

Report from Subgroup Education, Training, Infrastructure and Patient Involvement under OECD GSF Working Group to Facilitate International Cooperation in Non-Commercial Clinical Trials



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ABSTRACT

The rapid development and completion of academic clinical trials should be viewed as a priority in order to prevent disease, and to reduce the morbidity and mortality associated with disease. International cooperation in the field of multi-center clinical trials is essential for the optimal performance of this research activity. However, there are several impediments to conducting multi-center clinical trials. In recognition of this, the OECD Global Science Forum established a Working Group to facilitate international cooperation in non-commercial clinical trials. A major focus of this work has been on the need to improve supporting infrastructure, education and training of trial investigators, and patient involvement in clinical research. The present article describes the work of the Education and Training Subgroup of the OECD Working Group. This includes a description of the scope and status of related initiatives in these fields in different countries as well as consensus recommendations arising from the Sub-group. The report is one of the background documents for the final Working Group report "Facilitating International Cooperation in Non-Commercial Clinical Trials" from OECD-GSF
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1. INTRODUCTION

A Working Group was launched by OECD-GSF to facilitate international cooperation in clinical trials in response to an initiative from the German and Spanish delegations. This resulted in the report "Facilitating International Cooperation in Non-Commercial Clinical Trials," October 2011¹⁾. Leading up to this report, the Working Group conducted a broad survey based on interviews with international experts in various areas related to clinical research including representatives from health authorities, regulatory bodies, ethics committees, clinical researchers and others. In addition, three subgroups were established by the Working Group corresponding to areas representing major challenges for further development of international multi-center trials covering regulatory issues, risk-based approaches to clinical trials and the fields of education, training, infrastructure and patient involvement.

The present report is one of the background documents of the final Working Group report delivered by the Subgroup of Education, Training, Infrastructure and Patient Involvement. It contains information related to these areas from the survey as

well as descriptions of the status and initiatives around the world. In the last part of the report the subgroup presents its recommendations for strategies and actions to support international cooperation in clinical trials.

2. PURPOSE OF SUBGROUP COVERING THE FIELDS EDUCATION, TRAINING, INFRASTRUCTURE AND PATIENT INVOLVEMENT

Propose a set of recommendations covering the field of education, training, infrastructure and patient involvement to be discussed for inclusion in the final report from the Working Group OECD-GSF to facilitate international cooperation in clinical trials.

3. MEMBERS OF SUBGROUP

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4. RESULTS AND RECOMMENDATIONS FROM SURVEY

The main contributions and recommendations from the interviewed international stakeholders based on the survey are summarized in the following section.

1) Results of survey

Training of staff conducting clinical trials

According to Good Clinical Practice (GCP) principles, "the investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies) and should maintain a list of appropri-

ately qualified persons to whom the investigators has delegated significant trial-related duties.”

In all countries surveyed, investigators need to be appropriately trained as specified previously, but the training is not regulated by law and the content of the training is not specified. In addition, there is no mention of requirements for other staff involved in clinical research.

In some cases (for example, Canada, US), the medical curricula can include formal education in the regulatory issues and conduct of clinical trials.

Requirements and certificate or official recognition

In all countries, the training of investigators and staff involved in clinical research is available either through face-to-face training, tutorials, or e-learning and includes :

- GCP training
- In the US and for US funded projects : training on protection of human research participants
- In South Africa, initial GCP training is followed by a refresher course every 3 years
- Training on study specificities, therapeutic area
- Specific training such as data management, pharmacovigilance, coordination of studies for specific staff

A demonstration of skills can be requested by the sponsors, the ethics committees, hospitals, funders or research governance bodies, institutions, and auditors.

Ethics committees (EC) and IRBs are responsible for checking the suitability of the investigator and staff participating in a given clinical trial. Some ethics committees in Europe have issued a catalogue with training and experience required to be part of a clinical trial as an investigator. In Germany for example, ethics committees request 2 days training of investigators and coordinating investigators should have in addition at least 2 years' experience in clinical research. They are also considering adding a refresher course after 2 years.

But even in countries where such catalogues exist there is no harmonization at the national level and no common requirements across the ECs.

Sponsors (mainly commercial, but also institutional), infrastructure and support organizations have their training rules and request mandatory training that goes beyond the basic GCP training for their own staff and for the investigators and the investigators' staff they work with.

Although most of the training organizations (private or public organization) provide a certificate of achievement or completion there is no official certification or national recognition.

Infrastructure and support that exist for training

- In all the countries surveyed there are no structured or coherent public offers for training of staff conducting clinical trials.
- There is a lack of resources and funding for academic institutions
- Training can be provided by :
 - Support organizations (such as clinical trials units in the UK, Coordination Center for Clinical Trials (KKS) in Germany, R & D offices, clinical research centers in South Africa, New Zealand, core institutions designated by Ministry of Health, Labour and Welfare (MHLW) in Japan)
 - Competent authorities
 - Non-profit organizations (examples : European Organization for Research and Treatment of Cancer (EORTC), Vienna School of Clinical Research, e-learning organizations funded by members states (European and Developing Countries Clinical Trials Partnership : EDCTP)) other examples of this include the GCP web-based training that is mandatory for all participants working on NCIC-Clinical Trials Group (Canada) trials¹.
 - Universities
 - Hospitals
 - Private organizations (either face-to-face training or e-learning)

¹<http://www.ctg.queensu.ca/membership.html>

No coordinated initiatives were collected, except the one developed by the KKS network with a working group dealing with standardized content of the training program and the evaluation of the programs. For many investigators, one of the main sources of training on clinical trials remains the pharmaceutical industry or Clinical Research Organization (CRO).

Training for ethics committees members

- In Europe, there is no obligation or definition on the training required for ethics committees' members in the Directive.
- In the UK, there is an assessment of the competencies of the ethics committees and a national training facility provides training courses for ethics committees' members.
- In Norway, a three-day training period is mandatory at the beginning of the mandate, but updating competencies is the responsibility of each member. In addition, regular meetings are organized to harmonize the practices.
- In South Africa, the National Health Research Ethics Council (NHREC) is a statutory body responsible for the national oversight of research ethics committees and processes. The NHREC provides common guidelines for ECs and plans an accreditation process to assist ECs to reach the same level of quality.
- In the US, there is no formal training program for members of local ethics committees although many training courses are available from scientific societies.
- In Japan, the education of ethics committee members is required by the Ethical Guideline on Clinical Research and is provided by institutions, but the content and training methods are not harmonized and vary from one institution to another.

Training for patients' associations or lay people

For patients' associations or lay people, the main source of information or training is provided by

disease specific groups or organizations and the focus is on the disease, with a lack of information on clinical research, on how research works, the value of research, and how innovations can be provided to patients.

There is usually no coordination between groups to share basic information on clinical research and provide tools to train the citizens and patient advocacy groups.

Patients' associations are not always involved in the IRBs.

2) Recommendations

- Training and education programs should be developed at the European level or better still at an international level with a common syllabus. The Innovative Medicines Initiative (IMI) initiative would be a good approach² for developing a common framework.
- The knowledge should be included in the initial training.
- The development of a clinical trials "license" was proposed by several interviewees. There is a need to really demonstrate that people (including all staff and not only the investigators) are correctly trained. Realization of audits to evaluate the training, to verify that people acquired the knowledge and the ability to perform studies, could be considered.
- Academic infrastructure for training should be developed and the cost of training must be taken into account and either covered by the funding for the infrastructure or by the funding for the project.
- Training should not be limited to GCP but adapted to the specific needs of the study and continued during the whole duration of the project. A real clinical research culture needs to be developed. The objective of the training should be clearly specified and people need to understand their role in clinical research.

²Innovative Medicine Initiative : <http://www.imi-europe.org/Pages/topic.aspx?Item=9> & ListId=DA41E506-DF1A-46A3-A541-548CE8F0D9B5

- Clinical research should be made more attractive and a carrier development promoted.
- Standards should be established with minimal requirements valid everywhere.
- The teams should all be trained with different modules.
- The regulatory bodies including EC and CA should be trained.
- Training should be included in funds either for infrastructure or for projects.
- Core training for all countries in the world should have the same basis everywhere (see core competencies proposed by the Clinical and Translational Science Awards (CTSA)³).

From patients' perspective :

- Comprehensive networks of centers to share basic information on clinical research and provide tools to train the citizens and patients advocacy on clinical research and their disease should be established⁴.
- The transparency of clinical research should be enhanced by developing registers on clinical trials including the results of clinical trials.
- Patients or patients' associations should be involved early in the discussion of clinical projects and in the decisions concerning the use of funds (as for example in Japan, the establishment of a national cancer control board where patients have rights and can vote on the decision and can provide recommendations on how to use the budget to make clinical trials more efficient).

5. STATUS AND INITIATIVES IN DIFFERENT PARTS OF THE WORLD

The following section gives supplementary background information from different parts of the world describing the status and initiatives in the field of education, training and infrastructure related to clinical science.

UNITED STATES

Education, training, and infrastructure for academic clinical trials : current status in the US.

1) Education and training

There are several levels of training in clinical research : that which is incorporated into standard educational programs in medical and paramedical fields, and specialized training that may be obtained by those whose careers will focus heavily upon such activities. There are no requirements that physicians, nurses, statisticians or pharmacists responsible for research programs have advanced training, but the increasing regulatory demands and complexity have increased both the demand for such programs, and the need for formal training if investigators are to successfully meet all the requirements.

Professional education and training

In US schools of medicine and nursing, the basic curriculum generally includes the topic of clinical trials to develop the basis of evidence in medicine. This is aimed at enabling practitioners to appreciate the basis of evidence and interpret the literature ; it is insufficient preparation for investigators, site managers or research coordinators. In addition, at US universities, students majoring in biostatistics, epidemiology, or public health receive didactic education on clinical trials as part of their education in bachelor's, master's and doctoral programs.

Numerous US universities offer one-or-two-year graduate programs in clinical trials for doctors and nurses. Support for many of these programs comes from the US NIH.

Post-graduate training for physicians occurs in two phases : primary specialty training (residency), which takes places in the initial post-graduate years, usually lasting 3-5 years, and postdoctoral fellowship for those pursuing such training (postgraduate years 4-9), which includes further instruction regarding clinical trials, as well as opportunities to participate in clinical research.

³<https://www.ctsacentral.org/core-competencies-clinical-and-translational-research>

⁴For example : <http://www.healthtalkonline.org/> (formally DIPEX)

The bulk of formal training in clinical research for physicians occurs at the fellowship level (PGY 4–9). Subspecialty training is usual for physicians pursuing a career in academic medicine. In addition to the training incorporated into fellowship programs, many professional societies organize short (often one-week) courses on clinical trials, some of which are also supported by the US NIH. Many institutions/university hospitals also offer lecture series on clinical trials for both physicians and nurses, with 1–2 hours of didactic teaching about clinical trials given every week for one or two semesters.

In the US, pharmacists generally receive on-the-job training about clinical trials when they work in centers active in clinical research. Pharmacists who specialize in research often have doctoral degrees in pharmacy (“PharmD”) and focus heavily on research activities. The specialty of Pharmacology has assumed increasing prominence in hospital systems and withered in basic science departments in medical schools.

Additional training for professionals (physicians, nurses and pharmacists) varies in intensity. Certificate programs in clinical research are pursued by many who feel they need additional formal training but do not want to pursue a full degree program; this path is taken largely by those who engage in multicenter research or conduct research as part, but not a major focus, of their overall career activities.

Increasingly, those whose careers are built largely around design, organization and conduct of clinical research elect to pursue master’s or doctoral degrees in clinical research, epidemiology or biostatistics. Many of these courses are offered by schools of public health, and are supported in part by NIH funding.

Education of support personnel

Training for data managers/clinical research associates is available both in short courses and on-line. The Society of Clinical Research Associates (SOCRA) has developed an educational curriculum for data managers and offers examinations leading to

certification. The Association of Human Research Protection Programs has developed an educational curriculum for administrators of local ethics committees and offers examinations leading to certification.

Research administration at institutions requires a unique set of skills in research administration/management, contracts and grants management, financial management, intellectual property and technology transfer, training and educational programming, human resources management, regulatory compliance, ethics and IRBs, information services, or many other areas. Both formal training program and on-the-job training are common for research administrators.

There is no formal training program for members of local ethics committees, although the relevant professional society does offer both on-line and in-person didactic teaching.

Education of the public and of potential participants in trials

The US government, NGOs, research institutes, universities, hospitals and professional societies have developed extensive public education programs on clinical research and trials. These include programs targeting the general public, as well as programs targeting patients with a specific diagnosis and their families. The educational material available includes print, video, and web content.

2) Infrastructure for academic clinical trials

The NIH, both through its National Center for Research Resources, and through individual NIH institutes, underwrites much of the infrastructure for academic clinical trials at both the national and institutional/university hospital level. In addition, local institutions/university hospitals devote some of their own budgets, often supplemented by funds raised through charitable campaigns, to help support the infrastructure costs for academic clinical trials, including the costs of local ethics committees and clinical trials offices. Mechanisms for NIH support include both support for ongoing clinical trials networks, as well as grants and contracts for specific

trials. On a per-patient basis, however, the money provided by NIH, charity, and local institutions/university hospitals is generally less than a third of that paid by industry for trials of new pharmaceutical agents or devices. In general, NIH funding does not fully cover the costs incurred by the institutions to conduct research, while industry payments allow the institutions to more than cover costs and make a profit.

Ongoing clinical demands often leave doctors and nurses with relatively little time to plan, implement, or conduct academic clinical trials. Just as the US healthcare system is fragmented, so is the US system for academic clinical trials. Only a small fraction of patients in the US has access to academic clinical trials. For example, less than 3% of adult patients with cancer, most of whom are cared for in non-academic settings, enroll on NIH-sponsored clinical trials. In contrast, over 95% of pediatric oncology patients are cared for in teaching hospital settings, and over 60% enroll in trials. Integration of academic clinical trials into the healthcare system is also fragmented. Not all the various health systems in place in the US, for example, have agreed to pay the routine patient care costs associated with clinical trials.

