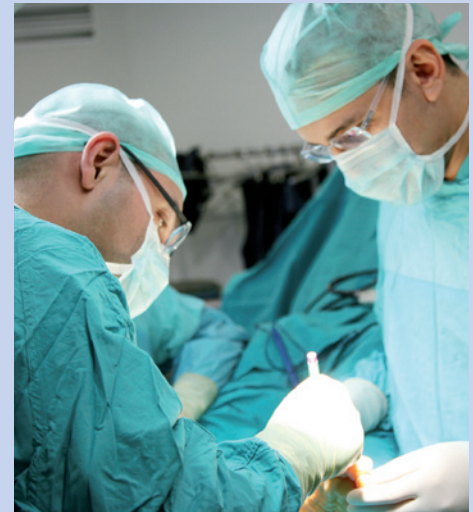


Implementation of Medical Research in Clinical Practice



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**“I have been impressed with the urgency of doing.
Knowing is not enough; we must apply.
Being willing is not enough; we must do!”**

Leonardo da Vinci (1452-1519) and Johann Wolfgang von Goethe (1749-1832)

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Executive Summary

Medical care has improved beyond recognition over the past half century. An important contribution to this improvement has been through clinical research. Clinical research includes different stages from basic-oriented research, disease-oriented research with animal models, translational research, patient-oriented research and outcome research.

When clinical research has been successfully implemented in clinical practice it can answer important questions relevant to practitioners and provide the evidence necessary to underpin practice.

It is important however, not to remain complacent and to strive for continual improvement. There is still much clinical decision-making that is not informed by evidence, and research which is carried out in a way that is not methodologically robust.

This Forward Look examines how the quality of research can be improved, and how research results can better be implemented in practice. These issues were comprehensively analysed and finally discussed and debated by more than 90 leading experts from Europe and the rest of the world in a series of workshops culminating in a consensus conference held in October 2010 at the Council of Europe in Strasbourg.

After rigorous debate and discussion, identifying gaps and highlighting best practice, a number of recommendations and conclusions were drawn, the principal of which were as follows:

Patient-oriented research questions should be framed so that they address problems that are relevant to end-users of research: patients and the public. It is important not to waste resources on duplicating research – seeking to answer questions that have already been answered; this can be avoided by carrying out systematic reviews of the literature.

Research must be methodologically sound so that the answers it delivers can be viewed with confidence and used with confidence. The protocols and results of all clinical trials should be made publicly available and reported in an unbiased way and with adequate detail.

There need to be more studies on the comparative effectiveness of drugs and other technologies and toxicological and clinical information should be made public.

Education and training for clinical researchers are not well developed and there is an insufficient number of professionals with expertise in methodology, or an understanding of evidence-based medicine (EbM), health technology assessment and health economics.

Clinical practice guidelines are one important way to implement research findings. Various models exist to produce guidelines, including those produced by scientific learned societies and those produced by central

government agencies; the different approaches have advantages and disadvantages. However, in general there is little evidence relating to the best way to ensure that research is implemented and research in this area is needed. For the future, systematic clinical practice guidelines of the highest quality is the way to go, to assure implementation of the right research results in clinical practice – so that EbM is used in each and every patient treatment, everywhere.

A key way to improve quality of care is through audit and feedback. Quality indicators can be valuable but need to be constructed with caution. Registries can also provide a rich source of information and they can be used for the generation of new research.

Primary care has a key role to play in both research and implementation, given that family doctors encounter almost the whole population, whereas fewer people go into hospital. Research results derived from specialist areas of medicine can be difficult to implement into general practice because people who see their family doctor often have a multiplicity of medical conditions that influence each other. There is a need to gain better knowledge relating to primary care.

We need greater involvement of the public at all stages of research, and healthcare professionals should be well equipped to communicate about research – including issues such as risk. Funding agencies should require researchers to report their plans for involving patients and the public in their research project.

The ten recommendations in this Forward Look are our attempt to summarise the many relevant and important recommendations in this report – gathered and developed to improve the quality of research and to improve the quality of patient treatment and healthcare, for patients and the public – here in Europe and globally. The full set of recommendations can be found in the report (page 41).

