ICONE: An International Consortium of Neuro Endovascular Centres

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Summary

The proliferation of new endovascular devices and therapeutic strategies calls for a prudent and rational evaluation of their clinical benefit. This evaluation must be done in an effective manner and in collaboration with industry. Such research initiative requires organisational and methodological support to survive and thrive in a competitive environment.

We propose the formation of an international consortium, an academic alliance committed to the pursuit of effective neurovascular therapies. Such a consortium would be dedicated to the design and execution of basic science, device development and clinical trials. The Consortium is owned and operated by its members. Members are international leaders in neurointerventional research and clinical practice. The Consortium brings competency, knowledge, and expertise to industry as well as to its membership across a spectrum of research initiatives such as: expedited review of clinical trials, protocol development, surveys and systematic reviews; laboratory expertise and support for research design and grant applications to public agencies. Once objectives and protocols are approved, the Consortium provides a stable network of centers capable of timely realization of clinical trials or preclinical investigations in an optimal environment.

The Consortium is a non-profit organization. The potential revenue generated from client-sponsored financial agreements will be re-directed to the academic and research objectives of the organization. The Consortium wishes to work in concert with industry, to support emerging trends in neurovascular therapeutic development. The Consortium is a realistic endeavour optimally structured to promote excellence through scientific appraisal of our treatments, and to accelerate technical progress while maximizing patients' safety and welfare.

Introduction

Endovascular and percutaneous image-guided therapies of neurological diseases have introduced a new world of treatments, actual and potential, in the treatment of neurological diseases. New indications, novel approaches and the emergence of a rapidly proliferating array of neurovascular devices has created a challenge in the assessment of their relative safety and clinical merit. Conversely, many promising ideas from investigators and new enterprises cannot find the support and structure necessary to help

these important ideas come to fruition. The current system is deficient with infrastructure to aid investigators in the design of pertinent research, in support for application of peer reviewed funding, in construction of preclinical assessments and the execution of mandatory clinical trials. This article will review the current problems and propose a potential solution to promote research in neurointerventional practices.

The challenge

The neuro-interventional field is going through the growing pains of a new medical field at the edge of maturity. The therapeutic alternatives that it offers are becoming increasingly popular, sometimes without proof of their benefit. The array of available devices is rapidly proliferating, many being implanted into human cerebral vessels without prior demonstration of their safety or efficacy, and some without appropriate preclinical assessment. This type of clinical behaviour challenges the credibility of the specialty, and hampers progress and excellence in the management of patients.

With the increasing use of endovascular techniques, the medical device industry has recognized the rise of a new market. With industry investment comes technological growth marketing, and a whole new set of opinions promoted by powerful corporations. Technical advances are welcome, and industry deserves credit for the advances made over the past 15 years in neurovascular device technology, but independent critical appraisal of this rapidly expanding repertoire of endovascular devices is mandatory. Technology creates its own necessity[1] and the introduction of a new device on the market has become a sufficient indication for its use[2]. Many interventionists believe that a 'good practice' is an attempt to keep up with the ever increasing number of fashionable or 'state-of-the-art' devices that are introduced to the market at escalating costs. The literature about these devices is of poor quality, and at best confusing[2]. Continuing medical education is increasingly being delivered by symposia in which both speakers and audience are financed by the industry. It is unfortunate that over the last ten years we have treated patients, not necessarily using what works, or what has proved beneficial, but according to what industry tells us to buy. But should the industry be blamed? Its responsibility is to assure maximum profits at minimal risk to investors and shareholders. In this perspective, a good marketing program is more appropriate than a valid clinical trial, unless the individuals responsible for purchasing the material are more likely to be convinced by sound science than by fervid sale pitches.

We must remember that the safety of our procedures and devices is our responsibility.

As the specialty has evolved from a pioneering phase to a more standardized expertise, caring for patients with common clinical problems, and competing with alternative treatment modalities, some organized and rational method to discover and implement the right approach and technique for various neurological problems becomes inescapable. There is now an urgent need to justify our decisions and guide our actions on a rational and reliable basis. Fortunately methods to do so are well accepted in other fields such as cardiology, and they are scientific. Without science to guide our actions we are condemned to rely on biased and often misleading case series, authoritative opinions, sale pitches, custom or fashion[3-4].