CANADA

The current status in Canada for education, training and infrastructure for academic clinical trials is described below.

1) Education and training

Formal education in the regulatory issues and conduct of clinical trials is a component of most medical curricula in schools of medicine in Canada, but is not standardized. Most medical students are exposed to the principles of Good Clinical Practice (GCP) as a part of the medical curricula, and the methodology and biostatistics of traditional clinical trial designs (phases 1, 2, 3 and 4). The bioethics of clinical research are taught within the curriculum and are measured as exit competencies in most curricular

models. This includes the principles of informed consent of trial subjects, reports and access to clinical trials. The exposure to these elements in the formal curriculum in non-medical health professional education programs is inconsistent. Specifically, pharmacists, nurses, rehabilitation therapists, and biostatisticians have varied exposure to the principles of clinical trial conduct.

Postgraduate medical training provides access to specialized programs that incorporate advanced curricula in the methodology, design, evaluation and conduct of clinical trials. This may be done through a two-year clinical investigator program, recognized by the Royal College of Physicians and Surgeons of Canada, designed to augment the number of clinical scientists in academic centers. Alternatively, trainees may choose to pursue a master's level degree during their postgraduate medical training. This is often a master's degree in Clinical Sciences, Community Health Sciences and Biostatistics, and/or Healthcare and Epidemiology. Embedded within the curriculum of these master's programs is an advanced understanding of biostatistics, clinical trials methodology, and biometrics. A smaller number of individuals may choose to pursue a doctoral level degree (PhD) in these areas as a component of their education and training.

Beyond postgraduate medical education in the core disciplines, fellowship training or sub-specialty medicine training is usually structured for those seeking to pursue a career in academic medicine. Under these circumstances inherent in most sub-specialty fellowship programs are core curricular elements around biostatistics, bioethics, clinical trials methodology and regulatory policies.

Additional training for pharmacists, nurses and other health professionals is available in the form of a master's- and/or Doctoral-level degree program of the same nature as those available to physicians. The evolution of doctoral degrees in pharmacy has fostered greater interest in the regulation and conduct of clinical trials. More recently, with the devel-

opment of Schools of Population and Public Health within existing universities, there has been increased interest in both the provision of formal courses and access to these in the domain of clinical trials methodology.

2) Education of the public

This process is still somewhat limited in Canada, and is primarily related to non-governmental organizations, and disease-specific advocacy groups. For example, the Heart and Stroke Foundation is promoting the conduct and inclusion in clinical trials of patients affected by cardio-vascular disease. Similarly, the Canadian Cancer Society Research Institute and the Canadian Cancer Society promote conduct and inclusion in clinical trials related to cancer. However, this is not coordinated at a broad level across all disease sites, or broadly in healthcare.

3) Infrastructure for academic clinical trials

The infrastructure for the conduct of clinical trials in Canada is varied. The Federal Government does issue guidelines and regulations applicable to clinical trials in Canada through Health Canada, and also through funding agencies at a federal level. However, the actual delivery of healthcare is provided at a provincial- and/or territorial-level. The conduct of clinical trials involving drugs is regulated by Health Canada Food and Drug regulations. Additionally, this may also be the US FDA regulations. Health Canada approves applications for clinical trials, changes to the protocol, premature discontinuation of trials, and reporting of serious adverse drug reactions. It requires that good clinical practice guidelines are mandatory, and the investigational product must be labeled specifically for the trial. Health Canada may inspect sponsors and/or sites. The Research Ethics Board (REB), or the Institutional Ethics Committee, is responsible for safeguarding the rights, safety and well-being of all trial subjects, especially vulnerable subjects, and is responsible for obtaining and reviewing protocols and amendments, recruitment procedures and advertisements, investigator's brochures and information, investigator's curriculum vitae and

qualifications for a trial, informed consent and updates, any information provided to a subject, subject payment and compensation, and any other information that the REB might require. The REB is at an institutional-level. In addition to Health Canada and the Institutional REB, there is a Tri-Council policy statement on ethical conduct for research involving humans. The Tri-Council are those Canadian granting agencies, including the Canadian Institute for Health Research (CIHR), the Natural Sciences and Engineering Research Council (NSERC), and the Social Sciences and Humanities Research Council (SSHRC). These granting agencies will not only fund individuals and institutions in the conduct of clinical research, but ensure the ethical conduct of research. This is not a force of law, but a widely adopted ethical standard for human research.

In addition to Health Canada, the Tri-Council granting agencies and the Institutional REB, there are varying levels of infrastructure support provided. The most robust is that provided through the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG), which requires that all investigators complete specific GCP certificates and modules on a regular basis, with regular updates. These modules include an introduction to GCP, investigator responsibilities, investigators responsibilities as related to informed consent, ethics and the ethics research board, and safety reporting. All five modules must be completed within the Clinical Trials Group. There is a web-based educational modular training utility that is available to all investigators once provided access by the Clinical Trials Group. This utility is regularly updated, evaluated and monitored. It is specific to cancer trials, and is not included as a core component of all other chronic disease trials and/or disease sites. However, all investigational new drugs are under the regulatory authority of Health Canada, and compliance with GCPs is mandatory.

4) Patient engagement in clinical trials

The expectation in Canada is that patients and their families together with lay representatives of the public will have input into the design, conduct, and dissemination of the results of non-commercial clinical trials. This is multi-faceted. There is some federal oversight provided through the Ministry of Health and the Canadian Institutes of Health Research (CIHR) and additionally, there are disease site specific strategies for this.

The Canadian Institute for Health Research, which is one of the major competitive research funding agencies in Canada for health and life sciences, has a specific strategy on patient oriented research. This is currently being implemented with broad based principles that require patient engagement and input throughout the process. In addition to specific patient and lay representation on various committees, there is an informal open process through a “café scientifique” that has been posted on the CIHR website (www.cihr-irsc.gc.ca) that allows for a direct interaction between the public and scientists in any given health field as the research strategy is developed and implemented. CIHR also has a specific framework for citizen engagement. This framework is to help guide the CIHR in developing a cohesive and consistent approach to engaging citizens in its research processes including participating in decision making and informing strategic priorities. This key document is available on the CIHR website. It is guided by five principles that include :

1. Working with citizens will add value to the program or project.
2. Mutual learning/understanding will build trust and credibility.
3. Openness will enhance transparency and accountability.
4. CIHR will be inclusive in its approach to citizen engagement.
5. Citizens will be supported to ensure their full participation.

It is also noted in Canada that disease site spe-

cific agencies provide strong patient and public input into the research process, and also advocate for research in their particular domain. Such agencies as the National Cancer Institute of Canada Clinical Trials Group, the Heart and Stroke Foundation, the Multiple Sclerosis Society, the Canadian Diabetes Association all have active patient and public input on their committees, and require that lay representatives are part of the decision making process on research grant panels. Furthermore, these agencies will advocate for and lobby on behalf of their organization with federal governments for ongoing funding support as appropriate. However, these agencies are largely dependent on philanthropic contributions from the public and thus feel directly accountable to the public as their donor.

Recently in Canada, there has been a formal linkage of many of the patient support groups and advocacy groups to provide a more concerted voice on the process of research and funding decisions. Agencies, such as the Cancer Advocacy Coalition of Canada, promote interest and information regarding significant issues for patients in Canada affected by cancer. There are similar networks and coalitions for other disease sites.

It is expected and accepted in Canada that patients and the public are direct participants in the clinical trials research agenda that is developed and implemented, however, it is also noted that any opportunity for improvement in this process is welcome and new pathways are consistently being sought.

LATIN AMERICA

It is estimated that there will be over 12 million people diagnosed with cancer, but less than 10% will receive proper diagnosis and treatment all over the world²⁾. Clinical research is vital to the development and improvement of methods to prevent, detect and treat cancer, but the majority of clinical trials take place in the developed world through sponsored pharmaceutical company research.

The corresponding lack of research in developing countries results in unmet needs related to cancer characteristics and treatment in the developing world :

- First, recommended treatments do not reflect ethnic (genetic), cultural and resource differences between developed countries and developing countries that are not subject to clinical research.
- Second, there is little research conducted on those cancers that are primarily found in developing countries. Thus the ability to diagnose and treat these diseases is impaired.
- But, third, research conducted in developed countries frequently does not consider the high variability of their own populations.

Frequently, clinical trials performed in developed as well as in developing countries do not consider racial differences, epidemiological factors, genetic variability, environmental disparities, socio-cultural aspects, economic aspects and or variability in healthcare systems.

In a recent survey of 100 breast cancer experts from 12 Latin-American countries with regard to clinical research, 94% of the respondents considered that clinical cancer research is insufficient. The main reasons for this were insufficient economic retribution (68.3%), lack of time (55.7%) ; lack of structure (50.6%) ; lack of education (49.4%) and lack of support from the institution (29.1%)³⁾.

Another characteristic of clinical cancer research in the region is that it is mainly performed in public institutions (46.8%). Public and private (22.1%) and private (16.8%).

Universities and national cooperative groups are practically nonexistent (1.1% each one) and regional oncology groups are also very infrequent (3.1%).

Please note that these are data arise from perceptions of the experts, due to the lack of other available source of data.

Clinical cancer research education is generally not included in the medical undergraduate curriculum. There are some ongoing educational post-

graduate training tools, mainly in the form of workshops of 1–3 days duration.

One example of this type of activity is the International Clinical Trials Workshop (ICTW), a joint development of the American Society of Clinical Oncology (ASCO), the National Cancer Institute (NCI-US) and the Latin American and Caribbean Society of Medical Oncology (SLACOM). The first pilot was organized in Buenos Aires in 2009 and others were later organized in 2011 in Uruguay, Romania and Egypt. This workshop has a program that includes all the internationally accepted norms and criteria, but adapted to international audiences and with regulatory issues according to the specific country or region⁴⁾.

With respect to training, practically the only existing activities are related to CRO's or pharmaceutical companies. There are some isolated initiatives through regional or local scientific societies.

In summary, regardless of the fact that clinical research activities are important in Latin America, that many groups are active and that hundreds of patients are included in national and international trials, the great majority of activities are directly or indirectly related to pharmaceutical companies.

Finally, biostatisticians and data managers are usually trained through CRO's and pharma. Pharmacists and nurses educational activities are only occasionally available.

JAPAN

1) Education and training

Education and training for investigators

Although physicians recognize the importance of clinical trials for evidence based medicine, physician-investigators in Japan tend to choose their research topics more in basic science. Education for clinical research usually takes place as on-the-job training after graduating medical school or post-graduate schools of medicine. The core institutions including 20 designated institutions by the Japanese government (Ministry of Health, Labour, and Wel-

fare) to promote clinical trials, as well as several university hospitals, trial groups, non-profit organizations, and various medical societies offer basic information on clinical trials by lectures or e-learning programs.

There are no uniform programs that physicians need to take to become qualified as investigators. The qualification of the principal investigators and sub-investigators is the responsibility of each participating institution. Some hospitals require investigator certificates, which can only be obtained after taking 1-2 days educational programs annually provided by the hospitals. The educational contents for physician-investigators are usually more focused on scientific issues, with minimum information on the regulatory issues and research methodologies/operations. The research seminars sponsored by pharmaceutical companies have provided good opportunities for physician-investigators to learn various aspects of clinical trials.

Medical societies in Japan often provide educational seminars in relation to clinical trials for their members. However, the contents of the educational program remain inconsistent with substantial variations. Physicians' Education Council of Japan for Clinical Trials (PECJCT) was established in 2010, to indicate comprehensively standardized educational items on clinical trials for physician-investigators, to evaluate and certify educational programs provided by each of the Japanese Board of Medical Specialties, and to provide educational support for each medical society. The Japanese Organization of Clinical Research Evaluation and Review (J-CLEAR) provides lectures for investigators mainly on large multi-center clinical trials for cardiovascular diseases. The Japanese Association of Pharmaceutical Medicine (JAPhMed) is also an active organization to promote Pharmaceutical Medicine by enhancing the knowledge, expertise and skills of pharmaceutical physicians. It is still at the planning stage how to provide good education/training effectively for future certification of investigators in Japan.

Education and training for the clinical research professionals

Nurses, pharmacists, and lab technicians generally receive on-the-job training regarding clinical trials only if they work in hospitals active in clinical research. In Japan, schools of nursing (4 year undergraduate, 2 year master, and 4 year doctorate programs) barely include topics regarding clinical trials in their curriculum, whereas schools of pharmacy (4-6 year undergraduate and 4 year doctorate programs) generally include them in courses related to pharmaceutical development.

Additional training for the clinical research professionals depends on the personal plans of career development, thus varies in intensity. Several universities offer 2-year master's courses specialized in clinical research for professionals, including physicians, nurses, pharmacists, lab technicians, and data managers. The programs often focus on didactic teaching in the area of research design, biostatistics, clinical epidemiology, research methodology, research ethics, GCP and relevant regulations, informed consent issues, and communication skills and the research team management. Emerging educational needs for clinical research professionals in Japan may include the following topics: pharmacogenomics, translational research, project management, regulatory science, and international collaborations in clinical trials.

Clinical Research Coordinators (CRCs) and Clinical Research Associates (CRAs) in Japan are generally highly motivated to learn more about clinical trials. However, the interests of clinical nurses and pharmacists are relatively low in the clinical setting. Effective involvement of clinical staff in clinical trials would be critical especially for academic clinical trials, where CRCs might not be fully assigned.

The Japanese government has been playing an active role in educating CRCs since 1997 when ICH-GCP was introduced to the New Japanese GCP. More than 3,000 CRCs have taken the introductory CRC seminars sponsored by MHLW (one week pro-

grams with a series of lectures and an option of one month internship at selected training hospitals). Since 2007, the Advanced CRC seminars (2 day program with various topics of lectures and group discussion time) have also been offered by MHLW, where regulatory updates, as well as educational roles of CRCs in the research team have been emphasized. In addition, there has been a clinical research seminar specifically for nurses annually since 2007, held by Kitasato University under the sponsorship of the Japanese government, in order to promote active participation of nurses in the clinical research team.

