Strategies to improve clinical research in surgery through international collaboration

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More than 235 million patients undergo surgery every year worldwide, but less than 1% are enrolled in surgical clinical trials—few of which are international collaborations. Several levels of action are needed to improve this situation. International research collaborations in surgery between developed and developing countries could encourage capacity building and quality improvement, and mutually enhance care for patients with surgical disorders. Low-income and middle-income countries increasingly report much the same range of surgical diseases as do high-income countries (eg, cancer, cardiovascular disease, and the surgical sequelae of metabolic syndrome); collaboration is therefore of mutual interest. Large multinational trials that cross cultures and levels of socioeconomic development might have faster results and wider applicability than do single-country trials. Surgeons educated in research methods, and aided by research networks and trial centres, are needed to foster these international collaborations. Barriers to collaboration could be overcome by adoption of global strategies for regulation, health insurance, ethical approval, and indemnity coverage for doctors.

Introduction

About 11% of the global burden of disease can be treated by surgery, and 80% of deaths from surgically correctable disorders occur in low-income and middle-income countries.[1,2] About 235 million major surgical procedures are done every year worldwide.[2] By contrast with the number of operations, few patients are enrolled in trials; for example, less than 1% of patients with cancer in California, USA, enrol in cancer trials.[3]

Key messages

- More than 235 million patients worldwide undergo surgery every year, but very few are enrolled in surgical clinical trials
- Benefits of global research collaboration include faster recruitment of patients, and larger trials with more generalisable results
- Barriers to collaboration could be overcome by adoption of common, global strategies in regulation, insurance, ethical approval, and indemnity
- Surgeons educated in specific research methods, aided by surgical research networks and trial centres, should foster collaboration in international research
- International research collaboration in surgery between developed and developing countries should result in capacity building and quality improvement, and mutually enhance surgical care
- Low-income and middle-income countries increasingly report much the same surgically treatable diseases (ie, cancer, cardiovascular disease, and metabolic disease) as developed countries; research collaboration is thus of mutual interest
- Emerging technologies, including telemedicine and web-based modules, might ease collaboration in surgical research

In terms of global and public health, disorders needing surgery are under-represented in funding and programme initiatives compared with infectious diseases (eg, HIV, malaria, and tuberculosis), although injuries are expected to supersede infectious diseases as causes of death in Africa in the near future.[4]

The number of global clinical trials is expanding, especially for novel drugs and biological agents, and developing countries are increasingly involved.[5] The number of countries participating in trials more than doubled during 1995–2005, from 33 to 77 of 150 countries included.[6] This increase was driven by lower costs (eg, in Latin America, Eastern Europe, and Asia), improved access to previously untreated patients, and improvements in health-care infrastructure in these regions. However, surgical trials have not undergone the same global expansion. Although widespread

Search strategy and selection criteria

We constructed a narrative Review on the basis of our experience in general and subspecialty surgery, including networking and collaboration across countries and continents. We searched PubMed, Medline, and Google Scholar with the search terms "surgery", "consensus", "multicentre studies", "international", "collaboration", and "research" alone or in combination, with a main focus on the past 5 years (January, 2007, to March, 2013). We examined reference lists of articles identified by this search strategy to identify other potentially important publications, including books and book chapters on related topics. Additionally, we contacted a network of surgeons around the world, representing surgical research groups, surgical societies, and surgical specialty representatives from all continents, of whom collaborators are listed in the IRIS ad-hoc working group (appendix).

infrastructure and coordination for research exists for pharmaceutical trials,[5] it is less developed in surgical disciplines. Achievement of global health goals needs a robust, competent, and professionally capable surgical workforce,[7] which is not available in many parts of the world.[4] Surgical services have focused on clinical goals, often at the expense of non-clinical activities. Surgeons in most countries cite excessive clinical workloads as the predominant reason for non-participation in research, although this factor is largely undocumented.

International collaboration in surgical research might improve the number of trials done, the quality of data obtained from these trials, and the generalisability of the results achieved. The potential for major public-health gains through international collaboration in surgical research is high. Examples of international research collaboration across countries of different socioeconomic development include the WHO checklist development in the Safe Surgery Saves Lives project,[8] the CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) trial[9,10] on tranexamic acid in trauma haemorrhage, and development of globally agreed metrics of outcome surveillance.[11] The potential benefits of research collaboration suggest that investigation into mechanisms to improve and enable collaboration are needed. Many potential impediments exist to international surgical research collaboration, although some examples of successful collaborations (table 1), including educational and networking initiatives[15,16] and randomised controlled trials,[8–10,17] have provided some solutions.

In this Review we aim to examine international research collaboration from a surgical perspective. We describe levels at which international collaboration can take place, provide examples of how multinational collaborations have been successful and might be enhanced in the future, and describe global aspects of collaboration.