The top recommendations to strengthen implementation of medical research in clinical practice are the following:

1. **Strengthen European work, collaboration on, coordination in and funding of systematic reviews of existing evidence, comparative effectiveness research, health technology assessments, and clinical practice guidelines.**
2. **Foster transparency and require evidence on comparative effectiveness and costs of drugs and other new technologies to demonstrate added value before approval.**
3. **Improve education and training of and career structure for health professionals.**
4. **When relevant, inform patients and the public about the prioritisation, funding, planning, conduct and reporting of clinical comparative effectiveness research and evidence-based medicine.**
5. **Support and facilitate methodologically sound high-quality clinical research inspired by gaps and uncertainties identified in systematic reviews that answers the needs of patients, health professionals and society.**
6. **Promote rigorous reporting of all clinical studies.**
7. **Strengthen shared national and international open access databases on protocols, data, reports, systematic reviews and health technology assessments.**
8. **Generate, through multidisciplinary teams and with patient involvement, high-quality evidence-based clinical practice guidelines according to common standards and criteria.**
9. **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.**
10. **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.**

We hope that this Forward Look will form a blueprint for new strategies to ensure that medical research will continue to play a key role in the improvement of healthcare for all European citizens, that the research will be of the highest possible quality and relevance, and that new findings will be introduced in clinical practice as speedily and efficiently as possible. Implementation of research in clinical practice is dependent on local tradition, healthcare and wealth of societies, but science is global and improved medical research can benefit patients, citizens and society globally.

Foreword

Implementation of high quality medical research in clinical practice is essential for the continuous improvement of patient treatment and care. Biomedical research must be of high quality, and it must be implemented in patient treatment by use of the principles of evidence-based medicine.

The European Medical Research Councils (EMRC) at the ESF has carried out a Forward Look on 'Implementation of Medical Research in Clinical Practice' with an analysis of current practice for the different stages of clinical research from knowledge generation via knowledge interpretation to knowledge implementation in clinical practice.

Clinical research can be looked upon as a broad term that includes basic-oriented research, disease-oriented research with animal models, i.e. translational research, patient-oriented research and outcome research. The terminology is varied across Europe and the rest of the world, but in spite of this it is important to stress that all aspects of biomedical research are necessary. Basic-oriented research aims to generate knowledge but may perhaps not be immediately relevant for practical applications in patient care. Clinical research is described by others only as research protocols involving patients. For everyone involved in this research area the important thing is that the whole spectrum of research is essential, from basic, through translational to patient-oriented research and back again. One part is ineffective without the other.

The Forward Look exercise was based around a series of workshops involving high-level experts from the different research areas and with many different backgrounds. There was expertise in biomedical research from bench to bedside, administration, health research funding, health economy and medical publishing. Perspectives from general practice were taken into account, as were issues of patient and public involvement in medical research.

The outcome of this activity, including recommendations for how to improve the identified challenges, was presented and further challenged by a broader high-level audience participating in a consensus conference at the Council of Europe in Strasbourg in October 2010. Following the conference, where participants made significant contributions, the Forward Look report was further revised and improved and subsequently sent to all involved. It was then finalised and sent for peer review. This thorough and comprehensive exercise is the basis for the present Forward Look report.

The Forward Look report makes recommendations on how to strengthen medical research and how to implement medical research in clinical practice on the basis of evidence. It aims to support the move towards

more widespread use of evidence-based medicine, with the ultimate goal of achieving better patient diagnosis, treatment and rehabilitation. This will not only improve patient care, but will also benefit wider society. Science is global, so strengthened medical research and better ways to use research results in Europe will surely benefit the rest of the world.

As Chief Executive of ESF and Chair of EMRC it is our privilege to express a warm thank you to all who have been involved in this Forward Look process, and to congratulate them for the impressive and important result. We hope that Europe will listen and implement the recommendations, which we believe are urgently required. If we can collaborate on this important issue and improve conditions for medical research and for implementing medical research in clinical practice we can bring better health and prosperity to Europe.

Professor Liselotte Højgaard
EMRC Chair

Professor Marja Makarow
ESF Chief Executive

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The Forward Look was disrupted by the ash cloud from the Iceland volcano which impaired travel to the workshop meetings in Frankfurt in spring 2010. At short notice the UK participants gathered instead at the offices of NICE in London, hosted by Professor Peter Littlejohns. A special thank you to Sir Iain Chalmers and Professor Littlejohns for leading the way and for chairing and hosting the UK part of the exercise.

We hope that by broadly disseminating this Forward Look to the heads of ESF Member Organisations, the European Commission directorates and the various important stakeholder groups identified in the report, the recommendations will be widely implemented for the future benefit of all European citizens.

Professor Liselotte Højgaard, EMRC Chair, Denmark
Forward Look Chair

Professor Stig Slørdahl, RCN, Norway
Co-Chair

Dr Edvard Beem, ZonMw, Netherlands
Co-Chair

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Dr Stephane Berghmans
Dr Kirsten Steinhausen

1. Introduction

The aim of this Forward Look

This Forward Look 'Implementation of Medical Research in Clinical Practice' has been prepared by the European Medical Research Councils (EMRC). It addresses the question "How can the treatment of patients be improved through better research and better use of research results?" There are many things about which research can do nothing, but we can identify many actions for improvement which are both rational and possible.