CRCs and data managers have obtained their professional skills mainly by on-the-job training in hospitals. On the other hand, CRAs have been generally educated at the pharmaceutical companies or CROs. Since academic studies need CRAs to take care of the monitoring and central management of the research activities, more experienced CRAs and project managers are needed in academic institutions. However, there is very little job-to-job mobility from the pharmaceutical industry to academic centers in Japan. Therefore, the additional educational needs in the academic setting are now apparent in the field of project management and regulatory science especially for investigator-initiated, indication-directed clinical trials and international collaboration in academic clinical trials.

Professional societies and certification in the field of clinical research

Various educational seminars are offered by professional associations/societies in the field of clinical research such as the Association of Clinical Research Professionals (ACRP), the Society of Clinical Research Associates (SoCRA), and the Drug Information Association (DIA), all of which have Japanese branches in Japan. They have been providing their Japanese members a variety of educational seminars with speakers from the United States and European countries, as well as articles in English with the latest information with international perspectives in

clinical research. The Japanese Society of Clinical Trials and Research (JSCTR) also provides a series of educational programs for clinical research professionals in Japan.

ACRP, SoCRA, and Japanese Society of Clinical Pharmacology and Therapeutics (JSCPT) offer examinations leading to certification as a certified CRC or CRA or CPI/CCTI (CPI for physician investigators and CCTI for non-physician investigators), a certified CRP (Clinical Research Professionals), and a certified CRC respectively. JSCTR offers examinations leading to “GCP certification” in two levels showing introductory or advanced level of GCP knowledge and its application skills into real clinical practices.

Education for the members of IRB

In Japan, providing education for IRB members and ethics committee members is a responsibility of the research institution, according to the Ethical Guideline on Clinical Research. There are currently no formal training courses for IRB members/ethics committee members in Japan. The educational contents as well as the training methods vary, depending on the institutional policy. Many hospitals periodically provide short lectures on regulatory updates and ethical issues for their IRB/ethics committee members. MHLW provides a one day educational program once a year for representatives of the IRB/ethics committee members of 20 core clinical research centers designated by MHLW to promote clinical trials in Japan. There is no certification available to show the qualification as an IRB/ethics committee member in Japan.

Website resources

The following are some examples of web-based sources for education on Good Clinical Practice (GCP) and other relevant guidelines, research design, research ethics, and clinical trial methodology in Japan. Information in the website is prepared for each profession (investigators, monitors, CRCs, and IRB members), as well as for different levels of expertise in clinical trials (Basic, Intermediate, and Advanced).

1) E-Training Center for Clinical Trials, provided by Center for Clinical Trials, Japan Medical Association

<https://etrain.jmacct.med.or.jp/>

2) Introduction to Clinical Research (ICR) Web, provided by Dr. Yamamoto team at National Cancer Center

<http://www.icrweb.jp/icr/>

Education of the public

Information available to the public regarding clinical trials is limited. Some organizations, such as national centers, university hospitals, and study groups provide the information to the patients, professionals, and the public on the homepage. People may have the opportunity to see brochures, posters, and/or videos providing fundamental information on clinical trials when they visit hospitals. Even though the clinical registries on the web are open to the public, few people know about it. Opportunities to take clinical research education to a public audience are also limited. As a public service, highly motivated physicians and clinical research professionals give presentations at open city seminars, universities, or the patient advocacy group meetings. The presentations usually include an explanation of key concepts of the clinical trial process and implications of trial participation.

2) Infrastructure for academic clinical trials

In academic clinical trials, financial factors may pose obstacles to study implementation. The funding source for academic clinic trials can be from the government, the study group, the institution, or the pharmaceutical company. Except industry-sponsored clinical trials, many academic trials in Japan provide minimal reimbursement for costs and efforts to the participating sites, so that the investigators may have minimal staff support.

Depending on the approval status of the investigational agents/medical devices, applicable regulations for clinical trials are different in Japan. Investigator-initiated indication-directed clinical trials are strictly regulated by GCP. Other academic trials should be conducted according to applicable ethical

guidelines specified by the MHLW. Regardless of whether the law mandates it, the ethical principles and the methodological principles for conducting clinical trials are the same.

3) Patient involvement in clinical trials

Many patients encounter clinical trials for the first time when they are approached by a physician regarding a specific protocol in Japan. Patients are usually involved in clinical trials only as study participants. A very small number of patients, patient advocates, and family members of rare incurable diseases are actively involved in the ethics committee of the study groups or IRBs, as well as the advisory board for policy making relevant to clinical research. However, the influence of patients on clinical research itself remains limited in Japan.

See an added list of essential issues on education for Japanese professionals in clinical trials, derived from those for Japanese physicians⁵⁾ (Appendix 1).

SOUTH KOREA

1) Education and training

Education environment

In 2004, the South Korean government designated 14 “centers of excellence.” They are big hospitals with large patient volume along with good infrastructure for medical care and clinical trials in South Korea.

A national project supported by the Ministry of Public Health Welfare, named, Korea National Enterprise for Clinical Trials (KoNECT) was established in 2007 for developing better infrastructure for clinical trials in South Korea. KoNECT has designated 15 Regional Clinical Centers and supported these designated centers throughout three different phases: providing hardware facilities, equipment and human resources in the first phase, developing a specialization for each center at the second phase, and finally building international recognition at the third phase. These designated centers are similar to the National Institute of Health-General Clinical Research

Centers. KoNECT has been playing a leading role in human resource development for clinical trials. By 2010, the organization had selected 19 education centers for organizing and operating 8 different programs for educating and training clinical trial professionals.

Education and training programs

Twice a year, the KoNECT operates many programs for training clinical research professionals: Training programs for clinical researchers, clinical pharmacologists, clinical research coordinators (CRC), clinical trial monitors, medical professionals in drug manufacturing, biostatisticians, data managers. There is a master's program providing academic education in the field of clinical research in South Korea. Graduate School of Public Health at Catholic University offers formal courses in the methodological principles of epidemiology and clinical trials.

Educational opportunities for clinical research professionals

Various short-term educational programs or 1-2 day workshops for clinical trials are available for research professionals in South Korea. In general, major universities and medical centers, such as the National Cancer Center, Samsung Medical Center, Asan Medical Center, Seoul National University Hospital, and the Catholic Medical Center assume the responsibility of offering educational programs for those who are involved in clinical research. These programs are mainly designed for those working at their own institutions. Most institutions require the courses to be taken in order to become qualified as investigators.

The main contents of the educational programs are similar. They include a variety of ethical, legal, and operational issues that arise in the conduct of clinical research. Examples of the topics include fundamentals of research design (protocol development, data analysis methodology and interpretation), ethical issues (human subject protection, informed consent, IRB roles), operations (research project man-

agement, handling of investigational agents, roles and responsibilities of the research team, budget management, adverse event reporting procedure), data management (case report forms, data acquisition, monitoring and auditing), and the regulations (Investigational New Drug [IND]) applications, Korean Good Clinical Practice [KGCP], and contract related issues). There are a couple of good intensive programs specifically on biostatistics. The National Cancer Center and the Seoul National University Medical School offer 18-20 week programs for learning the biostatistical principles on which clinical research is based.

Education for IRB members

The Korean Association of IRB (KAIRB) was established in 2002. It is a non-profit organization with more than 50 IRBs. It provides IRB operation guidelines, along with education for IRB professionals. In 2007, the South Korean government endorsed the training requirement for IRB professionals. It is now mandatory for IRB members to hold a certificate of education when taking their position at the institution.

For those institutions that do not have their own IRB, the Ministry of Health and Welfare is trying to provide a common IRB run by one of the government agency so that those institutions can perform clinical trials once their proposals are approved by the common IRB.

2) Infrastructure for academic clinical trials

Electronic data management

Since 2007, the National Cancer Center has been providing services, education programs and necessary support for multi-center cancer clinical trials through a web-based clinical trial management system. In 2010, the South Korean FDA distributed guidance for electronic data management in clinical research.

3) Patient involvement in clinical trials

In South Korea, patient involvement in clinical trials is not in a mature situation compared to the USA and other European countries. There are only a

few patient advocate groups that are actively involved in clinical research and other related issues such as the pricing policy for very expensive drugs. There is a lack of programs for helping patients obtain more information about clinical trials. However, recently the Center for Disease Control (CDC), South Korea established a web-based platform for registering clinical studies performed in South Korea and allowed this information to be accessed by the general public. In the National Cancer Center Hospital, and some big hospitals in South Korea, there are meetings between physicians and the patients and their families on a regular basis. In these meetings, physicians explain about the patients' current conditions, treatment plan and the expected outcomes from the treatment. They also listen to the patients talking about the hardships they experience during the treatment. Sometimes, physicians introduce new treatment options and the clinical trials using those new regimens so that they can be enrolled in the trials if the conditions are met.

CHINA

Clinical trials education in China originated from setting up the GCP concept implementations. The Chinese government executed GCP regulations just over 10 years ago. We started translating, evaluating and comparing GCP information collected from different countries from 1993 to 1994 ; and in 1995 a Chinese GCP Guideline Drafting Committee was established. In 1998, with the reference of ICH-GCP, the first Chinese GCP Guideline was issued by the Ministry of Public Health, which was revised by the State Drug Administration (SDA) in 1999 ; and finally the current version of the Chinese GCP Guideline was re-revised by the State Food and Drug Administration (SFDA) in 2003. All the clinical research centers (usually public hospitals) that can conduct clinical research must be approved by the SFDA, and an ethics committee (IRB) must be set up in the clinical trial center, and all its members are required to hold a GCP certificate etc.

So the Chinese GCP's status quo is still in its infant stage, and currently it is mainly a learning process from western countries. But, especially in recent years, the SFDA has been exerting great efforts to strengthen both the regulatory and scientific administrations on clinical research. Although there may be more government accredited clinical trial centers, among the 251 Clinical Trial Centers designated by the SFDA across the whole country for either western medicine or Chinese medicine, 91 of them are anti-cancer drug clinical trial centers (data until Oct. 2008), and both the quality and the quantity of the clinical research need to be improved.

Usually there are no learning curricula on clinical research during education in bachelor's, master's and doctoral programs. A one-week training program on clinical training, more regulatory than scientific, is offered by many institutions accredited by the SFDA, since all staff directly involved in clinical research are required to hold a GCP certificate issued by the SFDA. This is insufficient preparation for investigators, site managers or research coordinators in practice. Generally, all the doctors, nurses and pharmacists involved in clinical research receive on-the-job training when they work in centers approved by the SFDA. So more advanced clinical research training programs or education about research administration/management, contracts and grants management, financial management, intellectual property and technology transfer, training and educational programming, human resources management, regulatory compliance, ethics and IRBs, information services, and many other areas are needed for those who actively participate in clinical research.

Clinical research-related officials in China are paying increasing attention to investing, strengthening and improving the levels of clinical trial centers' data management and hardware infrastructure.

Hong Kong

Although the teaching of evidence based medicine and the importance of clinical trials has been an

established core component in medical school curriculum, formal training for clinical trials usually begins when a physician starts his/her specialist training in a medical subspecialty (3rd to 6th year of postgraduate training), when the physician becomes involved as a co-investigator in a clinical research team.

With the launch of the International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines in 1996, we have seen a steady increase in the globalization of industrial sponsored clinical trials in past years. Hong Kong has a unique position as the meeting point of East and West cultures ; it has naturally become the central hub in the globalization of clinical trials in Asia. Clinical trial centers have been well established in the two medical universities to promote both the infrastructure and the quality and efficiency for clinical trials. They also provide education on clinical trials methodology and GCP training. Several clinical trial centers in Hong Kong have been accredited by both the China SFDA and the US FDA.

In Hong Kong, the infrastructure for clinical trials units has been well established in the medical universities and the tertiary teaching hospitals. It has also been extended to other district general hospitals over the past few years, which parallels the increasing development and globalization of industrial sponsored clinical trials in Asia. In the public hospital system under the Hospital Authority, a central guideline on research ethics committee organizations is available. Each hospital cluster has established its own clinical research ethics committee. Regular training workshops are provided for ethics committee members and clinical investigators on clinical trials methodology and regulatory requirements.

Website resources

1) Education and training on clinical trial methodology and Good Clinical Practice (GCP) in Hong Kong Center for Clinical Trials, The Chinese University of Hong Kong

<http://www.cct.cuhk.edu.hk/cctwebsite/Training/>

[tabid/58/Default.aspx](http://www.cct.cuhk.edu.hk/cctwebsite/Training/tabid/58/Default.aspx)

Clinical Trials Center of the University of Hong Kong
<http://www.hkuctc.com/education.php>

2) Informed Consent process

NIH Office of Extramural Research : Protecting Human Research Participants

<http://phrp.nihtraining.com/users/login.php>

3) GCP training

Quintiles Transnational's online educational program :

Introduction to Clinical Drug Development Process : ICH/FDA Good Clinical Practice for Clinical Trial Sites.

http://live.blueskybroadcast.com/bsb/client/CL_DEFAULT.asp?Client=6

4) Research ethics committee

http://www.ha.org.hk/ho/research_ethics/re_cluster.htm

INDIA

1) Background information

India has a double burden of disease i. e. in addition to communicable diseases as seen in the developing countries, non-communicable diseases seen mainly in the developed world are also significant. Thus India is the diabetic capital of the world, and there are about 30 million cases of cardiovascular disease and about 800000 new cases of cancer per year. Only around 200 million people can pay for healthcare and the need for healthcare can drive families into debt. Approximately 42% of people live on <1-1.25 US\$ per day and about 830 million people live on <2 US\$ per day. The result of this economic reality is that the visible and quoted medical statistics are probably only the tip of the iceberg and that the real burden of a particular disease is actually unknown as it is not possible for the large majority to actually seek medical treatment. The women bear the brunt of this financial crunch as the majority do not even seek medical care.

Healthcare has become an industry with private organizations setting up hospitals and also medical

colleges. Thus in India the ethos of the art and science of medicine has given way to the business of medicine.