The need for international research collaboration

The need for improved research collaboration can be considered from several perspectives. Research into specific disorders across different health systems should improve generalisability of the results, and fast recruitment into large trials made possible by international collaboration might clarify management of disorders with low incidence. Improvements in both areas might speed up adoption and breadth of specific practices. Additionally, some assumptions about the value of specific treatments might need to be reconsidered with more global evidence, because existing evidence is based on research done in a small number of countries. For example, large numbers of hip surgeries are done in the USA and Canada, but less than 10% of trials are from this region, with most randomised controlled trials done in Scandinavia and the UK.[18] Although developing countries might be

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See **Online** for appendix

	Applications	Examples
Consensus work	Agreement on definitions for complications, diseases, and outcomes; agreement on core database variables for data collection	PANCREA group on acute pancreatitis; Utstein template on trauma; the Core Outcome Measurement in Effectiveness Trials; IDEAL recommendations for surgical research on interventions
Capacity building	Assessment of surgical need by epidemiological investigations	Surgeons OverSeas (USA); Canadian Network for International Surgery; Surgeons OverSeas Assessment of Surgical Need survey tool
Case studies	Surgical safety programmes	WHO surgical safety checklist
Randomised trials	International randomised controlled trials of surgical diseases or interventions	CRASH-2[9,10] and CRASH-3[12] trials in trauma; COLOR I[13] and COLOR II[14] trials in colorectal cancer
Cohort studies or case series	Cross collaboration by national registries; international registries	International Consortium of Orthopaedic Registries; International Hernia Mesh Registry; European Registry for Abdominal Wall Hernias working group; LiverMetSurvey database
International audits	Audit of disease management across different countries; based on surveys, templates, or registries	Worldwide Esophageal Cancer Collaboration; transplantation registries and audits
Cooperation in health technology assessment		European Network for Health Technology Assessment and the EVIDENT database; Health Technology Assessment international; International Network of Agencies for Health Technology Assessment
Network and infrastructure provision in research	Creation of environments to foster collaboration and access to methods for conduction of research in collaboration	Comprehensive Clinical Research Network (UK); European Clinical Research Infrastructures Network; Study Centre of the German Surgical Society; Canadian International Network in Surgery
Evidence assessment and distribution	Establishment of best evidence for treatment of disease (for region)	Cochrane collaborations; South African Cochrane collaboration centre; organisations for health technology assessment
Standardisation for international reporting	Humanitarian crisis research	Harvard Humanitarian Initiative; International Standard Reporting Template for Surgical Care

IDEAL=Idea, Development, Exploration, Assessment, Long-Term Follow-Up collaboration. CRASH-2=Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage. CRASH-3=Clinical Randomisation of an Antifibrinolytic in Significant Head Injury. COLOR=Colon Cancer Laparoscopic or Open Resection. EVIDENT=Evidence Database on New Technologies.

Table 1: **Examples of international collaboration and research design**

considered an underused source of patients for clinical trials, the skewed distribution of patients in developed countries (where many procedures are done, but few patients are enrolled in trials) means that potential exists to increase the number of patients recruited in developed countries as well.

Understanding of the factors that limit participation in clinical trials is essential (table 2).[20] Ethical issues in international research collaboration should not be overlooked, and long-term solutions to dilemmas arising from the globalisation of clinical research need input from stakeholders in academia, industry, and regulatory agencies around the world.[6] Ethical and scientific integrity of surgical research must be ensured globally to promote harmonisation of international research goals and to provide information to potential trial participants about the benefits and risks of interventions, irrespective of nationality. These ethical challenges have been discussed by others,[21,22] and are beyond the scope of this Review.

