CLINICAL INVESTIGATION

COMMENTARY

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Moving forward: putting research into practice

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"I have a dream ... that such a hub or such a European Strategic Action for Healthier Europeans will help us move forward, strengthening biomedical research and putting research into practice with the aim of a healthier and wealthier Europe."

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Clinical trials are aimed at acquiring scientific knowledge and evidence to improve patients care. Clinical trials can either be run by industry, as private–public partnership in a collaboration between the pharmaceutical or medical device industry and hospitals or clinics, or it can be so called 'investigator-driven clinical trials' instigated by academic researchers.

Investigator-driven clinical trials are typically proof-of-concept studies, studies on orphan diseases, comparison of diagnostic or therapeutic interventions, surgical therapies or novel indications for registered drugs. The investigator-driven clinical trials may have a broader scope and a larger potential impact than industry-driven clinical trials.

Investigator-driven clinical trials have been under strain in Europe for a multiplicity of reasons. The most important areas to try and strengthen are the improvement of education, training and career structures, and opportunities for scientists involved in patient-orientated clinical research. This was described thoroughly in the Forward Look from the European Medical Research Council (EMRC), European Science Foundation (ESF), in 2009 [101]. The EMRC is the membership organization for all the medical research councils in Europe under the ESF. The Forward Look recommended an increased level of funding for investigator-driven clinical trials, an area where public funding has been sparse. Furthermore, it also recommended an adoption of a risk-based approach to the regulation of investigator-driven clinical trials, to ensure that these trials are carried out with an appropriate number of patients to produce statistically reliable results so that the trials are correctly designed and powered and the procedures for obtaining authorization are streamlined.

Aim one is to perform the necessary clinical trials in all research areas, and to perform them with proper design and the necessary funding, infrastructure and trained scientists to perform the trials. The next important step is to implement the research results in clinical practice through so called 'evidence-based medicine.'

The Forward Look from the EMRC in 2011, titled 'Implementation of Medical Research in Clinical Practice' has a series of recommendations regarding the implementation of clinical trials [102]. The Forward Look was developed by dedicated high-level panels of experts in the field of clinical investigation, who wrote a draft report that was then debated at a Consensus Conference by the Council of Europe in Strasbourg (France) in the autumn of 2010. After a thorough revision of the document, in collaboration with all panel and Consensus Conference participants, the Forward Look was finished, approved by EMRC and launched in May 2011.

The Forward Look launched in 2011 has ten recommendations:

- Strengthen European work, collaboration on, coordination with and funding of systematic reviews of existing evidence, comparative effectiveness research, health technology assessments and clinical practice guidelines;

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- Foster transparency and require evidence on comparative effectiveness and costs of drugs and other new technologies to demonstrate added value before approval;
- Improve education, training and career structure of health professionals;
- When relevant, inform patients and the public about the prioritization, funding, planning, conduct and reporting of clinical comparative effectiveness research and evidence-based medicine;
- Support and facilitate methodologically sound high-quality clinical research inspired by gaps and uncertainties identified in systematic reviews that answer the needs of patients, health professionals and society;
- Promote rigorous reporting of all clinical studies;
- Strengthen shared national and international open-access databases on protocols, data, reports, systematic reviews and health technology assessments;
- Generate, through multidisciplinary teams and with patient involvement, high-quality, evidence-based clinical practice guidelines according to common standards and criteria;
- Implement and improve guidelines in clinical practice through IT tools, audit and feedback, clinical indicators and continuous updates, and strengthen the research evidence base for effective implementation strategies;
- Increase use and implementation of high-quality health technology assessment reports and clinical guidelines in hospitals, primary care and all administrative processes, including financing of treatment and technologies.

The next steps will be to facilitate the implementation of the recommendations. It has been relatively easy to set these up, but the difficult part will be to ensure they are applied. Several important stakeholders are crucial for the implementation process. It is not the job of the EMRC to exert the recommendations; we can give them to the scientific community as inspiration and the whole community must work on it. The academic researchers at university hospitals, academic medical centers, university departments and other institutions are the important producers of clinical investigations. They are often linked to, or part of, universities, where deans of medical faculties have important roles for recognizing and strengthening the importance of clinical investigations.

There is a tendency towards broader recognition of basic and translational research than of clinical investigations from certain university leaders, perhaps influenced by the fact that the H-index and citation scores are sometimes higher in basic research than in clinical. In my opinion this should be changed, as it might also be laborious, complicated, time consuming and difficult to do proper clinical trials with proper design and following the Consort Criteria [103].

Recognition from the highest level of leadership is important for an area to thrive. Clinicians and other staff members at the hospital are crucial for clinical investigations and, in the future, not only physicians, but also nurses, technologists and other staff groups will be involved actively in research. All those participating in research should be motivated to do research and participate in conferences; an active engagement from all involved is mandatory for success.

Teachers in undergraduate and postgraduate medical training are crucial to ascertain that the students, physicians and other staff groups have the proper professional training for performing clinical investigations at the required quality level. When clinical research is completed, the methodologists, systematic reviewers, healthcare professionals, health economists, health technology assessment agencies, guideline agencies and Cochrane collaborators are the key stakeholders taking the results from the journal articles into the guidelines used in hospitals and clinics. The approval of a new treatment is dependent on national and EU regulators, ministry and so forth. A positive attitude towards clinical investigations is crucial among the authorities. A pedagogic role might be needed from universities and hospitals towards authorities in some countries, to encourage them to facilitate better conditions for clinical investigations and the translation of evidence-based medicine results into clinical practice.