2) Academic Education

Medical

The aim of medical education in India has been to produce professional health personnel for the country. However this has been a futile effort as after training and qualifying many leave for developed countries. The majority, who leave after acquiring the basic medical qualification, seeking further qualifications, rarely return. It has been estimated that >100,000 Indian medical graduates are working in the USA, the UK, Australia and New Zealand.

There are about 314 medical colleges in India. The medical colleges may be government (central or state) or private. Admission procedures to the medical colleges vary. However, all the colleges are regulated by the Medical Council of India. The colleges are affiliated to local universities. In certain states when there are many medical colleges, a Health University has been constituted and the concerned medical colleges are affiliated to the Health University of that state.

Undergraduate medical education consists of a course of 4 1/2 years duration. The successful completion of all examinations is followed by one year of compulsory internship during which period the candidate trains in various specialties such as medicine, surgery, obstetrics and gynecology etc. On completion of both requirements the candidate is eligible for the award of the degree of Bachelor of Medicine and Bachelor of Surgery (MBBS). Postgraduate degree courses e. g. MD Internal Medicine, MS General Surgery etc. are of three years duration and there are 68 institutions that offer such courses. Postgraduate diploma courses e. g. Diploma in Anaesthesiology, Diploma in Orthopaedics etc. are of two years duration and 55 institutions offer such courses. The duration of subspecialization courses i. e. for postgraduates, such as D. M. in Medical Specialties (e. g. Cardiology, etc.) and M. Ch. in Surgical Specialties (e. g.

Neurosurgery etc.) is three years and there are 24 institutions that conduct such courses. Courses leading to the award of Ph. D. in the various branches of medical sciences are available in 41 institutions. Courses leading to the award of a master's degree in certain branches of medical sciences e. g. MSc. Medical Microbiology etc. are available in 20 institutions.

There is another stream for postgraduates in the various branches of medical sciences that is offered by the National Board of Examinations and leads to the award of Diplomate of the National Board (DNB) in a particular specialty. These courses are conducted in medical institutions that do not run a medical college. Such institutions are hospitals that have sufficient clinical material and the required number of medical practitioners with the prescribed experience in a particular branch of medicine. This stream was started by the Government of India in order to train medical graduates in specialties as the numbers that were trained in the medical colleges were inadequate. It was also an attempt to put to use the clinical material available in the large hospitals (mainly private). Thus medical graduates who worked as junior doctors in these hospitals would acquire a postgraduate qualification.

Undergraduate

The majority of medical colleges do not have a training module for clinical research including clinical trials at the undergraduate level. There is no formal training for research and GCP in the curriculum.

However, the need for this has been recognized and at least three medical colleges in India have now introduced clinical research at the undergraduate level though it is optional and is left to the interest of the individual student. They have introduced undergraduate mentorship programs to expose undergraduates to research methods identifying a research question, writing up a protocol, submitting and presenting the same before the IERB, conducting and analyzing the study, preparing a report and making a presentation. An attempt has been made to source funding that can be made available as research grants

to the mentorship program for the various studies. This is not a structured program and is not a requirement of the syllabus of the affiliating University or Medical Council of India.

Postgraduate

Undertaking a research project under the supervision of a guide and submission of a dissertation is part of the curriculum except for postgraduate diploma courses. This is true for both streams of postgraduates. However, the problems such as the lack of funds, paucity of ideas of the guide, lack of training in research methodology etc. result in poor quality dissertations. Very few institutions conduct research methodology workshops for postgraduates. In some instances the affiliating health university insists on sessions of training in research methodology. Training in GCP may or may not be included in the curriculum.

Subspecialization

Both streams of subspecialization require a dissertation. The present syllabi for the various subspecialties do not include training in GCP. However, some institutions have a Department of Clinical Trials that conducts courses in clinical research methodology besides offering in-house facilities to their staff and students. Whereas in other institutions, individual specialties/units are involved in conducting trials and this is overseen by the institutional review board.

Nursing

The education for nursing is organized by the Nursing Council of India. The general nursing and midwifery course lasts for three years. Clinical trials are not included in this curriculum. There are also master's and doctorate university affiliated courses at which level there is requirement for research. This will involve submitting a proposal to the IERB and undertaking a study under the supervision of a guide but this does not include clinical trials.

Pharmacy

The education for pharmacists is organized by the Pharmacy Council of India and these are univer-

sity affiliated courses. These may be diploma, bachelor and master's degree courses. Most of the research is with animal models as most of these institutions are not attached to hospitals. The majority of the students are absorbed into the pharmaceutical industry.

3) Non-academic education about clinical trials

The Indian healthcare system has become useful to multinationals for clinical trials. The medical training is performed in English, the infrastructure costs are low, and enrolling patients in clinical trials has become a source of income for the medical profession. There are more than 31 contract research organizations that channel these trials for the pharmaceutical industry. To facilitate this mechanism there are training programs being conducted by various organizations that are not affiliated to any university. The eligibility criteria and duration of the courses are extremely variable. These organizations conduct these programs for graduates of various streams such as medicine, dentistry, science, arts etc., and attract candidates with algorithms for prospects in a career in clinical trials. Thus trainees would start their careers as data managers and clinical research associates and attempt to climb the ladder of a career in clinical research.

4) Non-academic clinical trials

The majority of clinical trials are supported by the pharmaceutical industry. The Indian Cooperative Oncology Network, which was set up mainly by medical oncologists and has been in existence for more than two decades, is supported by the pharmaceutical industry to conduct trials.

5) Regulatory agency for clinical trials in India

The Drug Controller General of India (DCGI) based in New Delhi is the formal body under the ministry of health to regulate the conduct of new drug/device clinical trials in human subjects. Schedule Y of the Indian Drugs and Cosmetics Act was revised in 2005. This schedule contains regulations for the conduct of preclinical and clinical testing of drugs and devices. The DCGI further mandates registering

of all clinical trials through a public domain called the Clinical Trials Registry of India (www.ctri.in).

The Indian Council for Medical Research is an institution under the Ministry of Health, the Government of India with a budget for funding research. It funds research through the following modalities—Task Force Projects that may be entirely funded by the ICMR or matched grant funded in collaboration with international funding agencies and takes ownership of the data. It also has funding for ad hoc grants given to individual academic institutions and also funds research fellows. It has also formulated the Indian Good Clinical Practice Guidelines and the Guidelines for Biomedical Research on Human Participants which lays down the guidelines for the composition of ethics committees. It is also the secretariat to the International Health Division which oversees non-pharma funded international collaborative research.

The Medical Council of India has included pharmacovigilance in the proforma used to assess medical colleges and institutions seeking affiliation to the Medical Council of India.

6) Infrastructure for clinical trials

Institutions interested in research and in the conducting of clinical trials, have set up infrastructure for the same through their own sources of funding (investigator driven) or through funding received by participating in sponsored clinical trials. Thus academic clinical trials are almost nonexistent in India.

Ethics committees

The Medical Council of India has specified that the constitution of such a committee is mandatory for affiliation of a medical college or institution. There are independent ethics committees that cater to those organizations that do not have institutional ethics committees. There is no formal training program for members of ethics committees. However, the Drug Controller General of India (DCGI) and other organizations do organize training programs though not on a regular basis. There is no registry of ethics committees. However, ethics committees in

India are in the process of applying for accreditation to the Forum for Ethics Review Committees of the Asia Pacific Region.

Training in medical law and ethics

The National Law School of India University, Bengaluru, conducts a postgraduate diploma in medical law and ethics that does include clinical trials in the syllabus of the course.

Center for studies in ethics and rights

This is a non-governmental Organization that publishes the quarterly Indian Journal of Medical Ethics and also takes the lead in organizing the biennial National Bioethics Conference. They are also attempting to create a forum to discuss the Indian scenario in the domain of clinical trials and also raise public awareness.

7) Training for patient and lay persons

There is no specific training available for this purpose at present though the print and television media do try to raise awareness though very often it is about accidents and malpractice.

8) Patient involvement in clinical trials

Patient involvement in clinical trials seems to be an unknown concept among clinical trial researchers in India. There are breast cancer support groups that try to promote early detection of breast cancer and also encourage patients in order to reduce non-compliance with treatment. Some of these breast cancer support groups are also interested in collaborating with 'Ayush'—Indian indigenous and other systems of medicine—ayurveda, unani, sidda and homeopathy. There is an organization called the Cancer Patient Aid Association, which has branches in a few of the major cities in India. This organization in addition to encouraging public awareness about cancer, (tobacco etc.) also assists patients by giving financial support for chemotherapy. Involving patients actively in research requires a significant change in the way medicine is practiced in India—steeped in patriarchal and defensive attitudes.

AUSTRALIA

1) Education and training

There are an increasing number of formal post-graduate courses being offered in Australia that offer clinical trials as single subjects within more general courses such as pharmacy, medicine or public health. Specific post-graduate qualifications in clinical trials, clinical research and/or biostatistics are also becoming more common, with some being listed in the table below.

Many condition-specific societies in Australia have special interest groups (or similar) that focus on the design, conduct and reporting of clinical trials within their field. Examples include the Clinical Oncological Society of Australia (COSA), the Perinatal Society of Australia and New Zealand, and the Cardiac Society of Australia and New Zealand. In

addition, some professional societies exist that specifically meet the ongoing training and education needs of individuals who work hands-on with clinical trials including the Australasian Health and Research Data Managers Association (AHRDMA), the Association of Regulatory and Clinical Scientists (ARCS Australia Ltd.), the Association of Clinical Research Professionals (ACRP) and the Drug Information Association (DIA).

2) Infrastructure for academic clinical trials

The National Health and Medical Research Council (NHMRC) is Australia's peak funding body for health and medical research, including clinical trials, with a research budget in 2010 of AUD 784.9 million. It has been estimated that this represents approximately one sixth of the spending on health and medical research in Australia⁵. The NHMRC pro-

Institution	Qualification/s	Web link
Australian National University	Master of Translational Medicine	http://www.masterstudies.com/MBA-MSc-Masters-Degree/Medicine/Australia/
Biostatistics Collaboration of Australia (BCA) *	Graduate Certificate/Graduate Diploma/Master's in Biostatistics	http://www.bca.edu.au/
Monash University	Master of Clinical Research Methods	http://www.monash.edu.au/study/coursefinder/course/2311/
Swinburne University of Technology	Graduate Certificate/Graduate Diploma/Master of Science (Good Manufacturing Practice)	http://courses.swinburne.edu.au/subjects/Clinical-Trials-Quality-Assurance-Management-HES6414/local#coursewithsubject
University of Canberra	Graduate Certificate in Clinical Trials Management (online)	http://www.canberra.edu.au/faculties/health/pharmacy/courses
University of Melbourne	Master of Clinical Research Specialist Certificate in Clinical Research (Oncology/Neuroscience/ Biomedical Research Management/ Clinical Trials Monitoring/Clinical Trials Coordination)	http://www.mccp.unimelb.edu.au/courses/award-courses/specialist-certificate http://www.mccp.unimelb.edu.au/courses/award-courses/masters/clinical-research-coursework
University of Sydney	Master of Clinical Trials Research	http://sydney.edu.au/courses/Master-of-Clinical-Trials-Research
University of Western Australia	Master of Clinical Research	http://courses.handbooks.uwa.edu.au/courses/c9/90620

*BCA is a consortium of 7 Australian Universities

⁵The Economic Value of Australia's Investment in Health and Medical Research : Reinforcing the Evidence for Exceptional Returns. A paper commissioned by Research Australia. October 2010.

vides funding for clinical research via a number of grant programs targeting individual researchers and research projects, as well as collaborative research groups and academic research centers.

Governments at Commonwealth, state and territory levels in Australia are responsible for the various aspects of clinical trial governance and regulation, including ethical and scientific review of clinical trial protocols, and have various schemes in place to provide financial and infrastructure support to universities, hospitals, research institutes and companies. Clinical trials involving any product not entered on the Australian Register of Therapeutic Goods (ARTG), or use of a product on the ARTG in a clinical trial beyond the conditions of its marketing approval, are required to comply with the Clinical Trial Notification (CTN) or Clinical Trial Exemption (CTX) schemes. These schemes are administered by the Therapeutic Goods Administration, a division of the Australian Government's Department of Health and Ageing. The key policies relevant to the ethical conduct of clinical trials in Australia are the National Statement on Ethical Conduct in Human Research⁶, the Australian Code for the Responsible Conduct of Research⁷, and soon to be released by the NHMRC Framework for Monitoring of Clinical Research.

In June 2011, the Australian Government published *Clinically Competitive : Boosting the Business of Clinical Trials in Australia*, a report of the Clinical Trials Action Group (CTAG), a joint venture of the Department of Health and Ageing and the Department of Innovation, Industry, Science and Research. CTAG was charged to work in consultation with relevant stakeholders "to improve the international competitiveness of the Australian clinical trials environment. The Group made eleven recommendations in six categories :

(1) To improve the timeliness of ethics and research governance review

- (2) To provide for cost recovery of efficient clinical trials
- (3) To ensure that clinical trials can take advantage of developing e-health systems
- (4) To improve patient recruitment
- (5) To facilitate better national coordination and greater collaboration across clinical trials networks
- (6) To progress key clinical trial issues

Many of these recommendations will be implemented through the National Health Reform Agreement, a partnership between the Commonwealth Government and the States and Territories. Of particular relevance to academic trials is the recommendation that the NHMRC provide greater support for clinical trials networks in priority health areas by encouraging collaboration across academia, clinical medicine and industry.

A review of health and medical research in Australia is currently underway with an expected completion date of September 2012. The review will "focus on optimizing Australia's capacity to produce world class health and medical research up to 2020," including the need to build and retain internationally competitive research capacity and a skilled research workforce, and opportunities to improve coordination and collaboration.

3) Patient engagement in clinical trials

Some CTAG recommendations are directly targeted at making it easier for consumers to have access to reliable information about clinical trials, and to hold informed conversations about clinical trials with their healthcare practitioners.