	Impediments	Solutions
Surgeon-related		
Academic knowledge	Absent or inadequate knowledge among surgeons	Improved education for surgeons (eg, Masters-level or PhD-level training in public health, clinical investigation, or epidemiology) for better design of and recruitment to trials; increased collaboration with epidemiologists and statisticians in early planning of research
Monetary issues and reimbursement	Academic work is perceived by surgeons as being less rewarding in terms of pay and effort than is clinical work; competing interests of private practice, government practice, and academic work	Provide rewards for academic work, independent of scientific results (ie, reward investigators both on trial quality and on the direction of results, to avoid focus on positive trials only); reimburse surgeons for trial participation
Time	Clinical overload prevents academic participation; private practice is better paid and more secure than a research career	Create time for research and academic activity; support auxiliary personnel to help enable research collaboration
Preference or bias	Surgeon preference or unwillingness to accept uncertainty of unfamiliar techniques and procedures	Accept uncertainty or equipoise as not inferior surgical care through education and consensus; attitude change in surgical community
Experience	Surgeons inexperienced or untrained in alternative procedures or techniques	Ensure proper training in new techniques, instruments, and procedures before the trial start; adoption of recommendations[19] of the Idea, Development, Exploration, Assessment, Long-Term Follow-Up collaboration
Patient-related		
Participation	Not willing to participate in a study because of preference or invasiveness of the intervention; preference or bias towards new treatments	Education in necessity of trials; acceptance of uncertainty or equipoise as not inferior to surgical care; information and background on uncertainty of old and new procedures and methods
Autonomy	Culture-related difficulties in acceptance of randomisation to treatment	Education in the need for experiment to arrive at improved trial results
Patient health or demographics	Ethnic minority and elderly patients, and those with comorbidities, are less likely to participate in or be recruited to trials	Wider recruitment and inclusion criteria are needed to ensure valid trial results, and improve recruitment, generalisability, and statistical power
Methodological		
Inclusion and exclusion criteria	Too narrow or too wide	Wider recruitment and inclusion criteria to ensure more valid trial results, and improved recruitment and generalisability; adoption of pragmatic trials
Sample size	Difficulty in estimation of appropriate sample sizes resulting in convenient or arbitrary sample sizes	Investigators should do a pilot study to assess the ability to enrol patients and do power analyses to calculate the sample size needed, and understand the effect size and expected attrition rate before the start of the study
Outcomes	No agreed definitions or poorly assessed definitions	Use commonly agreed definitions understood by all investigators
Centre selection	Failure to recruit or comply to trial	Select appropriate sites, including multicentre, multi-investigator, and international collaborations; include a sham enrolment period
Facilities	Surgical wards and departments are not built for recruitment of patients and clinical trials	Recognise the need for outpatient or in-hospital research facilities for trial enrolment and follow-up
Social or political		
Legislative	Regulations differ between countries	Agreed, common international regulations
Religious	Could prevent certain tasks or interventions	Upfront agreement between trialists and researchers on issues of potential obstruction to collaboration
Ethical regulations	Vary between countries	Create an overall framework for ethical approval that global trials can adhere to, beyond existing ethical frameworks (eg, the Declaration of Helsinki)
Medical device regulations	Vary between regions	Agreed, common international regulations
Funding	Surgical research less competitive	Multicentre collaborations increase competitiveness for large research grants
Insurance	Might not provide cover across nations	International agreement of liability and coverage for patients participating in trials
Indemnification	Might not provide cover across nations	Create multinational trial insurance and indemnification
Language	Restricted language proficiency hampers full consent of patients	Local translation and adoption of protocols to the target populations by local investigators

Table 2: **Perceived barriers and solutions to improved collaboration in surgical research**

Clinical trial centres and research networks

Surgeon scientists need to be educated in the general principles of academic work, and the specific impediments (and solutions) to conduct of research.[23] Several recommendations have been proposed by Jarman and colleagues,[24] among which increased collaboration through networking and participation in trials is central. Indeed, promotion of early involvement in clinical trials for surgical trainees, and support of trainee-led research collaborations, should be pursued. Five collaborative research hubs for surgery have been formed in the UK,[25] with planned or ongoing trials that include foreign study centres.

Centres or networks for surgical trials could, in addition to their main goal of fostering collaboration,[15,26–28] also serve as clinical research sites for surgical research[29] or, as for drug trials, act as contract research organisations. Not much evidence about this approach exists for surgical research collaborations, but initiatives such as the Comprehensive Clinical Research Network in the UK and the European Clinical Research Infrastructures Network[16] could be explored for collaboration in surgical research. The European Clinical Research Infrastructures Network is a sustainable, not-for-profit infrastructure that provides information, consulting, and services to investigators and sponsors to assist in preparation and conduct of multinational clinical studies, and has unlimited scope. Most surgeons, unfortunately, are not familiar with the existence or range of these organisations;[30] increased awareness is needed. Conference participation and educational courses designed to recruit, train, and develop the skills of surgeon scientists and contributors to clinical trials deserve greater attention.

A further example of successful collaboration with increased international involvement is the Study Centre of the German Surgical Society.[31] This centre aims to transfer the notion of evidence-based medicine to surgery by planning, conducting, and analysing large national and international randomised multicentre trials in surgery.[32,33] The centre is open to requests from all German surgeons for support to implement any clinical trial ideas. Another important task of the centre is the acquisition of trial funding from government institutions or industrial partners. 2500 patients in more than 100 trial centres have participated so far.[32] German regulations have been changed to improve the conduct and execution of randomised controlled trials in surgery.[34,35] At present, most trials run by the Study Centre of the German Surgical Society are in Germany, but large-scale international multicentre trials (involving 22 hospitals across several European countries) have been completed with help from the centre.[36]