Clinical research is the science of clinicians

Clinical trials frequently offer support and rationale for proposed medical treatments. Such trials however are sometimes perceived to be long and inefficient processes that impede progress. In spite of these shortcomings, clinical trials remain essential in the evaluation of novel therapies as well as assessment of new devices. For many of these therapies and devices preclinical studies remain insufficient or inappropriate. Hence clinical research remains a necessity. Clinical trials are only possible with the active participation of clinicians. Randomized trials continue to be considered the most effective means of determining objectively the relative efficacy of a novel treatments as well as determining their associated adverse event profiles. Clinical trials have shown their value in the evaluation of surgical techniques that were commonly performed without prior demonstration of their clinical benefit[8,9]. Clinical trials are not meant to substitute for clinical care and results do not apply uniformly. They are however powerful tools to provide facts as a basis for accurate clinical judgment and actions. Valid trials should address important clinical questions, as well as precede the widespread use of novel therapies. In the past the interventionist has of-

ten delegated this to others. Technical developments and the introduction of new devices were largely entrusted to industry. While industry as a whole behaves responsibly there is an inescapable inherent conflict of interest that exists. Hence trials in this field are frequently limited to non-randomized pilot studies, so-called safety studies, case series or registries, and regrettably, all too frequently the data is controlled by the industry [7]. This is not to suggest that we should delegate our responsibility to regulatory agencies. Such agencies roles remain essential in the regulation of manufacturing processes, quality control, and public security in a context of economic development and sales on a large scale. Regulatory bodies have proven not to necessarily be a rational agent capable of competence and discernment in the regulation of new devices. For example the approval, in the U.S.A, of devices on the '510(K)' clause are almost automatic, with little if any protection of patients at least in the neurointerventional field [10]. Regulatory agencies were not created to replace the judgment of clinical experts, to further science or promote progress in clinical care. A distinction between security, in the sense of control and power, and clinical care is crucial here, but it is unlikely to be perceived by such structures. They are not meant to regulate medical practice, and their actions are no substitute to the clinician's responsibility regarding the safety of their individual patients. Thus the design and promotion of trials on new treatments or new devices should not be delegated to the authority of distant bureaucratic agencies, but should come from a responsible autonomous initiative of clinicians themselves, those who care for patients.

Obstacles to clinical research and ill-considered effects of good intentions

There are numerous obstacles to clinical research. The endeavour is such a time-consuming, expensive, arduous task, that it is no surprise clinicians have been tempted to leave the field to drug and device companies that could hire the special expertise, devote the time, energy and budgets necessary to face the task at hand [7,11]. In keeping with a spirit of free enterprise and globalization, a world of stock exchange and returns on investments, public spending on medical research has decreased substantially in most western countries, and scientific and clinical progress has increasingly been relegated to industry. Developments propelled by private enterprise have increasingly focused on the potential for huge markets, involving large segments of the population of developed countries, 'medicalizing' many aspects of once considered normal features of human lives, such as aging, with its train of 'new' diseases, such as osteoporosis, andropause, impotence, alopecia, and anxiety, to the detriment of common but less frequent and more resistant clinical problems [12]. In response to this invasion of remedies offered to a substantial percentage of the population once thought to be 'normal', official organizations and public institutions have multiplied procedural, bureaucratic and legal controls that can simultaneously strangle real progress and assure that only the wealthiest and most powerful would succeed [13]. This evolution is only natural, since any research enterprise that would aim at palliating some of the woes of the human condition would now need to simultaneously nourish a long chain of essential experts and private businesses. These may specialize in official applications, patent writing, capital hunting, preclinical studies, regulatory issues, lobbying, procedure standardization, legal advice, insurance coverage, ethical and scientific consultations, trial monitoring, scientific editing, statistical expertise, quality control and marketing, ensuring that medical research remains a multi-million dollar business and that sick persons will continue to have the privilege of participating in the economic development of modern societies [11]. Since there is so much money involved, many consider that the responsibility of public and academic institutions, if not of professional associations, is to guarantee that they will not be exploited by the private enterprise, be liable to some responsibility, and to extract their fair share of revenues from this type of research. Hence may institutions will not even have a look at a clinical research project that does not assure a substantial financial compensation for the institution. Every bureaucratic structure has a strong and perhaps understandable tendency to forward it's own interests and much time and effort are devoted to forms, committees, contracts, and reports that purport to do things the right way and pretend to protect the patient but in effect are devoted to preserve the finances and good standing of the institution. The result of this system is that it commonly ends-up approving any trial sponsored