The Consumers Health Forum of Australia (CHF), funded largely by the Commonwealth Department of Health and Ageing, was formed in the mid-1980s to advise the government on health issues affecting consumers. It "encourages and supports consumer representation on national commit-

⁶National Statement on Ethical Conduct in Human Research. Developed jointly by National Health and Medical Research Council, Australian Research Council and Australian Vice Chancellors Committee. © Australian Government 2007. ISBN Print : 1864962690

⁷Australian Code for the Responsible Conduct of Research. National Health and Medical Research Council. © Australian Government 2007. ISBN Print : 1864964324

tees with a health remit.” In 2011 the CHF released a Consumer Guide to Clinical Trials Factsheet (<https://www.chf.org.au/clinical-trials-project.php>). There are also a number of condition-specific consumer groups with an interest in clinical trials, some of which work with collaborative groups of researchers in the design of clinical trials. These groups vary in their level of independence from the pharmaceutical industry. Some of the larger groups receive government funding (e.g., Cancer Voices).

AFRICA

The sub-Saharan African region bears a disproportionately high burden of disease⁶. A large percentage of this disease burden is attributed to Poverty Related Diseases (PRDS) but the incidence of non-communicable diseases is also reported to be on the increase⁷. Against this backdrop there is a great need for new, safe and sustainable interventions to combat these diseases. In response to this chasm, the last decade has been marked with a record increase in health research activities in Africa^{8~16}. These activities include clinical trials as an important tool to assess the safety and efficacy in the development of new medicines⁸ and improved interventions. Unconventional business models for research and development in tropical diseases have also emerged¹⁷ in order to provide cost effective product development approaches for products with limited potential markets in developed countries.

In general, there is limited capacity for both infrastructure and human resources to conduct high quality clinical trials in Africa. A number of national governments, bilateral, multilateral, and philanthropic agencies are engaged in creating such capacity in Africa^{9~11,13~15,17~19}. Nonetheless there are currently few African research centers with adequate infrastructure and a critical mass of scientists with requisite clinical trials expertise. Equally lacking is the capacity of clinical trials support teams with suffi-

ciently trained clinical research associates, clinical trial assistants, data managers, medical advisors, internal auditors, trial pharmacists, regulatory staff, data safety monitoring boards (DSMBs) etc. Several universities, clinical research organizations (CROs), pharmaceutical companies and organizations such as WHO TDR, the Swiss Tropical and Public Health Institute and Africa Malaria Network Trust (AMANET) are involved in providing short-term training courses in good clinical practice (GCP), good clinical laboratory practice (GCLP), clinical trials management, clinical trials designs, monitoring etc. Long-term training in clinical trials at master's level is also now being offered by universities such as the London School of Hygiene and Tropical Medicine (LSHTM) as a long distance course. With support from EDCTP and the Gates Foundation, this course has now been extended to African institutions such as the University of the Witwatersrand in Johannesburg, University of Ghana in Accra and Polytechnic University of Bobo-Dioulasso in Burkina Faso. Other institutions such as the Vienna School for Clinical Research, the University of Maryland in partnership with the University of Bamako and the University of Liverpool among others are also offering a wide range of clinical trials related training courses for participants from Africa.

The creation and strengthening of existing clinical research networks among southern and with northern academic and research institutions is facilitating strengthening of clinical research capacity in Africa. Various organizations are facilitating this approach in order to promote strong collaboration, resource sharing and cross-mentorship to mitigate the limited capacity in Africa^{13,19~21}. Since 2003, EDCTP funded more than 190 projects in sub-Saharan Africa including 57 clinical trials involving new or improved drugs, vaccines, microbicides and diagnostics against the three main poverty related diseases, namely HIV/AIDS, malaria and tuberculosis ; and

⁸Medicines here refers to drugs, vaccines, microbicides and other products requiring regulatory approval for use in humans

associated capacity building as well as giving support for ethical review capacity and regulatory framework.

The ethics infrastructure and expertise in many African countries is also weak, ill-equipped or non-existent in some countries^{22~25}). Africa is also faced with the challenge of low literacy, and a wide diversity of socio-economic and cultural factors²⁶) that heavily impact on the conduct of ethical studies. In some locations, clinical trials are the only ways in which the local populations have access healthcare. Moreover, as the number of clinical trials increases, the volume and complexity of the protocols requiring review also increases. All these factors create challenges related to the informed consent process, the need to train ethicists, ethics committee members, facilitation of countries to develop ethical procedures and guidelines, and strengthen the ethics framework in general.

Additionally, there is limited capacity and marked variability among countries of regulatory capacity for clinical trials which presents a major challenge especially where multi-center and multi-country trials are involved. Different strategies including joint reviews of clinical trial applications and joint inspections of clinical trial sites by groups of countries have recently been initiated as part of training to strengthen capacity for the regulatory oversight of clinical trials in Africa^{27,28}).

Clinical trials require genuine community involvement and this necessitates the training of different cadres of personnel²⁹). Community Advisory Boards are now progressively becoming standard practice for investigational vaccines, macrobicides and drug trials in Africa. Building research capacity and clinical trials in Africa through support for training and promotion of local scientific leadership is critical to the development of sustainable research ownership. Hosting countries however need to take the lead in these efforts.

South Africa

1) Infrastructure for academic clinical trials

There are numerous obstacles to conducting

RCTs in South Africa. Healthcare specialist training within the higher institutions in South Africa conventionally focused on clinical skills accrual and gaining clinical experience, lacking a strong research focus. Reduced tertiary service units have struggled to remain academically active over the past decade³⁰), reducing the opportunities for local clinical researchers to learn and develop the epidemiological or statistical skills necessary for conducting adequate RCTs. For those health professionals interested in clinical research, migration to develop their research skills may be a necessity and thereafter, the opportunity to practice those skills may only be present overseas. This contributes to the well-documented professional brain drain from the country³¹).

When research funding is not available from local sources, clinical researchers become dependent on funds from donor agencies or the drug industry. This has the potential to deflect priorities away from local needs³²). At the Mexico Health Summit in 2004 and again at the World Health Assembly in 2005, African governments committed to spending 2% of their health budgets on research³³). Figures of current expenditure on South African clinical research can be quantified by the annual Medical Research Council budget. In 2008/2009 the MRC received R236 million from the national Department of Health, far short of the promised 2%, even if dedicated monies from the National Research Foundation are added to this³⁴). The recent *Lancet* series on South Africa reports that the MRC has been chronically underfunded despite its important mandate for maintenance and development of the country's clinical research capacity³⁰).

Currently, there is no national institution within South Africa providing a coherent suite of support, available skills and training for clinicians wishing to conduct trials within their clinical fields in the public sector. In many countries, clinical trials support units offer such support to clinicians and researchers in a variety of settings, either embedded in medical schools or as part of national medical research

facilities³⁵). To this end, in 2008, the MRC funded a feasibility study to assess the need for establishing a national South African Clinical Trials Support Unit³⁶). The South African Academy of Sciences published a report on revitalizing clinical research in South Africa in November 2009 and recommended the creation of clinical research centers and research institutes as national hubs in the academic health complexes and other sites³⁷). Such large-scale research institutes could create opportunities for high-level collaborative clinical studies and a critical mass of principal investigators, post-doctoral fellows, graduate students and research assistants.

2) Patient Engagement in Clinical Trials

South Africa's Good Clinical Practice Guidelines (second edition) strongly encourage participation and communication with potential research participants and their communities.

There is currently no legal requirement for community oversight or participation in the development of research processes and protocols³⁸). However, the following is stated in Section 2.4 of SA's GCP (second edition, 2006) :

Research to be carried out at community level (e. g. vaccine trials) should ideally ensure adequate consultation with civil organizations that may exist within affected communities at all phases of the trial. Sponsors are encouraged to establish Community Advisory Groups (CAGs). A CAG can be viewed as a community representing body that may advocate for human rights and promote ethical conduct in clinical research ; contribute to addressing and resolving grievances about the research process ; give advice on accrual and retention of trial participants and voice concerns around the development, implementation and outcomes of specific clinical and related studies. Researchers are encouraged to ensure that : information flow mechanisms are developed between investigators and participating communities, and that communities are educated on the aspects of research before recruitment begins (p.29)

The imperative to develop community feedback methods is often driven directly from granting agen-

cies and/or funder requirements.

Some research has been conducted on the efficacy of Community Advisory Boards (CAB) or Community Advisory Groups (CAG) in the South African context³⁸). CABs or CAGs have developed out of a need to curb possible exploitation and with the aim of protecting community interests (through allowing a venue for community input and building capacity by educating the community on the research intention) as well as advancing the research goals (by providing information to community members, acting as a buffer for public relations, developing a means of communication with research staff and assisting in recruitment of participants)³⁸). CABs can be established in a number of ways, and the value of the group will depend on how much trust is present between the group and the greater community—as such, the methods for recruiting group members are dependent on the structures and hierarchies present in each community.

In South Africa, some trial sites have developed community education teams to prepare areas for trial activity and to assess the community's response to the possibility of research in their surroundings³⁹). The HIV Vaccine Division of the Perinatal HIV Research Unit at the University of Witwaterstrand made use of a number of methods to prepare potential communities for vaccine trials including mural advertising, community outreach workshops, media appeals, pamphlets, flyers and brochures, printed t-shirts, and including community members in campaigns as volunteers (p.19)³⁹).

Other formal methods that encourage research participant input and contribution in the development of protocols involve what is commonly called “community-based participatory research” (CBPR). In the region, the US National Institute of Health conducts brief workshops and courses to research clinicians-in-training on CBPR as a means of improving an intervention, or understanding what obstacles exist in adherence to particular interventions (personal communication).

Much of the debate around participation in research at a community level has been informed by the long history of activism in the country. Many community-based activist groups have been established since democracy. The Treatment Action Campaign (TAC) was established in December 1998 and advocates for increased access to treatment, care and support services for people living with HIV and campaigns to reduce new HIV infections. The TAC has held the government accountable for healthcare service delivery ; campaigned against official AIDS denialism ; challenged the world's leading pharmaceutical companies to make treatment more affordable and cultivated community leadership on HIV and AIDS (<http://www.tac.org.za/community/about>). In many of these situations the conflict has resulted in the community seeking researcher and media involvement and the scientific community has been assisted greatly in this regard especially in respect to the demand for evidence-based treatments.

EUROPE

1) Education and training

Clinical investigator training–European Science Foundation

In 2001, as one development of its action in relation to clinical trials, the European Science Foundation (ESF) and its European Medical Research Councils (EMRC) Standing Committee set up an Advisory Group on Clinical Research Training to investigate the opportunity and feasibility of developing a European basic education and training program on the conduct of clinical trials. In autumn 2002, the Advisory Group proposed a final draft of an ESF European Syllabus for Clinical Investigator Training, which was then approved by the EMRC Standing Committee and the ESF Executive Board (see Appendix 2). This syllabus covers seven areas. The intention is to define a common ground of ethical values, scientific and quality assurance principles covering all types of clinical trials, from which countries and universities can build individualized courses.

Innovative Medicine Initiative–European Medicines Research Training Network (EMTRAIN)

The Innovative Medicines Initiative (IMI) Joint Undertaking is a large-scale public-private partnership between the European Union and the pharmaceutical industry association EFPIA. Its 2 billion € research program aims at boosting biopharmaceutical innovations in Europe, funding research projects in the fields of safety, efficacy, knowledge management, and education and training (E & T). The current four E & T projects address gaps in safety sciences, medicine development and pharmacovigilance training. EMTRAIN will establish a sustainable, pan-European platform for E & T covering the whole life-cycle of medicines research⁴⁰.

2) Patient involvement

Report from European Science Foundation

The report “Implementation of Medical Research in Clinical Practice,” May 2011⁴¹, from the European Science Foundation (www.esf.org) raises challenges concerning patient involvement.

Major issues

Although patients are the principal “end users” of research, they are often not involved in the research generation, funding and implementation process. Involving patients actively in research represents a significant culture change and requires a number of barriers to be overcome including people's attitudes and levels of awareness.

Recommendations from ESF

- Patients and the public should be involved appropriately at all stages of the research process : priority setting ; planning ; executing ; reporting ; dissemination and implementation.
- Best practices for involving patients and the public should be identified and promoted.
- Training and education of both health-professionals and others should be encouraged and undertaken, with particular regard to research concepts ; communication skills ; understanding and communication of risk ; how to involve patients and the public in the research process.

- Statistical literacy modules should be introduced into school curricula.
- Citizens should be educated about research concepts ; citizens should be properly informed about secondary uses of patient data.
- Funders of clinical research should ask researchers to report on their plans for patient involvement in their funding applications and make good quality patient involvement a condition of funding.
- Health professionals and clinical researchers should receive training in patient involvement during their undergraduate and postgraduate training and as part of their continuing professional development.

EUPATI-project

The IMI-funded ‘European Patients Academy on Therapeutic Innovation’ aims to educate patient advocates and the lay public about therapeutic innovations.

The Innovative Medicines Initiative (IMI), a public private partnership between the European Commission and EFPIA, will fund a patient-led consortium to develop the ‘European Patients’ Academy on Therapeutic Innovation’ (EUPATI). From 2012, the academy will educate patient representatives and the lay public on personalized and predictive medicine, the design and conduct of clinical trials, drug safety and risk/benefit assessment, pharmaco-economics as well as patient involvement in drug development. EUPATI will provide educational material in six European languages targeting eleven European countries.

Pharmaceutical medicines development is a highly regulated, costly, long and complex process that is largely unknown to the lay public. Benefits and risks of existing and new treatment alternatives are difficult to understand for patients and the public. In an era of growing demand and emphasis on both quality and sustainability of healthcare, it is critical to address this major gap in public perception and knowledge.

Well informed patients and carers have a key role to play in the implementation of patient-cen-

tered clinical research strategies, approval processes, access to treatments and treatment optimization. With appropriate training, patient advocates can become accepted partners in scientific, ethical and regulatory committees which can accelerate and improve clinical trials, drug development and access strategies. Furthermore, educating the public can reduce resistance to clinical research and therapeutic innovations.