Barriers to research

Assessment requirements for new drugs, medical devices, and health technologies can vary substantially between countries. For example, although medical devices are not subject to the same strict requirements and regulations as are medical or pharmacological interventions in many countries,[37] some regulatory bodies in Europe now require proof of effectiveness from randomised controlled trials before market approval.[38] For manufacturers, test requirements, approval times, and reimbursements for new medical devices can substantially differ between the USA and European countries,[39] and differences in approval times or reimbursement can further affect where, when, and how the devices are brought to market or recalled for safety. These differences can discourage clinicans and patients from involvement in clinical trials of new medical devices (in comparisons with placebo or older devices) if the device is already available in a different region. Thus, mismatches in international regulations and guidelines can stifle publicly funded global research. This difficulty might be overcome by contract research organisations that are present in different regions and countries, and have sufficient local knowledge to take responsibility and organise international research collaborations in surgery across different countries. Such organisations should understand the feasibility of running a study in any country or region, have specific knowledge of the local regulatory landscape, provide appropriate training to primary investigators and coordinators (often across several cultures and languages), and be aware of adaptations that are needed to ensure the best chance of success.

In many countries access to health care is based on appropriate health insurance, but provision varies substantially, as reviewed in detail elsewhere.[40,41] High co-payments and lack of health insurance could prevent patients from taking part in studies investigating new and expensive surgical techniques or devices. The SAMMPRIS (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) trial[42] is an example of the successful use of a policy that balanced rapid access to innovative new procedures with the need to obtain rigorous evidence on risks and benefits before routine clinical practice. Free access to treatment with the stent was conditional on participation in clinical research.[43] However, this policy raises ethical concerns, including whether trial participants (or other patients in the country where the trial is done) will get affordable access to the device if any effect is proved and the device is available to purchase, but these concerns can be overcome. The government of Thailand insisted that trials into an HIV vaccine could only proceed if it was made available to Thai people if proven successful.[5]

Collaboration in health technology assessment

Health technology assessment—assessment of the costs and effectiveness of health-care interventions—is essential for management of health-care systems, but assessment systems for interventional procedures

(including surgical operations and minimally invasive procedures) are less developed than are those for pharmaceutical treatments. International cooperation and networking among organisations for health technology assessment could avoid duplication of effort and maximise outputs. Assessment systems have been introduced in some countries, but how they should be organised is debated, and no collated information about their location or operations exists. Findings from a survey[44] of organisations for health technology assessment in 25 countries showed substantial variation in the organisations' structure, assessment of available evidence, distribution of information, and use of available guidance from other countries. International collaboration in assessment of new interventional procedures could improve the efficiency of existing assessment systems, and make best use of the outputs of scarce international resources and skills.[44] Although international collaboration does exist through organisations such as Health Technology Assessment International and the International Network of Agencies for Health Technology Assessment, such assessments are done for different reasons by different organisations,[45] and recommendations are based on very variable evidence.[45,46] Although not much research has been done into the use of health technology assessment in low-income and middle-income countries, the use of available knowledge to help to build health-care-system and surgical capacity seems to have clear benefit.[47]

Collaboration during review and appraisal of the evidence is also important. The Australian Safety and Efficacy Register of New Interventional Procedures—Surgical, which previously only assessed safety and effectiveness of procedures, now includes guidance on policies and surgical training programmes and has a broad international approach.[48,49] On the basis of assessments by Plumb[46] and others,[49] international collaboration to gather new data could help to improve the evidence available to doctors and health-care systems. Furthermore, individual hospitals have initiated small-scale collaborations across international borders to reach common agreement on priorities and decisions when assessing health-care technologies.[50]

Definitions for data collection and comparison

The absence of proper definitions in various aspects of clinical research, including definitions of the disease itself (eg, severity), complications (eg, type and severity), or outcomes, has been overlooked in the past, preventing firm conclusions or even comparison of data between studies. Internationally agreed definitions are now available in several surgical specialties, and include defined international criteria for complications after pancreatic,[51,52] rectal,[53] or liver surgery.[54,55] Furthermore, collection of the same core variables by different registries is essential for comparison. The feasibility of collection of core variables has been studied for European trauma registries,[56] resulting in agreement of core data points for future collection,[57] which could evolve into a collaborative registry for trauma surgery across Europe to assist research across several countries for comparison of treatments, outcomes, and standards of care.

International collaboration in collection and collation of data can help gather information about real-world use of surgery in short timeframes.[58] In many surgical specialties, the scarcity of commonly agreed terms makes such work difficult. To assist registry research that is truly valid, standard definitions, development of common datasets (if necessary), and standardisation of device classification are needed. Several surgical specialties and disorders have established registries that cross national boundaries (table 1). One example is the International Hernia Surgery Registry, a multinational, prospective database involving more than 30 centres in the USA, Canada, Europe, and Australia, with explicit inclusion and exclusion criteria.[59] The registry has already produced results on inguinal[59] and ventral hernia repair.[60] Another example is an online platform for registration and outcome measurement of operations for ventral hernia (the European Registry for Abdominal Wall Hernias) with consensus on definitions for the data to be recorded.[61]

This approach could be used on a wider scale. The Worldwide Esophageal Cancer Collaboration includes researchers from 13 institutions across three continents (two institutions in Asia, two in Europe, and nine in the USA).[62] However, not all international registries have a truly global representation of contributing countries. The potential of large registries is obvious, but they need clear prerequisites for contribution to ensure quality, validity, and reliability.