There is a great diversity between the different European countries in the organization and level of clinical research, including the structure of the ethical commitees. Unfortunately, a large bureaucracy with lots of 'red tape' is predominant in many countries. Young researchers might find it easier to do basic research instead of highly complex clinical investigations where lots of paperwork is needed. Together with clinical everyday life in hospitals, where the demand for efficiency is increasing and increasing, a difficult situation is created for clinical research. We are facing trouble in Europe due to the complex bureaucracy, low funding, high demand for efficiency in hospitals and a low prestige around clinical investigations. If

universities, hospital leaders and authorities recognize this, it would be easier to try and revert the vicious cycle.

The most important and preeminent speakers for clinical investigations are often patients and the general public, where patient organizations and philanthropy organizations recognize the need for, and importance of, clinical investigations. In the USA, patient investigations have been prominent in collaborating with the medical community for strengthening biomedical research. In Europe we should involve patients more, both in planning of research areas, in ethical committee work and in prioritization, funding, planning, conducting and reporting clinical investigations.

For the implementation of clinical investigations into practice, the most important step is from trial reports in research articles, meta-analyses and Cochrane reports to guidelines. It is crucial for a country to have a system where learned societies and national guideline writers are linked. National guidelines should be written by all relevant stakeholders, according to local practice and possibilities, and National Boards of Health, ministry, universities, hospitals and, learned societies should work together to develop 'best practice'. In Denmark we have the 'cancer packages'. where diagnosis and treatment for the various cancer diseases are described in detail, including how many days are allowed from diagnosis to investigation and treatment. They have been a success in Denmark and have shown that it can be done as a collaborative effort [1].

From guidelines to everyday use in clinical practice in hospital departments, the key stakeholders are the hospital owners and the heads of department in the hospitals. Previously, clinicians went to conferences and took home new ideas, and those departments with a strong research profile were 'out there' to take home new knowledge and implemented new treatments first. It is still so, that research-active departments have the best treatment for patients. However, a more systematic use of evidence-based treatment is needed at present, as the complexity and the amount of knowledge has increased dramatically in recent years.

It is not enough to use the guidelines; we also need to check the use in everyday practice through IT tools, audit and feedback. Hospital owners and those responsible for the hospitals on a national level are crucial for this. IT tools are important for the whole chain, from idea from research to implementation. For several countries there is 'room for improvement' in this area.

There is a great diversity within Europe, not only in funding for hospitals and funding for medical research, but also in infrastructure and practice. To make Europe an area of first-class clinical investigations we need funding and a proper use of peer review, so that the best researchers and best ideas are funded; excellence is important. We must ensure that patients participating in clinical investigations, researchers performing clinicial investigations and physicians using clinical investigations, are looked upon positively and praised; and we need to make it easier.

The area of personalized medicine will provide a special challenge for clinical investigations in the future. With personalized medicine we will hopefully be able to give patients exactly the treatment they need on the basis of genes and epigenetics. Those patients where a new treatment is efficient because they have a certain set of genes and epigenetics can be identified, and then the right treatment can be established. For other groups of patients with another set of genes another type of medicine will be efficient. It might be expensive using gene and biomarker investigations, but it will inevitably be cheaper long term to do the right thing first in all patients. The great challenge for clinical research in this particular area is that we need to develop new trial designs, including new mathematical and statistical methodologies. It will be more complex, and involve transnational investigations and a solid and correct use of biobanks, IT and sharing of data. A new Forward Look from EMRC, ESF, is ready for spring 2012 with recommendations for the area.

It is very important to strengthen the implementation of research results in general clinical practice. An editorial in *BMJ* was written on this subject last summer [2] and special effort is needed. The opinion leaders in general practice, including those in universities, learned societies, organizations and journals, will hopefully take up the challenge and work for this. A whole chapter about the perspectives from general practice are in the Forward Look on Implementation of Medical Research in Clinical Practice [102].

In conclusion, it is mandatory that clinical investigations are designed so that they are about questions relevant to clinicians and patients. It is important that the design and methodology is appropriate, they are accessible after publication with open access, and that they are reported unbiased and in a useable form. After the research has been published and made available, the next important steps is the production of review articles, meta-analyses, Cochrane reviews, health technology assessments and the implementation in clinical practice through guidelines of high quality. This whole value chain needs to be strengthened. There is a great diversity between different systems in Europe: in some countries 'best practice' has

been developed with good guidelines implemented and used on an everyday basis, in other countries the chain is not as robust and well functioning. The learned societies and The Alliance for Biomedical Research are important for strengthening this area.

The new plans for a 'European Strategic Action for Healthier Europeans' might be the crucial step forward. We have at present serious societal and health challenges in Europe, with an aging population, and an urgent need for new therapeutic concepts that need to be both more efficacious and cost effective than existing ones. The European Strategic Action for Healthier Europeans could be a hub/house/academy/panel/forum where all key stakeholders in biomedicine and health can meet, preferably in Brussels, near to the European Commission in DG Research. The potential relevant stakeholder would ideally include (on a voluntary basis): Science Europe, the EU, charities, national funding agencies, scientists at all levels of research, the learned societies, the Biomedical Alliance, national research performing agencies, universities and deans of medical faculties, healthcare providers (e.g., the European Hospital and Healthcare Federation), patient organizations, healthcare and health research ministry, National Boards of Health, the EMRC, health technology assessment institutions and other methodologists such as Cochrane, industry with European Federation of Pharmaceutical Industries and Associations, Association of Imaging Producers and Equipment Suppliers, journal editors and healthcare insurers, healthcare economists, national and EU regulators (e.g., the European Medicines Agency), and ethic committees and guideline organizations.

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