The aim of the Forward Look is to give a broad view of the process from the generation of a new research idea and the publication of subsequent research results to the implementation of the research in clinical practice. The report describes best practices and gives recommendations to ensure the efficient use of research results. The Forward Look aims to support the move towards more widespread evidence-based medicine, which will lead to better care for patients through improved diagnosis, treatment and rehabilitation, as well as benefiting wider society.

Background

Modern medicine has been hugely successful. The development of effective drugs has revolutionised the treatment of heart attacks and high blood pressure and enabled many people with schizophrenia to emerge from mental hospitals to live at home. The effectiveness of drugs for stomach ulcers has removed the need for major surgery, and childhood immunisation has made polio and diphtheria distant memories. It is easy to forget that leukaemia was once an almost uniformly fatal disease; people now routinely live with a variety of cancers instead of dying from them. It has now been virtually eradicated by drug treatment.

Modern imaging techniques have also brought significant benefits. Ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) have helped to ensure that people are accurately diagnosed and receive the right treatment. For example, MRI can reveal what type of stroke someone has suffered. If the stroke is caused by bleeding into the brain (haemorrhagic stroke), then aspirin, which is useful in other types of stroke, might be dangerous. Surgical and anaesthetic techniques, too, have been greatly improved. Artificial joints such as knee and hip replacements have helped countless people, and organ transplants have become commonplace.

Of course many improvements in health have come about because of social and public health advances, such as piped clean water, sanitation and better nutrition and housing. But even sceptics would be hard put to dismiss the important impact of modern medical

care. Over the past half century, much of our increased life expectancy can be attributed to healthcare, as can years of improved quality of life for those with long-term diseases.

However, despite these impressive advances it is recognised that medical decision-making is still in many cases based on poor evidence; some medical treatments can actually harm patients, and there are worthwhile treatments that are not used widely enough. Almost invariably there will be uncertainties about effects and effectiveness when new treatments are devised – treatment effects are (very) seldom overwhelmingly obvious. For this reason carefully designed fair tests are necessary to identify the effects reliably. Without fair – unbiased – evaluations, the risk is that useless or even harmful treatments are deemed helpful or, conversely, that helpful treatments are dismissed as useless. Untested theories about treatment effects, however convincing they may sound, are not enough. Some theories have predicted that treatments would work, but actual evidence has revealed otherwise; other theories have confidently predicted that treatments would not work when, in fact, tests showed that they did¹.

Therefore an important prerequisite for the best treatment for every patient is information based on sound research where basic principles of research integrity have to be followed (as an example see Figure 1: Singapore statement on research integrity and the ESF report 'Fostering Research Integrity in Europe'²). In all healthcare areas, robust research should be performed and made available to help guide patient treatment. Research must be performed without bias: possible conflicts of interest³ have to be disclosed. Open access is essential to make research available to healthcare professionals and to the public.

New ideas for improving clinical treatments are generated in everyday clinical practice, as well as from basic and translational science, clinical research, epidemiology, social medicine and through the care taken of patients in all medical specialities.

After a new idea is generated research is performed to test its validity. After the research has been completed it is evaluated through peer review, and published in scientific journals if it is deemed to be of sufficient quality and interest. Studies that address similar issues should

1. Evans I, Thornton H, Chalmers I 2006. Testing Treatments. London: Pinter and Martin. Available to download free at www.jameslindlibrary.org

2. ESF Member Organisation Forum report 'Fostering Research Integrity in Europe', 2010. ISBN 978-2-9184-28-32-9

3. Council of Europe 2002. Developing a Methodology for Drawing up Guidelines on Best Medical Practices. Recommendation Rec(2001)13 and explanatory memorandum. Strasbourg. ISBN 92-871-4788-4. Internet:<http://www.arztbibliothek.de/mbd/edocs/pdf/literatur/coe-rec-2001-13.pdf>

Singapore Statement on Research Integrity

Preamble. The value and benefits of research are vitally dependent on the integrity of research. While there can be and are national and disciplinary differences in the way research is organized and conducted, there are also principles and professional responsibilities that are fundamental to the integrity of research wherever it is undertaken.

PRINCIPLES

Honesty in all aspects of research
Accountability in the conduct of research
Professional courtesy and fairness in working with others
Good stewardship of research on behalf of others

RESPONSIBILITIES

1. Integrity: Researchers should take responsibility for the trustworthiness of their research.

2. Adherence to Regulations: Researchers should be aware of and adhere to regulations and policies related to research.

3. Research Methods: Researchers should employ appropriate research methods, base conclusions on critical analysis of the evidence and report findings and interpretations fully and objectively.

4. Research Records: Researchers should keep clear, accurate records of all research in ways that will allow verification and replication of their work by others.

5. Research Findings: Researchers should share data and findings openly and promptly, as soon as they have had an opportunity to establish priority and ownership claims.

