Learn more to do better... even for participants in haemophilia clinical trials

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Performing large, adequately powered and well-designed clinical trials is crucial for the development of new treatments and the assessment of their effectiveness and safety. This task is, however, difficult in the setting of rare diseases such as haemophilia, the frequency of which is estimated to be approximately 1 case per 10,000 men across all populations. In the recent, largest available phase 3 trial investigating a new recombinant factor VIII concentrate in previously treated adolescents and adults with severe haemophilia A, 150 subjects were enrolled in 15 countries and evaluated in an open-label study. This number is 100- to 150-fold lower than the numbers of participants in the phase 3 trials investigating novel direct oral anticoagulants in randomised regimens against warfarin in non-valvular atrial fibrillation. This problem of study size is even greater when specific subgroups of haemophilic subjects should be investigated, such as previously untreated patients or those with inhibitors, and explains the general low level of evidence of recommendations for management and treatment in this setting. Nevertheless, clinical research has led to dramatic improvements in the treatment of people with haemophilia over the last three decades, with the introduction of safe plasma-derived and, in particular, recombinant factor concentrates and the widespread implementation of prophylaxis to prevent bleeding and its consequences on joint health. People with haemophilia, at least in developed countries, can now count on a highly satisfactory quality of life, with reduced morbidity and a life expectancy approaching that of men in the general population. These exciting achievements have been made possible thanks to the continuous commitment of researchers, but also thanks to people with haemophilia actively and diligently participating in clinical trials. Research is now being conducted to develop new recombinant products with improved properties, in order to overcome the limitations of currently available concentrates, in particular by extending factor half-life and enabling a reduction in the frequency of infusions and, possibly, costs of replacement treatment. Various different biotechnological approaches and strategies for new products are being investigated, so that many clinical trials are currently ongoing and most investigators face difficulties in enrolling appropriate participants, competing among the relatively limited population of people with haemophilia. Moreover, the well-established, widely available, effective and safe replacement treatment in developed countries contributes to reducing the interest and motivation of people with haemophilia to become involved in new treatment investigations. Participating in clinical trials may result in better or as effective and safe treatments as those previously received; it is not, however, risk-free. An example comes from the randomised, international, immune tolerance induction (ITI) trial, which compared a high-dose (200 IU/kg/daily) and a low-dose (50 IU/kg three times per week) factor VIII regimen in children with good prognostic factors. The study was prematurely terminated in November 2009 because of safety concerns, as a significantly greater number of bleeding episodes in joint and non-joint sites was observed in the low-dose arm, at all stages of ITI, but particularly in the first stage, when inhibitors were still detectable. Similarly, a phase 3, double-blind, randomised study comparing a standard three times-per-week prophylaxis with sucrose-formulated recombinant factor VIII with a once-a-week regimen of the same product reconstituted with liposome solvent, previously shown to provide extended protection from bleeding, was prematurely discontinued because the investigational drug was associated with a higher bleeding frequency and failed to achieve the study end-points.

With the increasing need to improve patients' involvement in clinical research in these times of development of many products and treatment approaches, the study by Henrard and Colleagues in the present issue of Blood Transfusion is, to our knowledge, the first attempt to explore the motivations and perceived barriers to participation of people with haemophilia in clinical research. The Authors report the responses to a specific questionnaire sent to adults with haemophilia regularly attending a large Haemophilia Comprehensive Care Centre in Belgium. As probably expected, age was an important predictor of willingness to participate: only 3.4% of patients aged less than 45 years stated that they were not motivated vs 30.3% of older patients.
Among the latter, however, haemophilic subjects who reported having no knowledge about clinical trials were significantly less motivated (28.6%) than those declaring some knowledge of clinical research modalities (80.9%). A trend to greater willingness to participate was also observed with increased educational levels. Interestingly, despite concerns about possible risks of new treatments were considered as an important barrier to participation, time-consuming involvement with many visits to the hospital was the most reported obstacle for patients who would have been willing to participate in a clinical trial. Although the relatively small number of questionnaires analysed and the high proportion of non-respondents hamper more relevant insights from being drawn, the study highlights the need to address these issues more extensively and to find effective means to provide people with haemophilia with clear and unbiased information on clinical trials. Leaflets and the website developed by the Centre, as described in the paper, are useful strategies to improve patients’ awareness but they are likely to work in particular in subjects who already show greater motivation (younger and with higher educational level). Collaborative educational efforts of all health professionals, involving local, national and international patients’ associations, should be specifically devoted to increasing knowledge about the conduct of clinical trials, the relevance of patients' participation, the safety guarantees and the assessment of risks and benefits for the haemophilia community. In this respect, the commitment of physicians treating haemophilia and their long-term relationship with haemophiliacs and their families play a significant role in enhancing patients’ willingness to participate in clinical trials in a shared pathway towards the exciting expectations of current areas of research.

Disclosure of conflicts of interest

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References