To improve the availability of both patient-centric information as well as educated patient experts, EUPATI will develop scientifically reliable, objective, comprehensive information on therapeutic innovations by

- establishing certificate training courses to create ‘expert advocates’ on therapeutic innovations,
- developing a “tool kit” of educational multi-media material to be re-used by patient organizations for educational purposes, and
- developing an Internet-based library of up-to-date, unbiased information on medicinal development for patients and the public.

The consortium, led by the European Patients’ Forum, comprises 26 leading pan-European patient organizations, academic and not-for profit organizations as well as EFPIA member companies. It features excellence across disease areas in state-of-the art, high quality, objective education to patients regarding therapeutic innovations. It will foster collaboration between patient organizations, academic institutions, regulatory bodies, ethics committees and the industry.

A Regulatory Advisory Panel led by regulatory authorities as well as a Project Advisory Board composed of high level experts with long standing credibility in patient involvement and pharmaceutical R & D will ensure objectivity, transparency and independence of EUPATI’s educational content, adhering to the highest quality standards on information for patients.

In its third round of calls, the IMI focused on seven topics. Six of them were on research areas

such as autism, tuberculosis, personalized treatment approaches in diabetes, liver injury, risk of antibodies as treatments and immunosafety of vaccines. The seventh topic moved onto new ground : ‘Fostering patient awareness of pharmaceutical innovations’. It aimed to address the lack of social awareness of the complexity of new drug development as a key factor in patients’ suspicion of and resistance to becoming involved in the development of new treatments, and to harnesses previously ad-hoc educational activities in a coherent, strategic, quality-oriented and sustainable way. The project is expected to start in the first quarter of 2012.

France

1) Initial education and training for medical doctors

In French Universities of Medicine, the basic curriculum includes the topic of “critical assessment of scientific papers,” aimed at enabling MDs to interpret the literature. French University also provides at the bachelor’s, master’s and doctoral programs specific training for investigators, clinical project leaders (i. e. DIUFIEC : Diplômes Inter Universitaires de Formation des Investigateurs aux Essais Cliniques de Médicaments).

2) Training for investigators

Specific training provided by French University also address active investigators.

Initiative from stakeholders and Afssaps

In January 2009, Afssaps, LEEM (French Pharmaceutical Industry Association) and AFCRO (French association of CROs), developed a guidance document for investigators training.

Guidance

This guidance, with its charter for use, is available on the websites of Afssaps, LEEM and AFCRO (Afssaps : [This guidance provides the standard table of contents of the training, the headlines are :](http://www.afssaps.fr/Activites/Essais-cliniques/Formation-des-investigateurs/(offset)/2)))</p></div><div data-bbox=)

- (1) General principles and scientific aspects

- Development of a medicinal product : definitions and different steps of the development
 - The clinical trial in the frame of the development
- (2) Main aspects of a clinical trial
 - Ethics and protection of people
 - General documentation of the trial
 - Investigational medicinal products
 - Trial data : from the collection up to the database
 - Biological samples
 - Principles for filing and archiving trial documents
 - (3) Communication in clinical trials
 - How to manage communication
 - Communication with the patient, the family (specificity for vulnerable populations)
 - Communication with the Trial team
 - Communication with the GPs, and the other sites
 - Communication with the sponsor
 - Communication with media, patient associations
 - (4) Workshops
 - Information and consent
 - Organization of the trial site/center
 - Monitoring and audit
 - Adverse events management.
- The Charter for use provides :
- the minimum duration of training : 16 hours
 - the issuance of a certificate of attendance describing the topics covered by the training and the duration of the training
 - that a training document has to be provided to the trainees, with a basic set of documents on the summary on the topics covered, the regulations, the GCP guidance.
 - That it is strongly recommended to have an evaluation before and after the training course.
 - That the organizations that use this reference training document are requested to give a feedback on the training and the difficulties in the use of the support.

Feedback

After 2 years, this ‘reference document’ is used by many private sponsors, universities and CROs as a basis for their training course. The feedback is posi-

tive on the content, but users want a step ahead, with the development of training modules, a means of recognizing of training material developed in accordance with the reference document, and dispensation of training courses for trainers.

Perspective

In such a context, an initiative was settled, including the High School of Public Health, Cengeps (an organization dedicated to facilitate clinical research in the hospitals), Afssaps, ethics committees, representatives from university, public and private sponsors, CROs, and investigators. The aims of this group are as follows :

- Implementation of a training courses for trainers, with the possibility of 'labeling' training course materials and trainers trained by this school. The pilot phase (first mock-up training courses for clinical trial specialists) is planned for 2012, Q4.
- Implementation of a committee working on medium- and long-term perspectives for initial and continuing training for investigators.

E-learning initiative from academics

Based on issues found at investigator sites, DIRC GO (West interregional delegation of hospital clinical research) developed and implemented an e-learning training on good clinical practice, adapted to the constraints of training investigators, named Formedea.

Interactive and easily accessible on the web (24/7), Formedea explains, in practice, regulations based on real cases encountered by investigators and clinical staff.

Control of knowledge is integrated at the end of each training session, leading, when successful, in a statement being issued.

Three training modules are available, each about 1 : 30 hours : Subject/Patient Information and Consent, Safety Management, and Data Management. These are based on the guidance developed by Afssaps, LEEM an AFCRO. Formedea is available to all institutions, after contracting (low level fees covering the maintenance and evolution of the system).

Germany

1) Education and training

Koordinierungszentren für Klinische Studien in Germany, the KKS Network, has developed standardized curricula to train investigators, study nurses and CRAs for their special tasks/functions in the planning and conduct of clinical trials. For courses conducted according to those curricula (see example, Appendix 3) and for which the results of the evaluation of the course meet the requirements specified by the KKS Network a certificate is provided that confirms the quality of the course. The different curricula reflect the requirements in the special field of activity of each professional group. The KKS Network has developed rules for the contents, prerequisites and duration as well as for the continuous evaluation of their courses.

2) Patient involvement in clinical trials

There is no general and formal patient involvement in clinical trials. However, there have been a number of studies and there are certain indications where patient groups and potential study patients are involved from the beginning. These are very specific rare diseases such as muscular dystrophy (TREAT-NMD) but also some long-term oncology studies with special impact on QoL data. We found in our own institution over the years, especially in long-term trials with outpatients, was a very close relationship of the patients with the study nurse (s) on site. We therefore used study nurses in a number of our trials to obtain an accompanying feedback on collateral study objectives during the trial course. It could be advantageous to add some specific training into that direction in the SN-courses and use their intensive patient contacts for continuous patient involvement during the study course.

Portugal

1) Ethics committee training

-all the 35 members of the Central Ethics Committee for Clinical Research (CEIC) meet every month and in all meetings 1 h is reserved for training/edu-

cation : that means that one of the members, or more frequently,

-one invited expert gives a 30 min lecture on a topic followed by discussion. Although some previous educational meetings on ethics in human research have been organized (including a national one promoted by CEIC last year) more formal educational meetings as an organized training program have not been set up yet.

-anyway, CEIC is promoting the establishment of a working group to work closely with local ethics committees and training will be one of the issues. Ideally we all (including CEIC members) should have a minimum training certificate.

2) Patient participation in clinical trials

Patient groups have not yet been very active in this, but in some centers, such as in the Cancer Institute at Lisbon, patients, their relatives and the general public are invited once a month to an evening session on a cancer topic. These sessions have been a success for the last 2 years and patients are eager to attend these kinds of sessions. Psychologists and social workers understood the need of the patients and their relatives and promoted these meetings. The dynamics of these sessions may be used regularly for discussing issues in clinical research and they can contribute to increasing awareness about clinical research and the need for patient involvement in the several phases of clinical research. Central cancer centers in Portugal are the main contributors for clinical research.

Feedback from patients organizations in Portugal

Main points are :

Information

-the language and terms used are crucial in the understanding of science information by patients

-channels by which such information is reported must be independent and the information should be checked previously by patients organizations to ensure its understandability by patients in general.

-Many NGOs would be willing and able to serve as conduits for information from the Portuguese govern-

ment and international research organizations through websites, social networks, printed information (books and pamphlets), emails, phone helplines etc. In addition, there are international umbrella groups (for instance Europa Donna in Europe for breast cancer), which are excellent vehicles for disseminating information across regions.

Participation in all stages of clinical research

-sponsors should promote the inclusion of patients in the validation of objectives for research. This could be achieved if academic sponsors contact patients' organizations to discuss this.

-Several ways in which sponsors could include patient organizations in the discussion of clinical trials :

-promotion and organization of certified expert-patients' associations, could facilitate this. Certified expert-patients' organizations could have sittings, with sponsors, to discuss and validate objectives for clinical research. The proposal is that certification could be issued by the regulatory authorities.

-the other way is to contact the main patient organizations, in each country. For instance, for Portugal, in a breast cancer trial three associations could be reached. Two of them, Reach Out and Europa Donna are part of major international organizations.

-the relevance of hearing patients during the design phase of research is that patients may contribute with their own agenda, concerning the objectives of clinical research (prevention studies, to develop less toxic and individualized treatments).

Another comment

Ideally the subgroup working on this topic will include representatives from patient and health advocacy organizations to ensure that patients' needs are understood and that the language used with patients is accessible and clear.

Norway

There is no organized, obligatory training or education in clinical trials for medical doctors, nurses or other health personnel involved in clinical science

in Norway. However, various courses exist and the personnel take part in GCP training in relation to the single trials.

The Norwegian Medical Association, on behalf of the Specialist Committee in Clinical Pharmacology, has recently proposed to the Norwegian Health Authorities the establishment of training and courses in clinical science/drug development and GCP for medical doctors in various disciplines.

Oslo Cancer Cluster consisting of 30 medium and small sized pharmaceutical companies located at the Campus of Oslo University Hospital will develop a mutual training program in GCP for employees in the companies and in the hospital. Nurses and MDs dealing with phase I / II studies in oncology must formally undergo training in GCP. Due to a lack of academic driven courses most of the education is provided by specialists from pharmaceutical companies. Once a year, academic driven Scandinavian courses in GCP for MDs and nurses in oncology are organized in collaboration with academic institutions from all Scandinavian countries. The initiative is taken since several clinical trials are already being conducted among clinics in Scandinavia. A similar model can be considered among countries that already have ongoing collaborations in running clinical trials.

6. WEB-BASED EDUCATION IN CLINICAL SCIENCE

Below are listed some examples of web-based sources for education and training in clinical science around the world.

General sources

Key information for health research management

<http://www.healthresearchweb.org/common/index.php?lg=en>

GCP-Online-Training

Koordinierungszentren für Klinische Studien in Germany, the KKS Network

[http://kks-netzwerk.de/media//dokumente/KKSN_Online_Flyer_08\[1\]-final.pdf](http://kks-netzwerk.de/media//dokumente/KKSN_Online_Flyer_08[1]-final.pdf)

Global Health Clinical Trials Program

(www.globalhealthtrials.org)

Internet forum where trialists can ask questions, post answers, share information on practice, process and ethics

www.cohred.org

IRENSA (International Research Ethics Network for South Africa)

Trials of Excellence in Southern African (TESA) program funded by EDCTP

<http://www.clinicalresearchtrainingonline.com/signon/>

(US-based, for-profit)

http://www.westafricanbioethics.net/wabcms/index.php?option=com_content&task=view&id=23&Itemid=2

Training for staff in clinical research

US NIH Clinical Research Training On-Line

<http://www.cc.nih.gov/training/training/crt.html>

US NCI Education for HealthCare Professionals about Cancer Clinical Trials

<http://www.cancer.gov/clinicaltrials/education/clinical-trials-education-series>

Training for members in Institutional Review Boards

South African Research Ethics Training Initiative SARETI

(<http://www.up.ac.za/sareti/sareti.htm>)

www.trree.org

(Training and Resources for Research Ethics Evaluation for Africa)

Education and training for students

London School of Hygiene and Tropical Medicine, University of London, offers PG Diploma and MSc in Clinical Trials by distance learning.

<http://www.lshtm.ac.uk/prospectus/masters/dmsct.html>

The School of Public Health at the University of Ghana offers an MSc in Clinical Trials, which is a "sister" program to the London School of Hygiene and Tropical Medicine's MSc.

http://www.ac-bridge.org/index.php?option=com_content&view=article&id=10&Itemid=25

Master of Health Science (Clinical Data Management), University of Sydney, offers advanced study in the design and management of clinical trials and other related projects.

http://sydney.edu.au/handbooks/health_sci/18_himtpg.shtml#mhscdm

Information and education for patients

US NCI Education for Lay Audience and Cancer Patients about Cancer Clinical Trials

<http://www.cancer.gov/clinicaltrials/education/clinical-trials-education-series>

www.healthtalkonline.org

www.youthhealthtalk.org

7. RECOMMENDATIONS FROM SUBGROUP THEME STATEMENT

The speedy development and completion of academic clinical trials must be viewed as a priority in order to prevent disease, as well as reduce the morbidity and mortality of disease.

1) The culture of clinical science

Cultural issues as they relate to education and training in clinical trials

The domain of clinical trials is nested within a larger domain of clinical research in the healthcare environment. This is again nested within the broader community. The individual is the ultimate stakeholder in clinical research. The perception of the benefits and harms of clinical trials for both citizens and the more specialized healthcare community drives the cultural ethos underpinning clinical trials research.

Culture at the level of the healthcare community

A healthcare culture supportive of clinical trials would allow a clinical investigator the opportunity to attend to his or her research duties without compromising, or being perceived as compromising, their clinical duties. Clinical colleagues would have a high degree of understanding of the importance of clinical research and would be encouraging thereof. This can

only be achieved if the necessary infrastructural and capacity support is available to allow for protected research time for the investigator without the burden of a double workload. Provision must be made to allow for fewer clinical duties and for additional staffing to cover time away from the clinic.

It is of importance that clinical colleagues, not involved directly in clinical trials, can take advantage of education and training in clinical science as a basis for their knowledge and understanding as well as cooperation with the clinical scientific staff.

