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EDITORIAL

Investigator Initiated trials

In medicine, as in other worlds, fads and fashions come and go. The current hot medical fashions are for propensity analyses (which few of us probably understand), the “Heart Team” approach, and, in Cardiology at least, Investigator Initiated Studies.

The reasons for the proliferation of Investigator Initiated Studies (IIS) are clear - from the company point of view Industry does not act as overall “sponsor” of the study, and therefore their liability is limited. Costs are also fewer, and Investigators do more of the work. From the Investigator point of view, they have a chance to take their own idea to Industry and get it funded. They take more responsibility them selves but we all look after our own babies better than those of others !

Many companies have now realised the value of setting aside an annual sum of money to these potential sources of positive advertising and marketing, and the costs are usually a fraction of the costs involved in a company-driven trial - which have escalated to up to $60 million dollars in the last few years - a tough sum to recoup by any means !

Equally, there are now high quality Clinical Research Organisations (CROs) who will run the study on behalf of the sponsor (the investigator) and the costs will be met by the “surrogate sponsor” (the Industry partner). In this way, for a fraction of the cost and a fraction of the legal liability, the company and the Investigator can both participate in high quality research.

The issue of legal liability is tricky, and varies from country to country. This is a potential banana skin for the Investigator with plans to do an IIS across a number of countries. In the UK, there is the concept of “NHS Indemnity” which allows such studies to go ahead, but in other European countries, hospitals or investigators themselves may find that the insurance premiums associated with such IIS may make them prohibitive. Even within countries, the application of the rules are variable.

To those of you therefore who are considering an IIS (borne of my own personal experience of the pain of running such studies with limited support) I would say that it can barely be done successfully without a CRO partner, and that the Industry partner needs to recognise and pay for this aspect of the study. Especially for studies involving more than one country, the difficulties in making the Ethics applications, indemnity arrangements and contracts with the individual hospitals in different countries represents a major headache.

But for those who take an idea to Industry and have it taken on, the rewards can be great. Within a limited amount of time, and for a limited cost, a specific research idea can be formally investigated in a way which is rarely available to individual researchers outside their own national organisations. If you have an idea, many companies now offer Investigator-led programmes and these are well worth looking at for those with the drive and determination to see an idea come to fruition !

David Hildick Smith

The CERC / MCR merger

Initiated by Dr Antonio Colombo, this project has gradually come to fruition over the past year. In view of the CERC's growing renown in Europe, Antonio saw that, in addition to their common involvement in the field of interventional cardiology, the two companies had numerous converging aspects in their policy regarding the quest for excellence and cost-effectiveness in the clinical research services they provide.

MCR manages Italian and European clinical trials and the CERC French and European trials.

There is a long history of friendship and a close rapport between the founders of MCR and the Directors of the CERC.

Furthermore, the involvement of Alaide Chieffo as a CERC Council member has been instrumental in bringing the two companies together. It is anticipated, therefore, that she, along with Antonio Colombo, should become one of the prominent figures of CERC Italy, the new Milanese entity.

The two organizations will be in a position to manage jointly a number of European trials and more specifically, protocol submissions to the regulatory authorities and monitoring activities in each individual country where they will operate. MCR is particularly renowned for its corelab and a transfer of part of this activity to CERC is considered.

The Board of Directors is hoping that other dynamic and eminent Italian practitioners will soon become actively involved.

The objective of the CERC has always been to operate in a star-shaped pattern rather than concentrate all its teams in one place. This goal will be achieved through the merging of CERC and MCR and thanks to the determination of their respective boards of directors.

Marie-Claude Morice
CEO

Dr. Chieffo & Dr. Colombo

Latest info from CERC

ITALIC PLUS

The ITALIC PLUS multicenter, randomized trial is an Investigator-Initiated Trial which was designed in order to extend to other countries the inclusion of patients into the ITALIC trial, initially conducted in France. The objective of this study is to determine whether, after a period of 6 months following DES implantation in patients regarded as sensitive to aspirin, dual antiplatelet therapy may be replaced by aspirin alone. Primary and secondary endpoints, inclusion and exclusion criteria are identical and consequently, data of both studies will be pooled.
The international ITALIC PLUS trial has started successfully, especially in the United Arab Emirates where patient recruitment has been outstanding.
CERC is in charge of the study management.

CONNECT II

CONNECT II is a non-randomized, prospective, multi-center global clinical study of the Avinger Ocelot System used to cross chronic total occlusions in the superficial femoral and popliteal arteries.

This study was designed to evaluate the safety and effectiveness of the Ocelot System to provide OCT-assisted orientation while simultaneously crossing totally occluded femoropopliteal arteries. Connect II will include up to 134 subjects at up to 17 sites (14 U.S. sites and 3 E.U. sites). The primary efficacy endpoint was defined as successful femoropopliteal CTO crossing using the Ocelot System as identified by guidewire placement in the distal true lumen confirmed by angiography. CERC has been appointed as the CRO in charge of the study monitoring.

STRATO

This multicenter, prospective, non randomized study was designed to evaluate the efficacy and the safety of a multi-layer stent and its delivery system in patients at high risk presenting with type II and type II thoraco-abdominal aneurysm. This study should involve a total number of 33 patients.

The primary efficacy endpoint was defined as aneurysm exclusion and patency of the side branches (collateral branches) within 6 months after stent implantation. The CERC is in charge of coordinating the CEC, data management and statistical analysis.