by powerful companies, who 'tick' all the necessary bureaucratic/financial boxes, even those trials that are disguised marketing vehicles for new products and devices. In the mean time, publicly-funded clinical research designed by clinicians for the benefit of patients (not considered as a market) are often perceived as suspiciously amateur endeavours that may drain the institution's resources. They have to run through the same procedures and confront the same obstacles as the medicine-as-profitable-goods programs [13]. In some legislation, even the text of the law assumes that research can only be piloted by the industry, as if physician-driven research for the sake of patients was no longer possible or advisable. There must be a way of doing clinical research in a different manner, and we must work hard on it. But unfortunately, there are other obstacles.

Other Obstacles: expertise in clinical trials and the clinical mentality

Many centres are entirely devoted to routine clinical procedures. Developments are often limited to training sessions in the use of a new tool under the supervision of a company-sponsored proctor. Indications for the new device, as well as their risks and potential benefits, are often unknown. Our field is just starting to integrate trials into clinical practice [14]. But the world of neurovascular specialists is too small to afford delegating progress to a scientific elite, while the majority of clinicians continue to practice 'standard care', often based on opinions and fashion. We must remember that clinical trials are not designed to impose science at the detriment of care. Trials are the means to use science as a tool to solve clinical dilemmas, and hence provide solutions to patients in whom no reliable information as to the best therapeutic option is yet available. A centre that participates in trials is one that continuously appraises the quality of its services, the rigour of its scientific knowledge, and the ethics of its practices. In this sense we all share a responsibility in participating in trials to advance our common objectives and to better serve our patients. It is a well recognized effect that clinical outcomes in units actively participating in trials are better than average overall, even amongst those patients not actually randomized into a trial. However, very few of us have the expertise in the design and realization of clinical trials. When industry contemplates the task involved in assessing a new device by a clinical trial, it faces a paucity of consulting expertise necessary to assure the scientific rigor of the protocols. There are few centres that can implement the exacting methodology, few interested individuals, a lack of standardization of clinical or radiographic outcomes, diverging poorly informed opinions, and the absence of an organized milieu. The enterprise becomes slow, ineffective, and financially risky to their organization.

When a clinician contemplates applying for financial support from public grant agencies, he has to compete with other fields and specialties that have a longer and stronger tradition in clinical research and evidence-based medicine, along with formal training in statistics and epidemiology. They also need to gather many clinical centres and colleagues that possess the expertise and demonstrate the will and time investment to proceed with clinical experimentation. An infrastructure possessing the capacity to provide expert advice and a network of participating centres that have shown their commitment to excellence will increase the credibility of the grant application immeasurably.

Even once a grant is obtained or a product approved, there is an increasing gulf between available resources and budgets necessary to perform trials in the current fashion. The result is that very few devices or treatments have been tested using standards of modern clinical research. We must in a collective effort, find the means to achieve the most rigorous scientific knowledge about our treatments while simultaneously minimizing obstacles and costs.

A solution: the formation of a consortium

The formation of a consortium with the intent of progress and excellence in neurovascular interventions may be a way of managing these difficulties. Goals would include: gathering the scientific expertise, the know-how of clinical trial realization; providing advisory or consulting services; constructing an international network of high-volume neurovascular centres, staffed with highly-skilled experts, communicating and coordinated in a central fashion; reporting in a standardized way the outcome of their treatments, whether positive or negative. Once a research program is designed, approved, or conducted by the consortium, which would represent a substantial portion of the world ex-

pertise in the field and be independent of extraneous influences, the outcome of the research will more likely to be accepted by the community of experts themselves. In this way promotion of a procedure or device will follow and not precede the demonstration of clinical benefits, and progress will continue in the interest of patients, not of industry or individual clinicians.

