Successful Recruitment for Medical Device Clinical Studies

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Inadequate subject enrollment represents a significant obstacle during a medical device clinical investigation. It can lead to costly delays and jeopardise the success of an entire device development project. This article discusses the importance of devising an effective subject recruitment strategy so that clinical and regulatory requirements can be met.

Adequate number of observations

Clinical investigations are conducted to provide evidence, where necessary, to support medical device performance and safety claims made by the manufacturer. To do this, an adequate number of subjects must be enrolled and retained throughout the clinical investigation so that scientifically valid conclusions may be reached.

Medical device companies are discovering that this task, if not successfully performed, can seriously affect the success of a new product development programme. It can also affect the ability of a company to expand its performance claims or modify a product safety profile. This is because a clinical investigation that does not enroll or retain an adequate number of subjects may not be able to be evaluated and used to support performance and safety claims. When this happens, changes in the clinical investigation plan may need to be made or other measures taken to "rescue" the clinical investigation. If there are multiple or complex reasons for recruitment problems, the entire clinical investigation may need to be repeated. Many medical device companies are not in a financial position to incur these types of added costs or project delays.

Factors leading to inadequate enrolment

Factors that may lead to inadequate subject enrolment or retention include the following.

- The number of clinical investigations has increased and companies may be competing with other companies for the same clinical research subjects.
- Subject recruitment may be hampered by strict selection criteria, an inadequate supply of investigational devices, or other technical aspects related to the use of the device.
- Investigators and sites may be accustomed to recruiting patients from their normal patient population, but a particular device may require more active recruitment, which has not been addressed during study planning.
- Some companies assume that recruitment rates in one country are the same in another country and this is not always the case.
- Some companies try to use recruitment techniques that are effective for drug trials for medical device studies, which often require different techniques.
- Some subjects drop out of studies because of the frequency of follow-up visits that are needed to complete the study.

When recruitment targets are not met, sponsors may consider additional measures (rescue plans). These include opening additional sites to enlarge potential sources of recruitment, amending the clinical investigation plan or protocol to broaden the eligibility criteria, increasing payments to investigators, and/or investing in additional advertising. However, before instituting these types of measures, sponsors should identity the causes leading to inadequate subject enrollment. Otherwise, they risk implementing ineffective solutions and incurring →

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additional costs that do not resolve their recruitment problems. For example, a questionnaire may be used to determine the factors associated with recruitment problems and selecting suitable corrective actions.

Regulatory requirements

The European medical device Directives and guidelines do not specify any requirements specifically related to patient recruitment. Therefore, companies conducting studies that may be used to support United States (US) product approval or premarket clearance, or companies wishing to operate according to established regulatory guidelines, should refer to US regulations on subject recruitment. Under US 21 Code of Federal Regulations (CFR) Section 812.7, a sponsor, investigator, or any person acting for or on behalf of a sponsor or investigator cannot

- promote or test market an investigational device, until after the US Food and Drug Administration (FDA) has approved or cleared the device for commercial distribution.
- commercialise an investigational device by charging the subjects or investigators a higher price than that necessary to recover costs of manufacture, research, development and handling.
- unduly prolong an investigation.
- represent that an investigational device is safe or effective.

To assist companies in complying with these requirements, FDA has published guidance on patient recruitment practices.[1] Even though this guideline applies to clinical investigations conducted under US regulations, it describes practices that should be avoided, including those listed above, when conducting clinical investigations in Europe or elsewhere.