Lessons learned from international research collaborations in surgery

Cardiac surgery

Although several examples of collaboration in surgical disciplines could be mentioned, we describe those that show methods for success or represent ways of enhancing international collaboration. The European Association for Cardiothoracic Surgery (EACTS) exists to promote and support all aspects of care for patients treated by cardiothoracic surgeons, encompassing surgical training, education, research, and quality improvement. EACTS established a database project in which information about patients from across Europe is collated and analysed to provide information and feedback for all stakeholders. The project data are published on the EACTS website, and contain information about patients undergoing adult cardiac surgery, with more than 1 million procedures from 29 countries and 366 hospitals.[63] Although EACTS is based in Europe, it has encouraged submission of data

from all parts of the world.[64,65] The report also includes data from Asia, represented by China (including Hong Kong),[63] and collaboration with Brazil, Russia, India, China, and South Africa (the BRICS countries), representing the emerging economies.[64] BRICS countries are quickly taking the lead in encouraging innovation, simplifying devices and processes, and applying newer, lower-cost technologies that are more adapted to consumers' needs.[64] For the purposes of comparison within the report, EACTS have grouped together countries into the large geographical zones of northern, central, and southern Europe, along with Asia.[63] For the first time, this allows investigation of differences in casemix and management on a global scale.

Orthopaedic surgery

Several advances in devices and surgical techniques have occurred in orthopaedic surgery. However, many of these advances have not been assessed in clinical trials or routine clinical use.[66] In recognition of the advantages of registries, the US Food and Drug Administration started a registry project specifically for orthopaedics, the International Consortium of Orthopaedic Registries,[66,67] to develop a scientific infrastructure through an international consortium between several existing national registries.[68,69] Several registries already had experience in collaboration with regulatory agencies; for example, the National Joint Replacement Registry in Australia collaborates with Australian national regulatory bodies and the US Food and Drug Administration, and the National Joint Registry in the UK collaborates with UK regulators.[66] Additionally, the initiative includes collaboration between the Australian and Norwegian national registries and the Kaiser Permanente registry in the USA to investigate synthesis of registry data. Such collaborations are important pilot programmes, and show the potential to assist, enhance, and expand existing research collaborations worldwide.[66] The conditions for collaboration in the International Consortium of Orthopaedic Registries include the use of standard definitions, incorporation of common datasets, agreement on standard implant classifications, and adherence to agreed rules for data ownership, sharing, and analysis.[66,67]

Humanitarian crisis situations

When disasters and major complex emergencies occur, especially in resource-poor settings, both governmental and non-governmental organisations can send foreign medical teams to provide humanitarian care. The teams might use participation in crisis management as a rehearsal in the possible event for disasters at home. However, surgical experience gained in these disasters might not lead to useful learning because of poor data collection and reporting standards. In a systematic review[70] of humanitarian surgical care, 185 reports in which surgical care was provided by a foreign medical team were examined, but only 11 articles could be included. The reporting of surgical activities varied substantially, with poor-quality reporting and unreliable estimates of both patterns of surgical consultations and data about burdens of surgical disease. Standardisation of data collection and reporting could improve knowledge of surgical disorders and operations done in crisis-affected populations.

To remedy this deficiency, the Harvard Humanitarian Initiative[71] has developed a form for collection of individual patient data, and an international standard reporting template for surgical care to record data about casualties affected by disaster and the pre-existing burden of surgical disorders in the community. The data collected include outcomes and perioperative mortality for patients undergoing surgery, along with referrals for rehabilitation and mental health and psychosocial care. The goal of the standard format is twofold: to ensure that all surgical providers, from first responders to national and international surgical teams, contribute to relevant and purposeful reporting, and to provide universally acceptable data to meet the needs of both national authorities and groups providing health care. The improved transparency and accountability provided by these forms should contribute to improved coordination, and help with objective assessments of the value of services provided to those affected by disasters.