Culture at the level of the broader community

At the level of the general public, a high level of knowledge of the need for trials and a better understanding of evidence-based healthcare is required for a community culture supportive of clinical trials. In many parts of the world, there is a growing distrust of the medical profession and the concern that members of the public are treated as 'guinea pigs' in clinical trials. Increased engagement between scientists and the general public is necessary to dispel such fears and to create positive perceptions of the work of clinical trial investigators.

Culture and the public good

At both levels outlined above, greater recognition is required that there is public benefit arising from non-commercial clinical trials that must be driven by a public service ethos. This is in direct contrast to research driven for private profit. This ethos is at the core of a culture supportive of non-commercial clinical trials³⁶.

2) Infrastructure

There should be adequate support for national and local institutional/university medical center infrastructure for academic clinical trials. This support may come from national, regional, and local governments, from charities, or some combination thereof. The support should include the facilitation of academic clinical trials, including effective and efficient regulation, timely access to standard and novel therapeutic agents, integration of academic clinical trials

into national healthcare systems, and overcoming barriers to international collaboration. In addition, the national healthcare system should pay for the routine patient care costs associated with academic clinical trials.

At the national level, infrastructure support should include support for clinical research units to coordinate academic trials conducted by networks of investigators. The responsibilities of these clinical research units includes data collection, biostatistical design and analysis, ongoing monitoring of trial sites, quality assurance, and regular meetings/teleconferences of academic investigators. In addition, national infrastructure to facilitate clinical trials should include support for national or regional ethics committees for multi-institutional academic trials as well as national biobanks and informatics.

At the level of the local institution/university medical center infrastructure support should include the costs of local ethics committees and clinical research units, time for physicians, nurses, pharmacists, and data managers to plan, implement, and conduct clinical trials, and educational programs for staff, patients, and their families about academic clinical trials. In addition, participation in academic clinical trials should be considered an important factor for evaluation and promotion at the local institution/university medical center and university. Finally, for certain high-risk trials, such as phase I trials or high-dose chemotherapy with hematologic support (“bone marrow transplant”) trials, additional infrastructure is required at local institutions.

Education and training

The general curriculum for schools of medicine, nursing, and pharmacy, required for all students, should include the principles of evidence-based medicine, including clinical trials. Graduate level programs in clinical trials should be available for both physicians and nurses. Post-graduate training for doctors, nurses, and pharmacists should include further education on clinical trials. These training opportunities, which should be provided both by institu-

tions/universities/academic medical centers, and professional societies, should include short courses, as well as ongoing lecture series. These educational programs should highlight the critical elements of Good Clinical Practice (GCP). The conduct of specific clinical research projects also provides another good opportunity to teach GCP to all the healthcare professionals participating in each research project.

In addition, undergraduate and graduate educational programs in biostatistics, epidemiology, and public health should include focused education on clinical trials. Didactic programs for data managers, with national standards for certification, should be available. Similarly, didactic programs for administrators of ethics committees and clinical trials offices, with national standards for certification, should also be available.

Global core competencies

Current guidelines require education & training of investigators in clinical trials. This is a mandatory prerequisite to fulfill the responsibilities of investigators. Investigators have to make sure that all staff involved has the proper qualifications and training to perform designated tasks. However, little is specified regarding the amount of training required, the content and learning outcomes, or the certification provided for investigators.

Aimed at the staff involved in Clinical Trials the concept of a Global Core Curriculum or Global Core Competencies is proposed as a model for the development of education and training within the field of Clinical Science. This concept has been introduced for medical oncologists in collaboration between ASCO⁴⁾ and ESMO⁴²⁾ in order to promote the same International Standards for medical oncologists training all over the world. Development of a Global Core Curriculum for Clinical Trials can take advantage of existing models built up on core areas of clinical science such as in Japan (Appendix 1) and in Europe (Appendix 2) and can be adapted to the needs of different health personnel professions including medical doctors, nurses, pharmacists and others.

Although each country has an independent responsibility as well as regulatory mechanisms in the field of clinical trials, it is crucial with support from governments and regional and international bodies to develop and implement a common strategy and framework for education and training. This will include, in addition to defining the contents of learning, systems to ensure learning outcomes and certification.

Specified training programs related to high-risk trials

High-risk trials, such as in phase 0 and phase I, represent particular challenges and tasks for the clinical trial staff in relation to performance of procedures, time lines for initiating study specific procedures with regard to the single study object/patient and high-level attention to safety/adverse events and more.

It is recommended that training programs should be established for those who undertake clinical research that may require specific expertise or have significant risk for study participants, such as phase 0 and I clinical studies. This requirement is considered to be in accordance with the introduction of a risk-based approach as a model in clinical research.

Harmonization and accreditation of education and training

In order to harmonize standards for education and training in clinical trials the following is recommended :

- Definition of standard education and training for investigators and other members of the clinical research team, according to agreed global core competencies, learning outcomes and re-training intervals is needed as a basis for accredited qualifications.
- Work towards standardized, mutually and internationally recognized *accredited qualifications* in patient-oriented clinical research.

Harmonization of degrees, diplomas or other certificates issued by a competent authority attesting the successful completion of a recognized program will require an accreditation process for recognition in other countries. Countries that have signed up to

the principles of the Lisbon Recognition Convention declare that the recognition criteria and procedures applied are in compliance with the Council of Europe/UNESCO Recommendation on Criteria and Procedures for the Assessment of Foreign Qualifications and Periods of Study. National ministers of education have committed themselves to improving the recognition system and established national action plans. These were subsequently analyzed by the ENIC/NARIC networks.

The European Network of Information Centres on academic recognition and mobility (ENIC) is a network created on the initiative of the Council of Europe and UNESCO and made up by national information centers of the States party to the European Cultural Convention or the UNESCO Europe Region (comprising USA, Canada, Australia and New Zealand, among others). The network serves to implement the Council of Europe's and UNESCO's Lisbon Recognition Convention and, in general, to develop policy and practice for the recognition of qualifications. The ENIC network works in close collaboration with the NARIC network and provides the same services in regard to information on higher education and mutual recognition. The ENICs were designated by national authorities in the respective countries, but the status and the scope of work of individual ENICs vary.

The National Academic Recognition Information Centres (NARIC) network was created in 1984 on the initiative of the European Commission and consists of national information centers in all EU and EEA member states and all the associated countries in Central and Eastern Europe and Cyprus. The network aims at improving mutual academic recognition of higher education programs by e. g. offering information on the procedures for recognition of higher education diplomas, on national education systems etc. The NARICs were designated by the Ministries of Education in their respective countries, but the status and the scope of work of individual NARICs vary. In most countries, NARIC is integrated with

the ENIC network and has responsibilities in the implementation of the Lisbon Convention.

In a number of countries ENIC/NARIC makes recognition decisions. In most cases the *de jure* professional recognition for employment in regulated professions is carried out by competent authorities (often professional organizations) nominated by the government, but in some countries specific ministries are in charge of recognition.

Training for members in ethics committees

All members of ethics committees should receive education in the principles of clinical research in accordance with the development of Global Core Competencies. These competencies and training programs should be developed and implemented in collaboration with the relevant international agencies.

Innovative training concepts

- A central catalogue of tools, resources and methods used for education and training in clinical trials should be established
- New and effective learning and teaching methodologies should be adopted

An important issue concerns the development and implementation of innovative concepts for education and training. As an initial step, a central catalogue of tools, resources and methods that can be used for education and training is necessary to share *best working practice*. Future integration of new learning and teaching methodologies into their respective training programs will have to determine on a comprehensive basis : (i) how to incorporate effective and relevant teaching methodologies and tools into the programs that exist or are being developed, (ii) how to maintain a ‘teaching technology and methodology’ watch to ensure that future education and training initiatives keep pace with developments in pedagogy, and (iii) how to develop new tools if necessary. A platform to address these tasks is currently developed by the IMI JU project EMTRAIN⁴⁰.

A best practice is in general a set of guidelines, technique or methodology that is effective, and through experience and research, has proven to consistently lead to a desired result of improved quality and speed, and is cost effective. Best practices are often proposed by an authority, such as a governing body or management in order to achieve improved control, influence and desired results.

Organizing of education and training in clinical science

This issue is dependent on organization and coordination both at national and local levels, as well as at the international level :

National level

Local scientific societies together with academic groups, universities and governmental regulatory bodies must participate in coordinate action for the development and implementation of country based programs for education and training in clinical science. At this level, universities and governments play a key role in this regard.

International level

International cooperation in education and training for clinical science is an essential tool to facilitate collaboration in the field of clinical trials. Development of a common basis for knowledge and experience for the participating health personnel may strongly enhance the efficiency of international cooperation and the quality of performance and results.

Leading national and international organizations with expertise in the field are important in providing advice and support to local organizations. This external support will provide already proven tools and programs that, adapted to the local needs, will facilitate the process, shortening the implementation time and avoiding duplications.

Examples of international collaboration

1. America : A network of National Cancer Institutes (RIC) is working to develop coordinated action considering different aspects of cancer research. The network comprises the NCI's from Mexico, Colombia, Peru, Brazil, Uruguay, Panama, Cuba, Paraguay and Argentina.

Some of the projects include establishing a tis-

sue bank and harmonization-coordination of research. The Secretary is located at the Brazilian NCI, in Rio de Janeiro, Brazil.

Another ongoing initiative is the Office of Latin American Cancer Program Development (OLACPD), an innovative partnership between the National Cancer Institute (NCI) and the Fogarty International Center (FIC), which was launched in recognition of the opportunity to support and enhance cancer research and care in Latin America.

This office launched the US-Latin America Cancer Research Network, a collaborative partnership between U. S. and Latin American countries to support high-quality research and clinical studies. The Network is responsible for developing a comprehensive understanding of the status of cancer disease burden, research, and care infrastructure, and currently includes Argentina, Brazil, Chile, Mexico, and Uruguay⁴³).

The mission of The Breast Cancer Research Foundation[®] (BCRF) is to achieve prevention and a cure for breast cancer in our lifetime by providing critical funding for innovative clinical and translational research at leading medical centers worldwide, and increasing public awareness about good breast health. BCRF is funding, for the first time in the region, independent breast cancer clinical research for a network of researchers of the Latin American and Caribbean Society of Medical Oncology (SLACOM). SLACOM has developed a Cancer Research Institute for the promotion of independent cancer research^{44,45}).

The American Society of Clinical Oncology has several tools promoting research at the international level. These activities are mainly focused on researchers, nurses and data managers. Some of the current activities are the International Clinical Trials Workshop (ICTW) and the AACR-ASCO workshop : Methods in Clinical Cancer Research.

2. Norway is participating in several international clinical trials in oncology both in Scandinavia, Germany and the UK. The advantages of these col-

laborations are many and especially for small countries since the number of patients available for clinical trials limit the country in obtaining their own experience within a short time period. International clinical trials require that each participating center has similar guidelines for conducting clinical trials.

3. The global academic breast cancer community has developed strong international networks to perform large breast cancer treatment trials and meta-analyses of treatment trials. These networks include the Breast International Group, the International Breast Cancer Study Group, and the North American Breast Cancer Group.

4. The global academic gynecologic cancer community has developed a strong intergroup to exchange information about current clinical trials and develop joint clinical trials, the Gynecologic Cancer Intergroup. The current membership includes 18 clinical trials groups from Asia, Australia-New Zealand, Europe, and North America.

5. Academic investigators in pediatric cancer have begun to develop a global consortium for clinical trials for children with cancer. The US-based Children's Oncology Group now has participation from centers with expertise in the management of pediatric cancer in Australia, Canada, New Zealand and Switzerland and is working to strengthen ties in clinical research with pediatric oncologists in Latin America, Asia, and Europe.

6. The European Organization for Research and Treatment of Cancer, established in 1962, now supports a network of over 300 hospitals or cancer centers in more than 30 countries. Each year, EORTC enrolls approximately 5000 cancer patients in academic clinical trials.

7. The European Clinical Research Infrastructure Network (ECRIN) is a pan-European infrastructure to support multinational clinical research⁴⁶). ECRIN is based on national networks, presently covering 14 countries in Europe.

3) Careers in clinical science

In order to build robust clinical trials research, investigators and potential investigators require a clearly mapped and appropriately funded career path. Creating career paths is dependent on suitable infra-structural development and funding streams as outlined in the preceding sections. Specific recommendations regarding career pathing include :

Establishing research chairs and Centers of Excellence

Within countries, relevant government departments should provide funding earmarked for the establishment of research chairs in clinical research. Such chairs can be sited within academic institutions and can provide start-up and maintenance funding. Currently, countries such as Canada offer a five yearly grant system for such chairs. However, investment in clinical research requires a longer term vision and that funding should be secured for a minimum of ten years. The number of such chairs will be determined by country level resources but we recommend that each country establish a minimum number of chairs.

At a regional level, economic structures such as the European Union, or in southern Africa the Southern African Development Community (SADC), should provide similar dedicated funding streams to establish research chairs and large-scale research institutes where opportunities for collaborative clinical trials exist. Such regional institutions can provide training opportunities for investigators and a critical mass of all disciplines required for clinical trial conduct. The model for this could be multiple collaborative institutional chairs sited in different countries, but together responsible for promoting the conduct of multinational trials within the relevant region.

Development of a clearly defined clinical research specialty track

Current medical specialization focuses on clinical skills accrual rather than gaining experience in research. Developing a clearly defined clinical research specialty track within graduate programs will allow trainees to choose clinical research as a

recognized career path. Country to country requirements will differ greatly in this regard, with some countries, such as the USA, already providing dual degree programs.

Establishing competitive pay and promotion structures for clinical research

Currently, clinical investigators conduct research within their clinical specialist positions. The creation of separate posts for clinical research with the appropriate level of payment linked to these posts will encourage more potential investigators to remain as leaders of non-commercial clinical trials rather than migrate to engage with pharmaceutically driven trials.

4) The patient perspective

The roles and perspectives of the public and patients should be emphasized in conjunction with the further developments of the clinical scientific field. Patients should be regarded not only as study objects, but as contributors and partners.

