Consortium funding strategy

In order to deliver on the credo that it is necessary to “team up for impact” in research, AO Exploratory Research (AER) adopted a funding strategy in 2009 which is novel to the AO Foundation. Instead of funding stand-alone projects from individual research teams, the AO Exploratory Research Board (AERB) is funding research consortia which work collaboratively, on a peer-to-peer basis, towards solving clinical problems. Consortium funds are distributed to research partners based on their project contributions. All projects applications are peer-reviewed by external reviewers.

Collaborative Research Programs

Bone repair/regeneration and cartilage-disc repair/regeneration were proposed by the AERB and approved by the Academic Council in 2009 as the two AER focus fields. Within each focus field there are one or two collaborative research programs (CRPs). Each CRP is composed of an international, interdisciplinary network of research teams which work on collaborative projects towards the consortium goal. To ensure proper function of the network, a “primus inter pares”—technically equal, but looked upon as an authority of the network, a “primus inter pares”—technically equal, but looked upon as an authority of the network—of collaborative projects of the new funding round. Participants of the meeting included several AERB members responsible for monitoring and guidance of the CRPs. At the end of the meeting it was decided that future annual meetings will be held at different research partner sites on a rotating basis. The 2010 annual meeting will be held at the Harvard Medical School in Boston, USA.

Outlook

By the end of 2009 the AERB initiated two new CRPs. One of them addresses the clinical problem of “Annulus Fibrosus Rupture” and the other, “Acute Cartilage Injury”. A program committee, including an external advisor, was assigned to each new CRP, with responsibility for establishing the corresponding research consortia. The plan is to have three CRPs by January 2011.

Large Bone Defect Healing

The CRP “Large Bone Defect Healing”, is aimed at finding solutions for healing large bone defects, a problem faced by many orthopedic trauma surgeons. This CRP entered a new funding round in January 2010 based on the consortium funding strategy. The fourth annual meeting was hosted in the Foundation’s headquarters in Davos. The meeting included a guided visit to the ARI facilities followed by summaries of the scientific progress achieved in the last twelve months. It concluded with presentations and discussions of the collaborative projects of the new funding round. Participants of the meeting included several AERB members responsible for monitoring and guidance of the CRPs. At the end of the meeting it was decided that future annual meetings will be held at different research partner sites on a rotating basis. The 2010 annual meeting will be held at the Harvard Medical School in Boston, USA.

Reorganization

AO Clinical Investigation and Documentation (AOCID) adapted its structure to take account of the focus on AO Specialties and to streamline its operations, leading to the closure of the US office in Princeton. All studies in this Region are continuing, with monitoring services outsourced where necessary and expert support provided by AOCID in Switzerland.

Studies

The year ended with 32 major ongoing studies at various levels of completion. Among projects concluded in 2009 was a pre-study investigating the handling and possible complications of the Angular Stable Locking System (ASLS) for intramedullary nails. Recruitment ended in December for a study examining the accuracy of navigation in the placement of sacroiliac screws. Nine clinics recruited 124 patients with 205 screws on schedule. Primary results will be available in mid-2010.

The recruitment end phase of patients for two studies which form part of the AO’s Clinical Priority Program “Fracture Fixation in Osteoporotic Bone”, was reached in 2009.

AOCID also proved its competitiveness in the commercial marketplace by submitting a Guided Visit to the ARI facilities to the commercial marketplace by submitting a Guided Visit to the ARI facilities. Ten clinics were awarded 218 procedures for the next year. Nine clinics were awarded 218 procedures for the next year.

Fellowship

Dr Joost van Middendorp from The Netherlands became the eighth AOCID fellow. He worked on methodological issues in spinal trauma research and attended the AO Davos Courses.

Publications and presentations

AOCID released a record number of 59 publications, presentations and posters and work conducted and published by AOCID in recent years can be found in 170 times in peer-reviewed publications in 2009.