Effects of technology

Electronic technologies, such as email and web-based support systems, enable researchers to communicate quickly and cheaply and to engage a wide audience. For example, efforts to improve definitions for acute pancreatitis were derived from a web-based international consensus conference that recruited more than 1000 physicians and surgeons from 77 countries, and lead to new definitions on acute pancreatitis.[72] A wide representation of researchers from different countries in research collaborations should yield increased validity of data and wider global adoption of the research findings. Internet-based modules could also aid research into relatively rare events such as equipment defects or device failures.[73] Investigators of a multicentre study of spine surgery in Germany reported that the number of cases recorded almost doubled with use of a web-based system, compared with paper questionnaires used in previous studies.[74] Web-based modules allow for real-time data capture. Software, questionnaires, and validation routines can be located on a central server, which can be accessed from participating hospitals with a standard internet browser. As reported by several studies in surgical disciplines,[73–75] this web-based approach reduces cost, can enhance participation in trials or registries, and avoids time-consuming installation of software in many different centres. Local data repositories do not need to

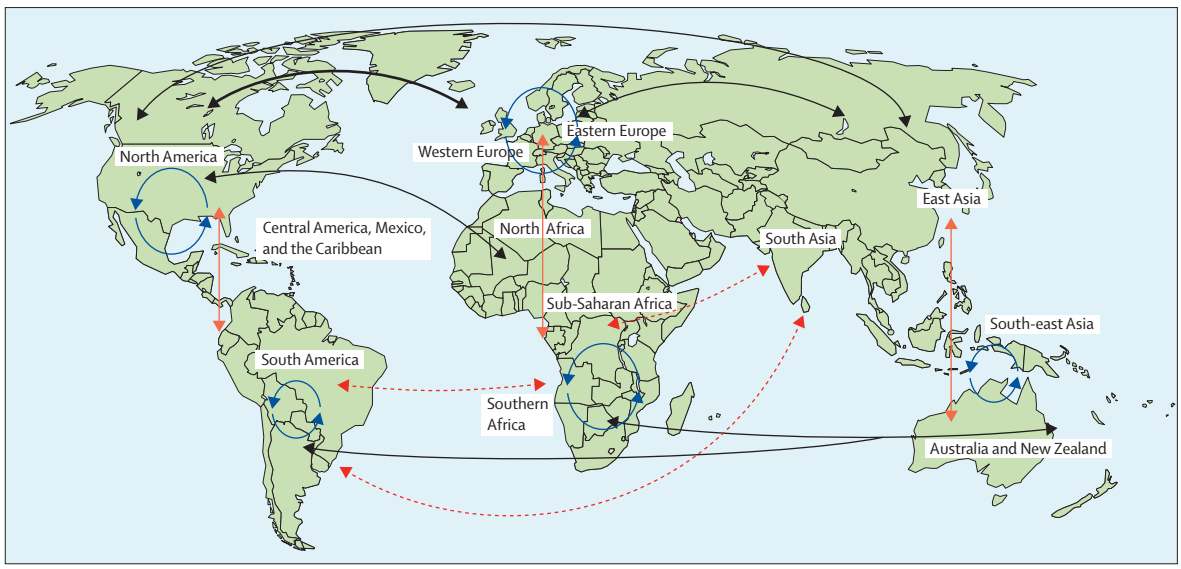

Figure 1: **International collaboration within and across continents and regions**
Arrows show either existing or strong collaboration (black arrows—eg, between Europe and North America), or proposed axes of collaboration between continents (orange arrows) or within continents (blue arrows—eg, within Africa, or within Europe). Red dotted arrows show potential international collaborations (eg, between South America, sub-Saharan Africa, and south Asia) that are either not described or non-existent at present.

be maintained, and transfer of data from paper reports (with its inherent risk of plotting errors) is not necessary. The success of web-based data collection systems has been reported by investigators of a multi-institutional study of urology in the USA,[76] and a bilingual English–German database for hernia repair.[77] Although international collaboration in surgical research is sparse at this time, web-based technologies could enable strategies for improved international research collaboration across continents and disciplines.

Programmes for integrative, collaborative, and translational cancer research across several national borders are underway;[78] such models could be investigated to establish their usefulness in surgical research. This type of collaboration is done with innovative techniques for collection and analysis of electronic information about patients, linked to prospective clinical registries and rapid learning systems. These learning systems allow for responses to the information gathered, such as correction of clinical practice for optimum care, and ensure reduction of errors. In cancer research two such systems are in place (the European EurocanPlatform, and the US CancerLinQ[78]), which integrate clinical, laboratory, radiological, molecular, and economic data. Such integrated systems can improve clinical care, and could also provide infrastructure to enable international collaboration in clinical research by sharing of patients' data, biological materials, and technological resources.[78] Surgeons should explore opportunities to use such systems in international collaborations.

Telemedicine, including consultation, support, education, and robotics, could become an integral part of surgery.[79] Incorporation of technology and recruitment of staff are only a few examples of how telemedicine can be used for research collaboration, but the specialty is developing. For example, the Raven-II platform for collaborative research on advances in surgical robotics uses open-source software (ie, Linux) to foster software development.[80] Although it is restricted to non-clinical studies, the system allows interaction among users, dissemination of results (including an electronic forum), sharing of software in an online repository, and the opportunity for incorporation in meetings and workshops at robotics conferences.[80]

The widespread use of social media and online virtual meeting rooms can enable networking and collaboration for study investigators, but these technologies might also jeopardise the conduct of research.[81] Not much research has been done on this topic, but findings from one study showed that participants were likely to seek information from websites and online forums that could potentially bias their views on participation and compliance in clinical research.[82] Identification of where and how potential trial participants obtain advice is an important component of clinical trial planning.[82] Because of the rapid increase in internet use for health-care information, a broad assessment of the benefits and potential risks of social networking among research participants before or during a clinical trial is needed.

