inclusion criteria that require an investigator's medical judgement per se, for example certain medical conditions, if not considered clinically significant by the investigator. Such criteria may need additional discussion between medical monitor and the investigator, considering the term of "judgement".

All these inconsistences had been identified by medical monitors during review of eligibility, and these patients were screened out.

At the same time, we have to admit that even a detailed and thorough review of eligibility does not guarantee 100% compliance. The main reason is unavailability of the complete set of information at the time of review. It may occur either by mistake, due to limited timelines, or, again, through misinterpretation of the protocol by the study investigator. Sometimes such situations are not straightforward. In a Phase II study of advanced gastric and oesophageal carcinoma, "intolerance to chemotherapy used in this study" was exclusionary. When the medical monitor was reviewing the clinical database, as a part of a periodic review, he revealed that the patient who had been considered eligible after a thorough review of eligibility was started on the study at a dose decreased by 30%. The investigator explained that the patient "was not fit enough to receive a full dose of chemotherapy". As a result, the patient was treated with a significantly reduced dose and died due to disease progression four months after initiation of the study therapy. This is below a median survival for this disease (nine months). The primary objective of the study was progression-free survival, and secondary objectives – overall survival and survival rate at 12 months. Thus, enrolment of this non-eligible patient had a potential to influence study objectives and statistical analysis.

Conclusion

Eligibility review is an essential part of risk-based monitoring and allows mitigation of enrolling non-eligible patients, ensuring safety of study subjects and providing reliable study data. We recommend using eligibility review, performed by CRO or/and sponsors' medical monitors, in every clinical trial. Depending on the complexity of inclusion and exclusion criteria and screening procedures, it may be either a simple check of investigators' statements confirming eligibility, or a detailed review of the eligibility packet, which may include pathology, radiology, laboratory and other reports. The process of eligibility review should be described in minor detail in the study-specific medical monitoring plan, and a review of patients' eligibility is to be performed by qualified medical monitors.

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