A highlight was the positive reaction to the AO Symposium entitled “Evidence—Motor or Brakes” at the EKOU Congress in Berlin demonstrating the topicality of evidence-based medicine.

The AOTrauma Statistics and Data Management Handbook: A Practical Guide for Orthopedic Surgeons by AOCID Director Beate Hanson, Dirk Stengel and Mohit Bhandari was published.

AO Davos Courses

Results from the AOCID survey “We care for our surgeons” conducted during the 2008 AO Davos Courses were released in 2009. Analysis revealed that although the 519 surgeons who responded feel themselves to be in good health, they are aware that their job places a strain on them both physically and mentally.
Bone Defects. A strong effect has been shown of PRP (Platelet Rich Plasma) on BMSC osteogenic differentiation, and on endothelial progenitor cell proliferation and differentiation. A pilot sheep study showed the beneficial effect of this cell mixture together with PRP for large bone defect healing. This project forms part of the large bone defect Clinical Priority Program network.

Disc. Research related to intervertebral disc degeneration and regeneration has shown a strong effect of high frequency load and limited nutrition on intervertebral disc explants after seven days' culture in a whole organ bio-reactor. Cell viability decreased under both culture conditions and declined even further when both parameters were combined.

Stem Cells. The mechanoregulatory effects on mesenchymal stem cell differentiation have been investigated in order to define the exact molecular mechanisms underlying initial stem cell differentiation toward the osteochondral lineage. It has been determined that mechanical upregulation of TGF-β is an initial and fundamental step in this process.

Global Clinical Trial Management AG (GCTM AG): Contract Research Davos

In 2008, the preclinical division of GCTM AG offered the full range of ARI services to commercial sponsors. Studies conducted included the use of BMP and cell treatments for the healing of critical sized long bone defects, tissue reactions to bone filling materials in cancellous bone and iliac wing defect models, in vivo Xray CT analysis of rabbit radial and calvaria defect models, fracture fixation models, efficacy testing of resorbable implants, large animal rotator cuff injury models, and ex vivo biomechanical testing of new orthopedic devices. In 2008, the turnover of GCTM AG Preclinical Division amounted to 1.6 million Swiss Francs (+ 10% vs. 2007). All projects were subcontracted to the ARI which provided the required resources.

The AO Research Fund

The AO Research Fund (AORF) celebrated its 25th anniversary in 2008. A total of 97 applications requesting over 15 million Swiss Francs (CHF) were received. These applications were subject to a rigorous vetting procedure by an appointed pool of experts. At the end of this process, 22 new projects were approved in 2008. Five of these are focus grants and the other 17 start-up grants. The AORF currently supports 36 projects to the tune of 2.18 million CHF. The best research project is awarded the AO Research Fund Prize Award. This year’s prize went to Dr Wolfgang Köstler for the project, ‘Clinical applicability of computer-assisted arthroplasty using bio-engineered autografts’.

Providing a full range of services of the highest caliber to the clinical investigation community, AO Clinical Investigation and Documentation (AOCID) is an essential pillar of the AO that is highly valued both by internal partners and external customers.

Harvesting successful results

Following the reorganization of AO Clinical Investigation and Documentation (AOCID) in 2001, whereby its orientation was focused on conducting evidence-based trials, in 2008 these efforts bore fruit when a substantial number of study results were published in high-ranked medical journals. Among these studies was a randomized controlled trial that looked at the patient benefit from endoscopically-assisted fixation of condylar neck fractures. Another study considered the open reduction and internal fixation of proximal humeral fractures using the LPFP system. And a third study analyzed the effect of unrepaid ulnar styloid base fractures on outcomes after operative treatment of distal radius fractures.

In 2009, a total of 18 clinical studies are recruiting patients, and six are in the planning phase, demonstrating that AOCID is on the right path to successfully meet the needs of its customers. Among these efforts bore fruit when a substantial number of study results were published in high-ranked medical journals. Among these efforts bore fruit when a substantial number of study results were published in high-ranked medical journals.