Collaboration between different geographical regions

Collaboration in surgical research can take place across various geographical boundaries (figure 1). These collaborations range from those between countries with shared or similar legal and health-care systems and

languages (within regions, such as Scandinavia, or continents, such as Europe or North America), to those between continents or countries of different economic, social, and technological aptitudes (ie, between developed and developing nations; see panel). Additionally, researchers in developing countries in different continents can collaborate together to answer common research questions. As the distribution of diseases in emerging economies and developing countries begins to mirror those of developed countries (ie, increased mortality from cancer and cardiovascular diseases), the mutual interest in collaboration between researchers in developing and developed countries will also increase.[90]

Few registered trials (usually <10%) involve Asian, African, or South American countries.[91] However, regions with increased economic growth in recent years, particularly China and India,[92] have increased the number of patients, sped up recruitment, and reduced costs in trials. The large populations of India and China mean that many individuals affected by any surgical disease can be enrolled in trials done in these countries. The increased participation of Asian countries in global clinical trials should lead to greater appreciation of the value of evidence-based surgery in those regions.[92] Perkovic and colleagues[92] reported that patients recruited from Asian countries in the clinical trials that they assessed were more likely to complete study procedures and follow-up, and to adhere to allocated treatment, than were individuals from Europe and North America. In the ADVANCE (Action in Diabetes and Vascular Disease: preterAx and diamicroN-MR Controlled Evaluation) trial,[93] more than 90% of participants from Asia continued the randomised treatment on long-term follow-up, by comparison with less than 70% of participants from western countries. However, not many data exist beyond extrapolation from a few drug trials, and further experience is needed in surgery. Furthermore, acceptance of study findings and communication between surgeons to improve generalisability is needed in addition to international collaboration in trials.[15]

The gap in provision of surgical care between continents is a major concern.[4] Resources and performance are not comparable, and do not allow equal inclusion of patients with common surgical disorders.[94] This discrepancy, however, still provides research opportunities, such as mapping of the patients who need surgical care and establishment of methods for auditing and capacity building, which can help to create a framework of both clinical and research improvements.

Previously, global models for surgical care used visiting surgeons and trainees to make considerable short-term contributions in a so-called vertical manner to the health of local populations in low-resource settings. However, these models failed to increase local surgical capacity or address the burden of surgical diseases that accounted for substantial mortality and

Panel: Capacity-building programmes

The Canadian Network for International Surgery has created templates for structured surgical courses to train health-care workers in African countries. Course topics include essential surgical skills, trauma team training, safer surgery and obstetrics, burns, nursing, and others, and the courses are often linked to clinical databases to encourage the research component of capacity building. The network collaborates with several Canadian universities to implement these courses in their twinned institutions in Ethiopia, Haiti, Mali, Rwanda, Tanzania, Uganda, and Ukraine.

The course in trauma team training was first implemented in Tanzania in 2003, during which a trauma registry was discussed and implemented, as was previously done in Uganda. Several publications and presentations have been developed from databases arising as a result of these collaborations.[83–86] The fundamental component in implementation of the courses and registries is training of local leaders. When the course was later implemented in Kigali, Rwanda, in December, 2011, the Tanzanian course director travelled to Rwanda to share experiences of the early development of the previous course. Rwandan surgical leaders subsequently travelled to Tanzania to learn about course administration. The course has since been run in Rwanda six times.

Additionally, broad programmes creating or augmenting post-surgical training have also been implemented in Rwanda[87,88] and Guyana[89] with use of multidisciplinary approaches, in specialties such as surgery, obstetrics, anaesthesia, and nursing. The coordination of these programmes is achieved through frequent meetings of all parties, either through the Canadian Network for International Surgery, or the Canadian Association of General Surgery.