Review of recruitment materials

The US FDA requires Institutional Review Boards (IRB), which are equivalent to European Ethics Committees, to review, approve, modify or disapprove all research activities covered by IRB regulations, which are specified in 21 CFR Part 56. Furthermore, IRBs are expected to review all the research documents and activities that bear directly on the rights and welfare of the subjects of proposed research. Therefore, FDA expects IRBs to review the methods and materials that investigators propose to use to recruit subjects, including any direct recruiting advertisements. In fact, FDA considers this type of recruiting material as part of the informed consent and subject selection process. This policy and expected practices are described in the guidance document mentioned above and in another FDA guidance document for IRBs and clinical investigators.[2]

The European Directives or guidelines for medical devices do not address the need for Ethics Committees to review subject recruitment materials. However, companies should note that Ethics Committees generally operate on the basis of established Good Clinical Practice (GCP) guidelines developed for pharmaceutical clinical research[3] and now under the European GCP Directive for medicinal products.[4] For example, section 3.1.2 of the GCP guideline states that IRBs and Ethics Committees should obtain subject-recruitment procedure materials such as advertisements, written information to be provided to subjects and other documents. Article 6 of the GCP Directive includes the arrangements for the recruitment of subjects among the elements of a clinical trial that should be considered by the Ethics Committee when preparing its opinion on the trial. Because of this, some Ethics Committees have developed policies for the submission of subject-recruitment materials, although others have not.

In spite of this variation in Ethics Committee requirements, companies should consider including in their standard operating procedures a requirement to submit subject recruitment advertisements not only to US IRBs where relevant, but also to European Ethics Committees. This establishes a clinical investigation policy, which is particularly important for companies conducting multicentre clinical investigations that may be conducted in the US and in Europe or elsewhere.

Recruitment strategies

To begin the planning process, sponsors should identify any regulatory requirements or policies that apply to the review of patient recruitment materials for clinical studies. They should then develop a specific recruitment strategy for each product or clinical study with the aim of enhancing the effectiveness and rate of the recruitment process. Other activities that may be useful include:

- Obtaining approval for the recruitment plan from their appropriate corporate management.
- Ensuring subject recruitment materials are consistent with the information presented in the clinical investigation plan.
- Ensuring that advertising and recruitment material (notices of availability, direct advertising and educational material for research subjects) comply with applicable regulations or requirements of the Ethics Committees or Institutional Review Boards.
- Discussing the proposed subject recruitment strategy and any advertising material with investigators to obtain their agreement on the materials and to ensure that recruitment issues are adequately addressed.
- Ensuring that advertising materials are submitted for review to Ethics Committees or IRBs, as required, and addressing any concerns expressed by these groups regarding the materials.
- Implementing the recruitment strategy and monitoring subject recruitment rates so that corrective actions may be instituted if recruitment targets are not being met.

In addition, several approaches for enhancing subject recruitment have proved to be successful, depending on the particular investigational device and study population from which potential study subjects will be drawn. For example, the use of direct, noncoercive advertising and building productive relationships with site physicians and research coordinators have resulted in effective recruitment. ➔

Site personnel should be motivated to work closely with sponsors, contract research organisations, health-care professionals, community organisations, potential participants and their families to develop a network of referral mechanisms for ensuring that subjects are well informed about participation in a clinical research study.

For studies involving high-risk products, which may raise concerns in the potential subjects, sponsors should develop specific patient education and information tools such as brochures, newsletters and other advertising material, which can be used by the investigator for appropriately informing the community of the study and convincing patients to consent to study participation. Announcements developed for these purposes may be drafted by any qualified sponsor employee, a qualified clinical research organisation, or other qualified individual, on sponsor approval.

In contrast, patient outreach tools such as mass advertising with broadcast and print campaigns are methods that have been traditionally used by the drug industry, but these may be less cost-effective for device studies with multiple inclusion and exclusion criteria. This is because of the difficulty in providing enough information on these criteria to potential subjects to allow them to judge whether or not they would qualify to be enrolled into a particular study. As a result, this approach may result in only a small fraction of responders being eligible for the device study in question.

For the reasons discussed above, companies cannot afford to leave subject recruitment solely under the responsibility of investigational sites. Instead, sponsors of clinical investigations should develop a recruitment strategy as early as possible during the planning phases of the clinical study and certainly before the first subject is enrolled. They should actively assist clinical investigators in fulfilling their duty of enrolling study subjects. In addition, recruitment rates should be regularly assessed during the conduct of the study and the strategy modified when the expected targets are not being met.

References

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