EuroIntervention

Scientific societies and clinical trials

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The progress of medicine is critically dependent on the conduction of well designed clinical trials. Modern science was born when beliefs based on the authority of Aristotle and Galen left the way to systematic observation and experimental research. A strict methodology defining inclusion and exclusion criteria, modalities of therapy with random assignment to one of the test treatments as well as the blind adjudication of events has become a standard in all fields of medicine. Interventional cardiology, as we discussed in a previous editorial, is a speciality joining medical and surgical elements[1]. Clinical trials testing a new antiplatelet agent during angioplasty do not differ, except for the number of patients enrolled, from trials testing the same drug in primary or secondary prevention. When a technique is under evaluation, results are critically dependent on the quality of execution and, if results must be applied widely, proper documentation of the procedural results and a multicentre approach with an appropriate centre selection is of paramount importance. The analysis requires more than head-counting, with extensive procedural data captured in the case record form, quantitative coronary angiography and intravascular imaging performed at the end of the procedure and at follow-up. What should the role be of cardiology scientific societies in general – and of our Association in particular – with respect to trials in cardiology and interventional cardiology?

The ESC congress and EuroPCR: shop-windows for interventional cardiology research

The involvement of scientific societies in clinical trials is often limited to offer a forum to report them in their congresses and host final publication in their journals, guaranteeing a process of blind peer evaluation from independent reviewers expected to ensure the congress participant or the reader that a fair and complete analysis is presented. The return of European investigators to present their main trials in the congress of the European Society of Cardiology and to publish them in the European Heart Journal is a consequence of this growth, and a boost to further growth of both these main activities of our mother society. For interventionists, despite the record number of 13,109 participants at EuroPCR this year and the popularity of EuroIntervention with its record number of downloaded articles[2], we still have a long way to go to match the quality of trials reported in other general cardiology congresses and journals. We may also ask ourselves whether prompting all investigators of interventional trials to present them at EuroPCR is a legitimate goal in the interest of the interventional community at large. We want all cardiologists and medical professionals to become aware of the opportunities offered by interventional cardiology, and this is better achieved when interventional trials with direct general clinical implications reach a wider audience in general

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congresses and journals. A fair distribution with preference of more technical studies in the subspecialty journal and congress is likely to be the best compromise.

Do we do enough clinical research in interventional cardiology in Europe?

In Europe, private enterprises and market laws dominate the development of new drugs and devices while social medicine or health insurances tightly regulated by state laws are the providers of health services. Despite the relatively high volume of interventions, the average low price of devices makes Europe a relatively unappealing market. Interventional cardiology has been invented in Europe, and the first balloon and stent industry was European. In the pioneering days of the first PTCA courses in Zurich, US physicians were leaving Switzerland with suitcases full of balloons and guiding catheters. The greater opportunities due to the high volume of interventions and unregulated price of devices in the USA, along with the atmosphere of dynamic venture capital in the United States, facilitated the growth of start-up companies. These, then, have eventually transferred their technology to the three or four big names, who have, in term, inverted the balance, with Europe losing in the mid-90s its largest manufacturer of these devices. American companies have continued in the 90s to use Europe as a source of well collected information to improve and test new devices. In the last 10 years, tighter regulations and high costs have discouraged testing of new devices in Europe, with emerging high quality centres in Brazil and South East Asia taking over Phase 2/small Phase 3 device trials.

The relative ease of the approval process of new devices in Europe (CE mark)[3], focused more on consistency of manufacturing and safety and with the need of limited clinical data, is often criticised. In reality this process has allowed Europe to remain an essential part of the research plan of companies offering a leading role in large Phase 3 studies to well respected European investigators and CROs. The expected changes in these regulations will require that trials be conducted for the testing of "experimental devices", with soaring costs and tighter control. You may have a cynical view and say that as long as these trials are well conducted somewhere in the world, moving them outside Europe will not damage European patients and doctors. These trials, however, provide most European hospitals the incentive and revenues to maintain a vibrant research infrastructure, with research nurses and fellows available to support other independent projects. Many key lessons which guide our practice have been learned as a spin-off of these trials, especially since specific requests of the regulating bodies have led to include all-comers in these trials[4-7].

The conduct of strategy trials is increasingly difficult

The main problem of clinical biomedical research in Europe, however, is the absence of financial support and the difficulty of coordination of non-drug or device oriented supranational projects. There is no European NIH equivalent, and the limited public funding for biomedical research from EU sources and national countries is channelled into basic research. Strategy trials, testing techniques and modalities of treatment rather than devices are essential to drive our practice. Primary angioplasty for STEMI, the real revolutionary change in interventional cardiology, and the advantage of rapid angiography and angioplasty in the majority of unstable angina syndromes were tested in relatively small randomised single centre or national trials with limited industry support or sponsored by national charity funds[8]. These indications represent more than 60% of the PCI population in most centres. If these trials were not conducted and had not led to widespread changes in practice guidelines, interventional cardiology was due to remain a small, highly controversial, niche activity.