CENTURY II

CENTURY II is a Prospective, randomized (1:1), single blind, controlled, non-inferiority multi center, two-arm trial. To demonstrate the safety and efficacy of the TCD-10023 sirolimus-eluting stent, by proving non-inferiority to the Xienceeverolimus with respect to the freedom from TLF at 9 months.
This study should enroll 1120 patients in up to 65 sites in Europe, Japan and other countries in Asia.

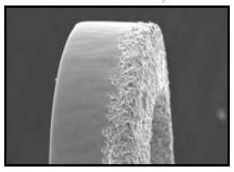
The Primary Endpoint of this study is the Freedom from Target Lesion Failure (TLF), a device oriented composite endpoint (cardiac death and MI not clearly attributable toa non-target vessel, and clinically driven Target Lesion Revascularisation (TLR)) at 9 months post stent implantation.

The CERC will be in charge of setting-up the e-CEC, DSMB and study monitoring.

PLATINUM PLUS

A **P**rospective, Randomized, Mu**l**ti-center Tri**a**l **t**o Assess the Everol**i**mus-Eluting Coro**n**ary Stent System (PROM**U**S Ele**m**ent) for Coronary Revascularization in a **P**opu**l**ation of **U**nres**t**ricted Patients.
An abstract presenting the procedural and in-hospital outcome of Platinum Plus has been submitted to the Hot line of the ESC 2012 Scientific Sessions.

Leaders Free trial



Most early randomized trials of DES focused on selected low-risk patient subgroups, considered best suited for the evaluation of a new technology. The past years, however, have seen some remarkable changes, both in DES design and in the trial methodology used to assess their impact on clinical outcomes.

The advent of metallic stent platforms with biodegradable polymers was one of these major steps forward in design, and the LEADERS trial, led by Stephan Windecker, pioneered the concept of "all comer" randomized trials in interventional cardiology. It successfully documented the similar early efficacy (Lancet 2008; 372: 1163) and superior late safety (Lancet 2011; 378: 1940) of the Biomatrix biodegradable DES when compared to the Cypher DES, a device that most interventionists saw as the gold standard in the field at the time.

In LEADERS, as well as in the subsequent "all-comer" trials, enrolled patients have however always been DES candidates, and therefore deemed suitable for at least 6 months of dual anti-platelet treatment (DAPT) according to current ESC guidelines. This in turn leaves 10-15% of patients with no alternative but to receive one or several BMS because of their increased bleeding risk, since a shorter course of DAPT is then considered sufficient. Very little is known about these "non-comer" patients, even though they definitely represent a very high risk subset. The availability of a new metallic drug-coated stent (DCS), the BioFreedom stent, entirely devoid of any polymer, now makes it possible to envisage having the best of both worlds: The BioFreedom DCS has been shown in the FIM trial to be superior to a paclitaxel-eluting DES in terms of efficacy, with an excellent in-stent median late-loss of 0.17 mm at 12 months, and, in terms of safety, it appears reasonable to expect that it will behave much like a BMS beyond the first month, at a time when 98% the drug (Biolimus A9) has diffused into the vessel wall (CircCardiovascInt 2010; 3: 174).

We therefore designed LEADERS-FREE, a randomized double-blinded trial to assess the combination of a short course (1 month) of DAPT with either the BioFreedom DCS (drug-coated stent) or the Gazelle BMS in patients with at least one of several criteria for an increased bleeding risk: advanced age, oral anticoagulant treatment, recent bleeding, anaemia, and co-morbid conditions such as chronic renal failure or cancer.
The trial has three central features:

- A focus on a "forgotten" patient subset
- A double-blinded design (neither the patient or the operator will not know whether a BioFreedom DCS or a BMS control is implanted)
- The use of two separate co-primary endpoints at 1 year: (BioFreedom vs. BMS) non-inferiority for safety (death, MI and urgent TLR) and superiority for efficacy (any clinically driven TLR)

Philip Urban
Associate Director

Advisory Board

The 2nd CERC advisory board was held on Monday, May 14th in Parc Monceau Chateau from just before the start of EUROPCR. This second edition replicated the model tested last year.

These meetings are divided into 90-minute sessions which are dedicated to each of the companies invited by the CERC Medical Council. The company representatives give a brief presentation of the topics on which the CERC medical council's advice is sought, and then the three 'burning' questions prepared in advance are freely debated under a confidentiality agreement.

Last year, the CERC was pleased to invite four companies, from start-up to major, to take part in an interactive meeting with the Council at no financial cost to them.

The outcome of this meeting was very fruitful with respect to clinical programs, market development and regulatory processes including reimbursement issues. It also proved to be an efficient tool for providing a better understanding of unmet clinical needs and of the suitability of the product pipeline to address them.

It is obvious that the sooner a clinical program involving products still in the development phase can be discussed, the easier it will be to carry out subsequent market introduction.

Should you be interested in participating in such a process, do not hesitate to contact us and please keep in mind that these sessions can be organized in conjunction with all major meetings attended by the CERC Council members. The format of these sessions is, of course, flexible, and can be adapted to your specific needs.

Bernard Chevalier
General Director

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CERC map & sites of council members

France - Germany - Israel - Italy – Kuwait - Latvia - New Zealand

Spain - Switzerland - United Kingdom