Proposed structure and characteristics

The proposed structure would be inspired by the Canadian Stroke Consortium [15]. The ICONE Consortium would be a not-for-profit organization, owned and operated by its members, who are leaders in international neurointerventional research and experienced practitioners in academic centres. The Consortium would bring competence, knowledge, and expertise to industry as well as to its membership across a spectrum of research initiatives such as: expedited review of clinical trials, protocol development, surveys and systematic reviews. The Consortium would provide support to clinical research design and help individuals apply to public agencies. Once objectives and protocols are approved, the Consortium would provide a stable network of centers capable of timely realization of clinical trials or preclinical investigations in an optimal environment. The Consortium could also suggest a uniform standardized agreement applicable to all participating centres and provide help in the submission of applications to various regulatory and legal bodies of each institution or country. The Consortium would represent a unified body of experts dedicated to work for the benefit of patients, using scientific rigor to test new treatments, and engaged in a long-term process determined to minimize obstacles that hamper progress in the medical care of patients and the developments in the neurovascular interventional field. The potential revenue generated from client-sponsored financial agreements would be re-directed to the academic, research and corporate objectives of the organization. For pragmatic reasons of making expeditious progress, the Consortium would be initiated by a group of founding members. Their task would initially be the production of a Charter that would enunciate the mission, function and composition, the rules and responsibilities of several necessary components of an international research consortium. The proposal would be to include an Ethics Committee, a Research Committee, a Credentials Committee and an Educational Committee. In addition, the charter would provide formal statements for the handling of important concerns such as expanding membership, conflict of interest, publication, and nomination-election policies. The Consortium would initially be hosted by an institution dedicated to academic research that would provide office space, communication, statistical, legal and clinical research services at no or minimal costs. The Consortium would be led by a Board of Directors, eventually assisted by a business manager. In the future, the consortium could be hosted for an agreed term by any institution elected by the Board of Directors, provided it can offer optimal conditions for the development of the Consortium; or it could become fully independent, if conditions permit and if such independence seems necessary for optimal functioning. The Consortium would use a web site, with both secured and public access, and a secretarial office. All activities would be controlled by an official independent auditor.

Progress

Since the pioneering efforts by A. Molyneux and colleagues, with the successful completion of the ISAT Trial, the value of the clinical research approach, funded by public agencies, has been increasingly recognized and the impact of results on everyday practices has been acknowledged and witnessed even in countries that have not directly participated in the research [16]. More recently, trials on the clinical value of new devices have been conducted with success; the HELPS trial has now completed the recruitment of 500 patients and the Cerecyte trial has recruited its 300th patient. These clinical trials conducted in an academic and independent fashion, but supported by industry grants, have already established that the necessary search for reliable evidence is possible. They have now set new standards for the widespread clinical use of new devices in our field: the demonstration that their use leads to better clinical results without increasing risks to counterproductive or prohibitive levels.

The TEAM trial, a crucial investigation into the potential benefits or harm resulting from the preventive treatment of unruptured aneurysms, a common procedure in many endovascular centers, is supported solely by public agencies [3,17-18]. The gathering of 60 international cen-

tres randomizing patients and collecting data for more than ten years is a unique opportunity to organize in a more stable fashion clinical research in neuroendovascular procedures. The PRET trial, aiming at finding the best treatment of patients prone to recurrence after endovascular treatment (patients with large aneurysms or with recurrences after previous coiling of the same lesions) is the first clinical trial proposed in the spirit of the ICONE network. The trial is dedicated to find the best treatment, between standard platinum coiling and the use of hydrogel-coated coils, in patients that do not constitute a profitable market for the industry and that are often excluded from trials on new devices. For obvious reason, the Consortium will first attempt to recruit experienced individuals and centres such as those that have been involved in these clinical research programs. They will form the nucleus of the Consortium, which remains open to all those interested. The Consortium is not meant to regulate clinical practices or research enterprises. Its primary intent is to offer expert consultation services to help those that aim at promoting progress in the clinical care of patients with neurovascular diseases and consolidate centres of excellence to implement clinical investigations.

Conclusions

ICONE is an instrument for the ethical, scientific development of modern neuroendovascular therapies. It is aimed at supporting sound clinical research, where the ethics and science of patient care are interwoven seamlessly. It is designed to promote confidence, trust and consistency in our endeavours amongst patients, clinicians and industry and to provide accountability. These principles will allow neurointervention to progress into a medical specialty underpinned by scientific reason with solid ethical standards. On such foundations we can face the future as a specialty with confidence.

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