It is thus recommended to :

(1) **Build comprehensive networks** of centers to share basic information on clinical research and provide tools to train citizen and patient advocates for clinical research (example DIPEX). Education and training for the public, patients, their families, and patient advocates. Public education programs regarding the importance of evidence-based medicine and clinical trials should be in place at the national and institutional/medical center level. Trial-specific educational material should be available for patients and their families considering participation in individual trials. Training in the principles of clinical research should be available for patient advocates who participate in the design, review, oversight, including ethics committees, and promotion of academic clinical trials.

(2) **Increase transparency on clinical research**

- access for public and patients to registers for clinical trials
- publication of results according to standards

- (3) **Involvement of patients or patients' associations** early in the discussion of
- clinical projects (e. g. usefulness/relevance of quality parameters/endpoints)
 - ethical issues
 - decisions concerning the use of funds

8. MAIN RECOMMENDATIONS

1) Education and training

Countries should develop and implement policies on education and training in clinical research. This will lead to a knowledgeable health research community, encourage health research to flourish leading to better healthcare decision-making and ultimately improve the health and welfare of the population.

One top priority must be the development and support of independent and publicly funded basic, epidemiological and clinical cancer education research and training.

Educational and training objectives must emphasize clinical and practical objectives. Studies must be oriented to the local and regional characteristics. Cultural, racial, ethnic and socioeconomic parameters must be included in the educational curricula.

Information, education and training regarding clinical research should be provided for clinical researchers, health personnel in general, students, patients, members of the public and members of ethics committees, regulatory bodies and sponsors.

The general curriculum for schools in medicine, nursing and pharmacy should integrate the principles of evidence-based medicine including clinical research trials. Graduate level programs and postgraduate training in clinical research should be available for all healthcare providers including doctors, nurses, pharmacists and allied health workers. Training programs for those who undertake clinical research that may require specific expertise or have significant risk for study participants, such as phase 0 and I clinical studies, should be established.

A concept of *Global Core Competencies* in clinical research should be developed as a basis for knowledge and skills for investigators and other members in the Clinical Research Team adapted to their different responsibilities and roles. Connected to this concept standardized, mutually and internationally recognized *accredited qualifications* in patient-oriented clinical research should be defined.

All members of ethics committees should receive education in the principles of clinical research in accordance with the development of *Global Core Competencies* always adapted to the local conditions. These competencies and training programs should be developed and implemented in collaboration with the relevant national, regional and international agencies.

National governments and international bodies should give priority to developing capacity for clinical research by facilitating and supporting the establishment of appropriate training programs, particularly in countries without such programs already in place.

A *Working Group* should be initiated under the umbrella of the World Health Organization with representa-

tion from scientific societies, clinical research networks and experts, academic institutions as well as representatives from regulatory authorities, ethics committees and consumer organizations in order to follow up and translate these recommendations into a plan for implementation. Periodic evaluations and reports, accountability and metrics must be included as part of the implementation plan. In accordance with the reported results, the Working Group must make proper adjustments periodically.

2) Infrastructure

Infrastructure for the performance of clinical research should be developed at the international, national and local level. *Global network* (s) should be developed in order to facilitate cooperation and performance of non-commercial multicenter clinical trials in an open and efficient manner.

A Working Group should be initiated to develop a framework for a global network structure covering the different therapeutic areas. It is recommended to challenge existing clinical network organizations and scientific societies in different parts of the world to take a lead in this Working Group through representation from :

Europe : European Science Foundation (ESF) , ECRIN, EMTRAIN, European Forum for Good Clinical Practice (EFGCP)

North America : *National Institutes of Health (NIH), Canadian Institute for Health Research, International Clinical Trials Working Group-ICTWG (ASCO)-AACR-Office of Global Health (NCI-US)*

South America : *Clinical Research Institute (SLACOM)-Network of LA Cancer Institutes (RINC)*

Asia : *Middle East Cancer Consortium*

Africa : *AORTIC, EDCTP*

Australia : *Clinical research networks*

At the national and local levels, infrastructure support should include development and funding of clinical research units with adequate staff and support functions as well as organizing networks of research units and investigators.

True professional and academic careers should be established for clinical research professionals including clinical research physicians, study coordinators, nurses, pharmacists, biostatisticians and data managers. To facilitate this ambition, competitive pay and promotion structures for clinical research careers should be developed. Accreditation, certification and continuous education must be encouraged and promoted, both at governmental as well as private institutions.

National governments, NGOs, and international bodies should give priority to developing, facilitating, and supporting the infrastructure for clinical science.

3) Patient roles and involvement

The individual is the key stakeholder in clinical research. The direct participation of patients in clinical trials as well as their contribution to improving the quality, safety and relevance of clinical research is of critical significance for the success and impact of clinical science as a whole.

The roles of patients in clinical trials should be strengthened by means of :

- (1) Participation from patient organizations in building up and running future activities of the global network (s) in clinical science (as described above)
- (2) Involvement in all stages of clinical research by
 - Participation as members in ethics committees
 - Influence on planning, designing, conducting, disseminating and implementing the results from clinical science mediated through participation in global networks
- (3) Improved information and education
 - Informed consent forms in clinical trials must clearly and in understandable language and terms specify the vital information needed for making informed decisions within a manageable document length.
 - Clinical trial databases and registers must be made available in a patient-oriented manner with general as well as specific information about clinical trials written in understandable language.
 - The Global network should develop an international website in clinical research in collaboration with its regional and local members with patient-oriented information and education adapted to local needs and requirements.
 - Local research units in the global network should arrange meetings with information and education for public, patients and their families.
- (4) All these actions must be implemented according to the local environment and particular sociocultural characteristics of the populations. The language must be simple and easily understandable. Education of the public, governmental bodies and medical community on the importance of cancer research must be emphasized and promoted in a proactive manner.

National governments and international bodies, together with all stakeholders involved should be responsible for facilitating improved information to and involvement of patients in clinical trials.

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10. APPENDIX

APPENDIX 1

Essential issues in education for Japanese professionals in clinical trials

Essential Issues				
	General	Scientific	Ethical	Regulatory
Main Items	Importance of Clinical Trials and Evidence Based Medicine	Protocol	Principles of Research Ethics	GCP
	History of Human Research	Case Report Form (Electric Form)	Human Subject Protection	Ethical Guidelines for Clinical Research
	Development of New/Unapproved Drugs and Medical Devices	Study Background and Study Purpose	Informed Consent	
	Type of Clinical Research	Drug/Medical Device Information	Patient Safety Issues : Reporting of Adverse Events (Handling of Safety information)	
	Non-Clinical, Phase I-IV Clinical Trial	Study Design : Comparison, Randomization, Blind, Placebo Control	Ethics committee and IRB	
	Research Terminology and Definitions	Outcome Measurement		
	Research team	Data Collection and Data Management		
	Conflict of Interest	Statistical Analysis		
	Clinical Trial registries			
	Quality Control (QC) and Quality Management (QA) of Clinical Research			
Additional Items	Biases in Clinical Research	Investigator-Initiated, Indication-directed Clinical Trial	Management of personal Information	Pharmaceutical Affairs Law Article 80-2
	National Health Insurance Coverage for the Patients on Clinical Trials (Hokengai-Heiyō-ryōyōhi)	Clinical Trial under the Evaluation System of Investigational Medical Care	Indemnification and Compensation	Personal Information Protection Act
		Research Management/Operations		Ethics Guidelines for Epidemiological Research
		Global Study Management		Ethics Guidelines for Human Genome/Gene Analysis Research
	Special interests, such as Clinical Pharmacology, Pharmacogenomics, Translational Research, Quality of Life, Cost			Guidelines for Clinical Research in Gene Therapy

APPENDIX 2

A European Syllabus for Training Clinical Investigators

Section 1 A critical review of the trial concept

The rationale of the trial
Stages and milestones
Clinical/public health importance

The rationale of the trial must be detailed, and the design must address the specific question according to present state of knowledge. The study should be put into a clinical practice context, and its hypothesis carefully defined.

Section 2 Clinical trial design

General issues

Type of design and rationale
Protocol and Case Report Form (CRF)
Use of control groups/active substance and placebo
Inclusion/exclusion criteria
Efficacy and choice of endpoints
Safety outcomes Quality of life/health economics, if appropriate

Statistical issues

Fundamentals of statistical testing
Power & sample size determination
Superiority or equivalence

Special populations

Children/elderly
Pregnant women/foetuses
Renal/liver failure
Ethnic factors Gender

Section 3 Ethical issues

Values and principles in clinical investigations
International guidelines
Patient care in clinical research
Responsibilities in research
Conflict of interest
Ethical review
Informed consent
Vulnerable populations
Biological samples
Genetic research
Databases and confidentiality Fraud & misconduct

Depending on the population studied and the type of study, the clinical trial may need to address

different ethical issues, e. g. in genetic research, when taking/storing biological samples, or in exportation of data outside the EU.

Section 4 Study organization

Clinical trial registration
Selection of investigators
Organization and delegation in the investigation team
Flow chart
Internal and external communication
Contracts and agreement
Liability and insurance
Essential and other required documents
Logistics Responsibilities for the development of the intervention (medicinal products, medical device, etc.)
Data management
Clinical trial committees

The success of a trial is largely dependent on its organization. There must be an organized flow of information between the principal investigator and the sponsor, the Ethics Committee, the national regulatory authority, if appropriate, other investigators and participants. Logistics including handling of informed consent procedures, eligibility, randomization, drug accountability and data flow should be established before the study starts. Involvement of other parties (e. g. pharmacies) should be considered.

Section 5 Legal, regulatory and good practice framework

Regulatory and legal frameworks
Good Clinical Practice according to ICH and EU Clinical Trials Directive
National regulations
Application to Regulatory Agency, if appropriate
Quality assurance systems
Standard Operating Procedures (SOPs)
Audits and inspections

Established quality assurance systems are crucial for the integrity of the study. They should adhere to national and international regulations and cover, when appropriate, GLP-good laboratory practice, GMP-good manufacturing practice, GCP-good clinical practice.

Section 6 Study conduct

Investigator's brochure or equivalent
Study monitoring
Safety monitoring and reporting
End-of-trial issues

The successful conduct of the study depends on all team members, their competence and understanding of the intervention. An appropriate level of quality assurance and monitoring is essential to ensure high quality of data and procedures in the study. This is based on an ongoing and continuous review of the accuracy and completeness of the data.

Section 7 Reporting clinical trials

Completeness of follow-up
Data analysis issues
Primary outcome analysis
Exploratory analysis

Clinical study report
Communication & publication of study results

Reporting of the study must be agreed beforehand in writing with investigators and sponsors. The report should address the question in the primary hypothesis and include exploratory analyses only as hypothesis generating. Missing data and incomplete follow-up should be reported. Negative results should be made public. The design should be outlined. What control groups are appropriate, what type of statistical testing is planned, and is the sample size adequate? What are the differences between superiority, equivalence and non-inferiority studies? What safety issues should be identified? The course must help the investigator to identify general and specific issues for trial design

APPENDIX 3

Example on course from the KKS Network-The Curriculum "Studienleiter" (Principal Investigator)

The Curriculum "Studienleiter" (Principal Investigator) of the KKS Network comprises a three-day attendance course. It is expected that attendees already have basic knowledge and practical experience in the conduct of clinical trials. The objective of the course is to provide knowledge of the process of planning and conduct of a clinical trial. Attendees will receive an overview of the relevant aspects and responsibilities for a principal investigator. They will be sensitized to problems which might occur during the conduct of a trial. Attendees should also learn to decide when support from other disciplines should be involved or asked for. It is not objective of the course, that the participants will be able to take on all necessary tasks in the planning, preparation and conduct of a clinical trial.

The detailed contents of the course are as follows :

- | | |
|---|---|
| 1) Organizational Information (1 Hour) | Patient selection (inclusion/exclusion criteria)/
Stratification |
| 2) Regulatory aspects (2 Hours) | Randomization |
| Tasks of the sponsor according to German drug law/
ICH-GCP | Quality of Life |
| German drug law | Patient number (number of cases) |
| Specifics of trials with medical devices | Aquivalence/Superiority/non-Inferiority |
| Other clinical trials | Adaptive designs |
| National law | Power calculation |
| Declaration of Helsinki | Practical examples |
| Informed consent | Specific questions |
| Data protection | |
| Application to ethics committee | 7) Data Management (1.5 Hours) |
| Application to competent authority (including IMPD) | CRF Design |
| 3) Principles of drug development (1 Hour) | Randomization |
| | Database/validation |
| | Data management software |
| 4) Study design (1 Hour) | Remote data entry |
| Evaluation of literature | Coding |
| Operationalizing clinical questions | Data quality/Data protection |
| Types of clinical trials/designs of clinical trials | Plausibility checks/consistency/query management |
| | Preparation for statistical analysis |
| 5) Protocol (1 Hour) | |
| Contents of the protocol | 8) Quality Management/Standard Operating Procedures |
| Questions and answers | (1 Hour) |
| Objectives/endpoints | SOPs |
| Benefit/Risk Evaluation | Monitoring |
| Clinical endpoints | Audit |
| Master protocol | Inspections/ |
| Practical information | 9) Statistical Analysis (1 Hour) |
| Amendments | Methodology of Data Analysis |
| Informed consent | Exploratory and confirmatory data analysis |
| 6) Statistical Planning (2 Hours) | Interim analysis |
| Process of planning of a clinical trial | Early termination of a trial |
| Statistical planning | Data analysis/report |
| Definition of endpoints/Primary and secondary
endpoints/ | Adverse events |
| Surrogate endpoints | Subgroup analysis |
| | Examples |
| | Project Management (2.5 Hours) |

Recruitment of study sites/cooperating partners (reference diagnostic, steering committee, etc.)	Definition of adverse events
Administrative issues (EC, insurance, competent authorities)	Reporting
Logistics	Handling of serious and/or unexpected adverse events and Suspected
Study team	unexpected Serious Adverse Reactions (SUSAR)
Financing of the trial/cost calculation	Annual safety reports/line listings
Contracts	End of the trial (1 Hour)
Supervision of recruitment	Reporting
Documentation	Report
Investigator/trial meetings	Publication
Handling of problems	CONSORT-Statement
Drug Safety (1 Hour)	Archiving