Sowing the seeds of research

Continuing its tradition of fostering young surgeons interested in clinical research, seven surgeons have already completed fellowships at the AOCD office in Dübendorf. A particular highlight was that one participant successfully submitted his study results to the JOT halfway through his fellowship.

Based upon the results of a small survey conducted during the 2007 AO Davos Courses, AOCID decided to conduct a more extensive analysis under the heading ‘We care about you’ that looked at the mental and psychological health of surgeons. Elements of their health that were measured included the SF36, blood pressure, and heart rate.

AO COIAC: answering a clear need

The AO COIAC version 3.0, the comprehensive injury automatic classifier, was made widely available to the surgeon community. AO Portal. This is the first and most important step toward providing a more comprehensive and standardized documentation software tool for the AO community. Within the first month of its release, almost 600 surgeons registered to download the software.

Projects supported by AORF:

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<th>Subject</th>
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<tr>
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Clinical Investigation: putting patient safety first

With its highly sophisticated clinical studies, AOCID helps establish a better understanding of the outcomes, risks, and costs of fracture treatment, thus contributing directly to AO’s Mission of improving patient care.

A total of 59 studies kept AO Clinical Investigation and Documentation (AOCID) busy throughout 2007, demonstrating the continually high interest in evidence-based medicine among AO surgeons. Nine studies were completed, among them four multicenter studies which assessed outcomes of different treatment options for proximal humerus fractures (PHILOS, LPHP, PHN, and conservative). Economic aspects were high on the agenda, especially for third-party studies such as the retrospective cohort cost-effectiveness study conducted in Chile.

Demand also kept up for research-related services provided by AOCID, including the recently launched medical writing service. Due to high levels of interest, a second editor was employed to provide professional writing and editing services.

Excellence in clinical research

In accordance with AO strategy, a growing proportion of AOCID’s work involves complex study designs such as prospective cohort studies and randomized controlled trials. As opposed to simple case series, these can better answer specific questions about the efficacy and safety of fracture treatment, allowing a direct and valid comparison of treatment options. The fact that two current studies meet the stringent requirements of the US Food and Drug Administration (FDA) testifies to AOCID’s high quality standards.

To ensure this excellence, AOCID runs a state-of-the-art quality management system based on the ISO 9001:2000 norm. In 2007, the regular three-yearly recertification process was passed after only a few improvements. The auditors especially noted the institute’s professional competence in managing clinical studies and the high quality of documents.

AOCID also fosters young surgeons interested in clinical research with a special fellowship launched in 2005. Fellows spend a three-month period working with AOCID at the Dübendorf office. During this time they engage in study planning and monitoring as well as data analysis and medical writing. The six fellows who underwent the program so far are all enthusiastic about their experience, and the program is fully booked until 2009.

A growing global network

As a leading clinical research organization, AOCID relies on a comprehensive global network of study centers. This network has grown further in 2007 and currently numbers 163 reference clinics distributed throughout 23 countries. While most are still located in Europe, Asia and North America are showing dynamic growth.

In the USA, this development is being driven by AOCID North America (AOCID NA). Since its foundation in 2003 as a small satellite office, this organization has grown dramatically in both size and capabilities. It currently manages two retrospective and three prospective studies, with five more studies in the planning phase. In April 2007, AOCID NA organized a “Study Coordinators’ Meeting” to strengthen its relationship with the existing reference clinics and to further expand its network in the USA.

1 Beate Hanson, Director of AOCID, presents the latest clinical research findings at the 2007 Trustees Meeting.
With the completion of 13 studies, 2006 was a year of harvest for AO Clinical Investigation and Documentation (AOCID). Preliminary analysis indicates that these studies produced valuable new and sometimes surprising evidence for the practicing surgeon. Most of the findings, however, will not become available until 2007, as it takes six months on average after completion of a study to analyze and publish its results.

**Bigger is better**

New dimensions were reached in terms of study size. More than 600 patients were included in a comparative study concerning different methods for treating fractures of the proximal humerus: internal locking system (PHILOS), locking plate (LPHP), and nailing (PHN). This study investigated outcomes of conservative versus operative treatment of this complex fracture.

