



## EDITORIAL

### Patients' retention strategies in clinical trials<sup>☆</sup>



### Estrategias de retención de pacientes en ensayos clínicos

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Patient recruitment is a key factor for success of a clinical trial. Once this critical phase of the study ends, retention of recruited subjects represents a similarly important challenge. Regardless of the objective of research projects, the required data collection is only possible if and adequate and sufficient number of the selected subjects continue to participate throughout the trial.<sup>1</sup> There are however several reasons, beyond design, experimental drug, or type of study that prevent 100% retention of the initial population. Losses to follow-up may be due to health-related events, adverse events, or deaths, but also to personal circumstances of the recruited subjects, transfer outside the working area of each participating site, impossibility to complete the procedures due to incompatibility with the new working situation of the subject, etc. Thus, retention of enrolled subjects is essential for both scientific and economic reasons. If retention is not adequate, the data set to be evaluated may be insufficient, cause an excessive decrease of statistical power and/or introduce bias that invalidates the work done.<sup>2</sup> If the study conducted does not reach the initially planned validity, it will not be possible to achieve, for an experimental drug, that submission to regulatory authorities results in a change in its indications or other conditions for use. Retention of subjects enrolled into

a clinical trial is therefore crucial, especially in long-term studies such as, for example, cardiovascular studies in diabetes mellitus.

The design phase of a clinical trial implies determination of sample size. This calculation of the population required for a study should include an estimate of potential subject losses, so that the sample size is increased over the theoretical size required. This is known as loss-adjusted sample size.<sup>1</sup> Errors in this process may cause the trial to be completed without an adequate number of patients, with a significant loss of time and resources for patients and investigators. However, a trial with a mathematically appropriate design may not achieve an adequate retention level of subjects recruited, as there are uncontrollable and unpredictable reasons that may endanger the validity of the study. This editorial will address the possible strategies for patient retention in clinical trials, with a special emphasis on mid and long-term studies. This is an opinion article, mainly based on our personal experience in our current and other previous work centers.

First of all, the following question should be posed: why does a patient leave a trial? Besides the reasons for withdrawal defined in each study, there are both reasons independent from and dependent on the investigating site. As regards independent reasons, there is usually no action that achieves continued participation of the subject, and the only thing a site can do is to record in detail in the history and to report as soon as possible the reason for withdrawal. Examples of this would be a patient who moves to a distant town or, obviously, the death of a subject. Is there no possible solution? Occasionally, some of our patients who moved

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to another city agreed to return for the remaining visits, the study sponsor paid the travel expenses, and the site adapted to the visit times required by travel. This example is intended to emphasize the importance not to confuse an unavoidable loss to follow-up with one for an avoidable reason. It should not be forgotten, however, that retention has the limits involved in compliance with good clinical practice standards.<sup>3</sup>

When does the risk of loss to follow-up of a subject enrolled into a clinical trial start? From the first visit. Retention measures should therefore start at this point, and strategies should be designed in the protocol preparation phase. Most retention measures should be proactive, reserving reactive measures for unforeseen cases, and should be started from patient arrival to the site for each visit. For example, a poorly managed appointment book, which causes crowded waiting rooms, delays in care, or need for repeat appointment without sufficient advance notice will cause a rejection that may result in avoidable withdrawals. On the other hand, the investigating team should assess their barriers, resources, and time available to adapt themselves to their possibilities, avoiding implication in more projects than they can successfully complete.

At the time of recruitment, patients may perceive benefits<sup>4</sup> such as access to innovative drugs, use of drugs for indications not approved yet, or greater availability of resources such as, for example, unrestricted access to test strips for capillary blood glucose and ketones,<sup>5</sup> access to non-standard measurement procedures such as continuous glucose monitoring, or the possibility to contact investigators for any question or problem that may arise. They will however also have doubts because of the potential disadvantages of being experimental subjects, the uncertainty about the possible therapeutic effects, random assignment of treatment, and their lack of understanding of both the study treatment and what will be required of them as participants in a clinical trial. The healthcare team should win the trust of the subject, dispel any doubts, provide a list of all activities to be conducted during the study, and repeat these explanations as many times as required throughout the course of the study. Subject selection is a critical factor. If, after receiving all explanations, the subject is not clearly convinced of his/her participation, he/she should not be recruited,<sup>6</sup> because doubts may appear again and cause different problems, non-compliance, missing visits, and even withdrawal. The initial explanation phase has sometimes required several hours, several days, or repeat explanation to another person trusted by the subject such as a relative, non-healthcare staff, healthcare professionals, and even members of an ethics committee or, in one case, the subject's lawyer.

Selection of the trial for participation is essential for future retention. It is essential to evaluate not only the tested drug, but also visit frequency, duration, procedures to be performed, rescue measures, etc. Availability of an adequate, qualified, motivated, and experienced investigating team is another decisive factor. Strategies should be aimed at maintaining interest not only of the patient, but also of the staff involved. Staff motivations include the possibility to gain experience with new drugs and to provide patients more individualized care than allowed by standard practice and with less limited time and resources. Participation in

the study should only be decided if the joint response of the whole investigating team is positive. In our case, we become involved in a project if the required facilities are available and if, based on the above considerations, we think that we would propose participation to any of our acquaintances or relatives who met the predefined criteria, or we would participate ourselves.

In our view, the main reasons why subjects stay in a study include their trust in the investigating team, which should be maintained proactively, visit to visit, more careful monitoring, a personalized and close relation, the possibility to contact investigators by telephone 24 h a day throughout the year, and the perceived benefits.<sup>7</sup> Various reports have concluded that subjects enrolled into a clinical trial frequently obtain results which exceed their expectations for the tested treatment.<sup>8</sup>

In addition to the above discussed strategies, participation may have for the patients other advantages which are not essential, but contribute to their retention during the study. A complete report prepared by the site including patient history, diagnoses, treatments, course, and results will facilitate revision by and consultation with other healthcare professionals. Provision of drinks or snacks out of courtesy (coffee, light soft drinks, ...) or as needed (e.g. sugary drinks in the event of hypoglycemia) is also helpful. The sponsor usually promotes continued patient participation through various actions including payment of travel for visits, breakfast or lunch, if required, plus materials that help comply with procedures and/or adherence (pedometers, alarm clocks, blood glucose or diet diaries, bags for transporting heat-sensitive drugs, ...). In some long-term study our site organized, with funding of the sponsor and after approval by the relevant ethics committee, cooking courses for people with diabetes which were highly appreciated by the patients and even resulted in improvements in follow-up parameters.

In conclusion, patient retention is essential for a successful clinical trial.<sup>9</sup> Planning for patient retention should begin before study start, and the designed strategy should be followed at each study visit. The site will ultimately depend on its retention capacity, because this will affect its future recruitment capacity, as patients often say that they want to be informed about future projects, 95% would participate in another study according to some estimates,<sup>10</sup> and they will even help contact other potential candidates, their relatives, neighbors, or friends.

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