How are we going to find funding to support the next challenges, trials possibly supporting the expansion of interventional cardiology to multivessel indications and left main stenting, indications to recanalise chronic total occlusions, understand the best modality of treatment of bifurcational lesions, clarify whether there is real need for universal use of thrombectomy during primary angioplasty, explore the application of mechanical revascularisation early after stroke, promote the comparison of mitral clipping with medical therapy in secondary mitral insufficiency and heart failure, and test the use of transcatheter aortic valves in acceptable candidates to surgical replacement? Some of these projects were fully supported by industry in the recent past, like SYNTAX for 3V disease and left main, and we have new projects approved in the pipeline like EXCEL (left main stenting). The high revenues expected from transcatheter valve systems make it likely that sufficient funding will be offered by the industry. For other "minor" projects that still involve large populations of patients, big ideas have been allowed to sink because they are unaffordable.

How can a scientific society such as EAPCI support interventional cardiology research in Europe?

If outcome trials are so important, why not create a research organisation and ask the influential members of the Association to lobby for funding with the industry and charities as well as seeking government and EU grants? It seems logical, but there are important caveats to consider. The Association should be involved only in trials expected to answer general questions on the application of cardiovascular interventions and improve their results, and should not be involved in "commercial" trials such as studies testing a new device for registration purposes. Proposals should be received from individual members or Constituent bodies, such a National Societies, and the Association should select the most promising, likely to coagulate enthusiasm from investigators and attract founding sources. Those proposing should have a leading role, but the concept of Principal Investigator should be revisited. If the trial is made possible by the contribution of EAPCI through the identification and motivation of study centres, and its credibility facilitates securing the grant, the person proposing the initial project should work in close cooperation with the EAPCI Committees in every step of the

project, from design to conduct and preparation of the final report. The natural rotation of officers within the Association and its Committees should ensure a fair distribution of roles, with investigators active in designing trials or maintaining large enrolment and complete data collection selected to be next to act as PIs or Officers of the Scientific Committee. The Association should promote the creation of a research infrastructure in Europe to streamline the current complexity of the trial machinery. A database of centres interested to work in research, with a large number of patients treated for various pathologies, sufficient research personnel and previous experience in trials will be invaluable to expand the participation to centres outside the traditional group of partners active in European interventional research. Most European countries have developed PCI databases where 90% of the data requested are filled on-line by the investigators, by far a more reliable source than the off-line work of research personnel. The adoption of similar definitions, easier for percutaneous treatment of valve disease for which databases are not yet crystallised and new definitions (VARC) have been proposed[9], and should be promoted, following the model of CARDS. In many European countries these PCI and valve registries are part of the auditing exercises promoted by the Health Ministries and are supported by automatic links with the National Institute of Statistics, allowing tracking of mortality, mortality causes and, often, presence and cause of new hospital admissions. This has the potential of ensuring a reliable complete long-term follow-up at low cost. This may allow the effortless conduct, also in centres without a local research infrastructure and tradition, of large trials with universal enrolment of the population of interest. Upcoming features of the SCAAR registry include a built-in randomisation code for patients with demographic and clinical conditions meeting the inclusion/exclusion criteria with subsequent data collection performed effortlessly by the those investigators who need, in any case, to fill-out the institutional database for legal and reimbursement purposes. In my view, this initiative can be repeated and expanded if we succeed in integrating the existing databases of European countries and convince our members of the importance of this development.

Should we build CROs directly controlled by the Association?

This is not our opinion, nor is it the opinion of the current leadership of the European Society. CROs require continuity of work facilitated by the involvement in trials covering various aspects of medicine. Their role of independent control is better achieved when they are truly independent enterprises than when the controllers are paid by the same doctors who are the target of these controls. Simplification of work, when all data are electronically entered, with the generation of queries, monitoring and scientific analysis as main remaining tasks, ensures drastic cost reductions. A preference for academic non-profit oriented CROs can also help reducing cost, but this should not be at the expenses of quality which, for very large trials, can be probably achieved only by using commercial and well proven CROs.

The key message of this presidential page is simple and shared by the Chairs and Vice-Chairs of its Clinical Research and Registry and Database Committees. The Association should serve the research needs of the interventional community and support the proposals of its active members when they focus on subjects of general interest. This support can be expressed in various forms, from a generic endorsement, providing access to a list of research centres to promote a more European flavour, to full support integrating the project into the research portfolio of the Association and actively seeking sponsorship. A non-profit research foundation is required to provide money and distribute it to participating centres as well as a CRO. The complexity of preparation of research projects, especially in response to EU calls, requires a dedicated research infrastructure. By no means should these structures change the general model that sees Association activities performed by volunteers holding their position for a limited time, but a permanent and experienced staff will be required in order to be successful in the bidding as well as in controlling the appointed CROs and maintaining contact with the various investigators. These proposals are little more than personal ideas at this stage, and need to meet the agreement of our mother society, the ESC in order to develop a viable model for research in Europe. The EuroObservational Research studies, involving Associations and National Societies, has been promoted by the current ESC Presidency, with an opportunity offered to our Association to develop a European Transcatheter Valve Registry for 2010-12. This is certainly a step in the right direction, and the President-Elect, as well as the two candidates for 2012-13, seem to be willing to continue in this direction. The Program Committee Chair for Clinical Research and Databases and Registries decided not to present a still unclear program in the recent general assembly at EuroPCR in Paris. We count on your feedback to help us in delineating this programme and discussing with us, in the democratic spirit of our Association, during the next general Assembly in Stockholm.

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