The global comparative study of the use of locking compression plates (LCP) in treating distal radial fractures also included over 600 patients. The three main arms of the study compared the use of plates of varying sizes (2.4 mm and 3.5 mm) and conservative treatment. An additional side arm focused specifically on China. Since fractures of the distal radius are the most frequent fracture of all, this study is of particularly high relevance for the practicing surgeon.

Despite their demanding character, both studies achieved a follow-up rate of over 80%. The follow-up rate indicates the percentage of patients initially included in the study for which a complete outcome record was obtained. An 80% rate is required to achieve scientifically sound findings which are representative of the entire sample group. With these two projects, AOCID has once again proven its ability to conduct complex multicenter studies with several side arms in a multicultural context.

**Mastering stringent FDA requirements**

While AOCID has run randomized trials for several years, an important milestone was achieved in 2006 with the successful start of the first Investigational Device Exemption (IDE) trial designed to meet the stringent requirements of the US Food and Drug Administration (FDA). Conducted on behalf of an external client, this trial investigates a synthetic bone filler used in cervical spine fusion. It started in the first quarter of 2006, and the database is expected to be completed within two years.

Clinical Investigation: reaching new dimensions

With the completion of its largest ever comparative studies and the preparation of a second FDA trial, AO Clinical Investigation and Documentation (AOCID) has firmly established itself as a leading clinical research organization. The strong increase in services provided by AOCID reflects the growing interest of AO surgeons in clinical research.
Key activities

Hopes that this first FDA trial will help establish AOCID as a clinical research organization in this demanding market have materialized more quickly than expected. Already, a second external client has chosen AOCID to run an FDA trial on its behalf. The setup is currently being prepared, and the trial is scheduled to be filed in spring 2007.

Increasingly complex study designs

In line with the strategic decisions taken in 2003, the general trend away from handling tests and case series towards the more demanding study designs of comparative studies and randomized controlled trials has continued. To make AOCID know-how in this field more readily available in the Americas, the US office in Princeton, New Jersey, was expanded in 2006 and staffed with a manager intensively trained at Swiss headquarters.

From among eight new studies initiated in 2006, two are directly related to the “Fracture Fixation in Osteoporotic Bone” Clinical Priority Program (CPP). They investigate complications related to osteoporosis in proximal humeral and distal radial fractures. Both fracture types are particularly common among elderly patients. AOCID was already strongly involved in the definition of this CPP, for example by providing extensive literature searches. Placing high priority on these new studies, it has continued its strong support of this program.

Another new project is a proximal femoral nail antirotation (PFNA) randomized controlled trial conducted in Spain. For the first time, this study compares the effectiveness of implants of two competing producers, in this case nails used for proximal femur fractures from Stryker and Synthes, Inc.

Strong demand for services

Providing research-related services, such as methodological support, literature searches, and the newly launched support in medical writing, is an important and growing part of AOCID’s work. The vast majority of these services are provided free of charge to surgeons from the AO community. However, external parties are also turning to AOCID, which illustrates the potential of these marketable services.

Teaching activities were also expanded in 2006 in Latin America and Asia Pacific, and a special certification is planned to ensure the future high level of AOCID clinical studies.
Annual Report 2005
Growing demand for clinical research

To meet the growing demand for evidence-based knowledge, AO Clinical Investigation and Documentation (AOCID) stepped up its core activities in 2005 while at the same time expanding into new areas including an FDA trial study.

Demand for evidence-based knowledge continued to rise in 2005, confirming the strategic goals of AOCID. In its core competence of clinical studies, AOCID initiated five new studies. Through its New York resources, two spine studies in North America were started under the leadership of the Scientific Committee (SciCom) with representatives from AOspine North America and AO North America, as well as AOCID. This successful new model, which unites the local specialty and AO organizations as well as international AOCID experts, may well lead the way for other specialties and regions. This development is supported by the continued expansion of AO’s clinical research network which creates a triple-win situation for patients, clinics, and AO. While patients benefit from independent studies and state-of-the-art knowledge in their regions, the clinics get evidence-based support and AO gains access to frontline surgeons. The option of setting up additional local resources is currently being examined.