A global network for international surgery has been developed by the Canadian Network for International Surgery, and the online African Injury Database is an example of successes resulting from it.[84–86]

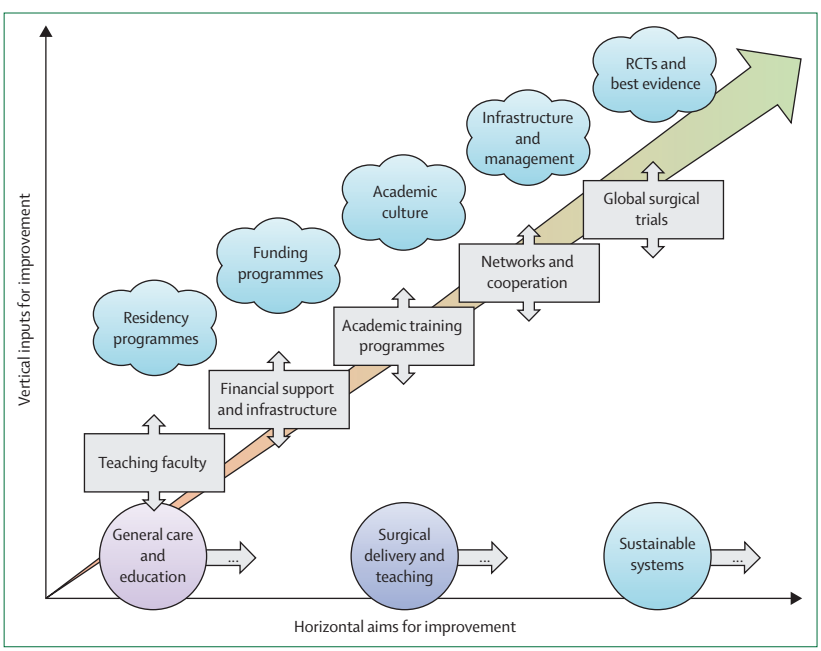

Figure 2: **Model for capacity building with collaboration in research and academic development**
The vertical model has been used to address infectious diseases and humanitarian emergencies. The horizontal model for health-care delivery tends to focus on long-term investments in public-health infrastructure and human capital. The so-called diagonal care-delivery model, as described by Patel and colleagues,[95] enriches surgical capacity through integration into sustainable, local care-delivery systems. Adapted from Patel and colleagues,[95] under the terms of CC BY 3.0. Copyright 2012 Pratik B Patel et al.

morbidity in the local population (eg, obstetric complications, trauma, and acute abdominal emergencies). Global health models have often used vertical approaches (such as targeted delivery of care to a medical specialty—eg, birth assistance, or hernia surgery) or have been based on horizontal aims (such as provision of electricity, running water, and auxiliary infrastructure). Alternative strategies incorporating both approaches have been used to overcome difficulties with the original approach. One example[85] used cleft lip and palate surgery to build surgical capacity through a so-called diagonal development model, combining vertical and horizontal aims (figure 2). As suggested by Patel and colleagues,[95] diagonal development not only imports clinical resources and services, with emphasis of deliverables that can increase capacity for one type of surgery, but also improves the medical and surgical capacity of local health-care systems. Thus, emphasis on diagonal development goals could result in improved infrastructure and manpower, and self-sustaining revenues, with positive implications for surgical care beyond the local area where assistance is given.[95] Much the same successes in countries in Latin America have also been reported.[83]

Augmentation of local health-care capacity through education, research, and increased human and material resources (such as that initiated by the Canadian Network for International Surgery in trauma care) has the greatest potential for effect (panel).[84–86] Several approved international programmes for research activity now exist in Rwanda[96] and several other African regions.[90,97,98] Formal investigative methods for research and evaluation of surgical capacity and need have emerged, such as the survey method used by the Surgeons OverSeas Assessment of Surgical Need in both Rwanda and Sierra Leone.[99,100]

For the **Canadian Network for International Surgery** see http://www.cnis.ca

Future directions

Active involvement of academics in research should be an essential part of surgical practice, not an optional extra.[101] The large number of operations done every year worldwide should allow for involvement by surgeons in clinical research. The present situation, in which few patients are included in trials, should be discouraged. Many of the barriers to recruitment of patients in modern trials are well described, and are not specific to surgery.[102] Improved academic leadership by surgeons in clinical trials could avoid the situation in which surgeons are minor players in clinical research, even for surgical research. Surgeons need to be trained in research skills, and encouraged to take part in international research collaborations. To paraphrase DeMets,[101] without academic involvement of surgeons essential research questions in surgery could go unaddressed, surgical diseases could be neglected, and surgical trials addressing important questions might never be done. To avoid delays in public-health improvements and unnecessary morbidity and mortality in surgical patients, international research collaboration should be pursued across surgical disciplines. The unrealised potential of international research collaboration should be exploited by surgeons to arrive at robust answers for questions about optimum treatment of patients with surgical disorders.

Contributors

KS, DA, AB, JB, CHD, JJE, and DCW planned the Review, contacted the network of collaborators for data acquisition, and did the first literature search. KS drafted the Review and tables. SC, DLD, PK, ROP, and YS participated in the literature search and covered their respective regions and surgical specialties. DLD and PK wrote the text for the panel. All authors critically revised the Review for content, contributed cited material, and edited context during revision. All authors revised and edited all sections of the Review, and gave approval for the final version to be submitted.

Conflicts of interest

We declare that we have no conflicts of interest.

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