All eyes on cost effectiveness
With increasing financial pressure on healthcare systems worldwide, cost-benefit analysis—an integral part of all AOCID studies since 2004—has gained in importance. In 2005, publications for the novel AOCID project with the Chilean Health Care Organization in Latin America went into review. A new study was initiated in Chile and another one in Mexico.

Ongoing clinical investigation in biotechnology
A large new study explores the benefits of COLLOSS. This substance is believed to induce osteogenesis in bone defects. Using high tibia osteotomy (HTO) as a standardized model, this randomized controlled trial focuses on the difference of patients treated with HTO receiving COLLOSS as an interponate and those receiving it without an interponate. The main outcome is early onset of bone healing. A second HTO study investigates whether HTO performed using computer-assisted navigation has lesser variance in the difference between the observed and planned correction angles in the leg axis than do nonnavigated HTOs.

The prospective bone-substitute study initiated in 2004 now includes more than the expected 60 cases. It was decided to extend the study to 12 months as the impact of the “chronOS Inject” bone substitute will be easier to evaluate.

Current studies and first FDA trial
With five new studies and six studies completed in 2005, AOCID is currently supervising 22 studies. A hallmark study initiated in 2005 is a US Food and Drug Administration (FDA) trial of the bone substitute P15. It is run in collaboration with the University of Washington in Seattle, the leading epidemiological university in the USA. Randomized FDA trials are considered among the most difficult studies. AO may leverage its expertise from this experience as the healthcare market is expected to request more randomized studies in the future.

Growing demand for AOCID services
The request by third parties for services continued to rise in 2005. In addition to clinical studies, demand was particularly high for evidence-based teaching activities (EBOS), which AOCID developed together

1 AOCID has been publishing extensively on study results and methods in peer-reviewed journals.
2 The progress of patient treatment is carefully recorded and then evaluated by the AOCID team.
3 Demand in 2005 was particularly high for training sessions on evidence-based orthopedic surgery (EBOS).
4 AOCID booths are an important platform for knowledge exchange and consulting.
AOCID was involved in four classification projects in different specialties. A web-based international multicenter agreement study with 275 fractures and 77 surgeons for the validation of the pediatric long-bone fracture classification was completed. Further evaluation is due in a prospective study. In addition, a comprehensive software solution for the classification of injuries has been advanced with the inclusion of a foot module and the Müller AO Classification of Long Bones.

In 2005, AOCID reached its strategic goal of increasing the proportion of RCT and comparative studies to over 50% of total studies.

Cost-benefit analysis:
**Conservative vs operative fracture treatment**

The importance of cost-benefit analysis is high as healthcare systems worldwide are struggling to contain cost. Where possible, the analysis includes a comparison of the benefits of operative versus nonoperative fracture treatment or other treatment options. Factors considered include the severity of the fracture type, the soft-tissue situation, and the socioeconomic situation of the patient.

As a rule, AO adopts the viewpoint of the patient. Studies are restricted to simple fractures for which the outcomes of operative and conservative treatments are identical. For example, the pioneer study in Chile from 2003 to 2005 showed that patients whose type-A tibia fracture was treated operatively were able to return to work (RTW) on average 85 days prior to conservatively treated patients. The extra cost for this reduction in RTW is USD 4,000. Decision makers use these results in combination with socioeconomic data. With an average local monthly salary of USD 100, the Chilean society, for example, is unlikely to opt for faster RTW.

A trend is emerging here toward more comprehensive health technology assessments (HTA), which go beyond cost-benefit analysis to include the standpoints of all players in a society. With its proven track record, vast expertise, and service orientation, AOCID is well positioned to be a preferred project partner.