6. Authorship: Researchers should take responsibility for their contributions to all publications, funding applications, reports and other representations of their research. Lists of authors should include all those and only those who meet applicable authorship criteria.

7. Publication Acknowledgement: Researchers should acknowledge in publications the names and roles of those who made significant contributions to the research, including writers, funders, sponsors, and others, but do not meet authorship criteria.

8. Peer Review: Researchers should provide fair, prompt and rigorous evaluations and respect confidentiality when reviewing others' work.

9. Conflict of Interest: Researchers should disclose financial and other conflicts of interest that could compromise the trustworthiness of their work in research proposals, publications and public communications as well as in all review activities.

10. Public Communication: Researchers should limit professional comments to their recognized expertise when engaged in public discussions about the application and importance of research findings and clearly distinguish professional comments from opinions based on personal views.

11. Reporting Irresponsible Research Practices: Researchers should report to the appropriate authorities any suspected research misconduct, including fabrication, falsification or plagiarism, and other irresponsible research practices that undermine the trustworthiness of research, such as carelessness, improperly listing authors, failing to report conflicting data, or the use of misleading analytical methods.

12. Responding to Irresponsible Research Practices: Research institutions, as well as journals, professional organizations and agencies that have commitments to research, should have procedures for responding to allegations of misconduct and other irresponsible research practices and for protecting those who report such behavior in good faith. When misconduct or other irresponsible research practice is confirmed, appropriate actions should be taken promptly, including correcting the research record.

13. Research Environments: Research institutions should create and sustain environments that encourage integrity through education, clear policies, and reasonable standards for advancement, while fostering work environments that support research integrity.

14. Societal Considerations: Researchers and research institutions should recognize that they have an ethical obligation to weigh societal benefits against risks inherent in their work.

The Singapore Statement on Research Integrity was developed as part of the 2nd World Conference on Research Integrity, 21-24 July 2010, in Singapore, as a global guide to the responsible conduct of research. It is not a regulatory document and does not represent the official policies of the countries and organisations that funded and/or participated in the Conference. For official policies, guidance, and regulations relating to research integrity, appropriate national bodies and organisations should be consulted. Available at: www.singaporestatement.org

Figure 1. Singapore statement on research integrity

be subjected to systematic analysis, as in Cochrane reviews.

Health technology assessment (HTA) is the term given to the systematic appraisal of health technologies. HTA seeks to answer questions about a given health technology: whether the technology is effective, what it is for, how much it costs, and how it compares with alternatives. HTA institutes exist in many countries, collaborate and have mutual guidelines. The concept has further developed into 'miniature health technology assessment reports' prepared by clinical doctors with support from HTA experts. This helps hospital owners and administrators to decide whether new treatments should be implemented or not, or, for example, to recommend that funding be made available for further evaluation where gaps in evidence have been documented. A good example of this concept is from Region Västra Götaland in Sweden, which has developed a successful activity-based HTA with support and quality control processes.

Research results are often implemented through clinical guidelines:

*"Systematically developed statements to assist important professional and patient decisions about appropriate healthcare for specific circumstances"*⁴.

Guidelines can be produced at a variety of levels: internationally and nationally as well as at regional and local levels for individual healthcare institutions or groups of institutions. Guidelines can be initiated and produced by national or international scientific societies or professional associations, as well as by public or government organisations – in close collaboration with healthcare providers, patients, researchers and methodologists. Clinical guidelines can be named and interpreted differently depending on the country in which they operate, such as 'reference programmes' or 'standard operating procedures'. The implementation of national and international guidelines in everyday clinical practice in healthcare varies across Europe and often there are several guidelines on the same subject.

The use of new information from research occurs at all levels and in all institutions involved in healthcare. For example, in hospitals, the hospital owners, directors, managers and clinical staff are responsible for taking account of research results in clinical practice. There is no single procedure to implement new treatments within Europe. The most frequent routes for implementation are through HTA evaluations and national and international guidelines or authorities' recommendations. Sometimes implementation is on the basis of knowl-

edge about research results published in peer-reviewed journals. Sometimes implementation follows the publication of new guidelines. Sometimes a new treatment is implemented as a consequence of clinical development without adequate supporting research evidence.

It is generally agreed that new knowledge and technologies that have been proven to be sound, beneficial, effective and cost-effective should be taken into account in clinical practice. This involves many challenges.

Mapping of new knowledge: overview of the current situation

The use of knowledge from research in clinical practice is complex and influenced by a variety of non-scientific factors. The political systems in different countries vary, there are economic influences and there is diversity in the organisation of healthcare.

The European and global medical and pharmaceutical industries influence the practice of medicine. National and European laws, rules and regulations are important. The different nations in the EU have full national responsibility for their healthcare, but directives from the European Commission influence both member states and countries outside the European Union.

HTA and guideline development systems differ among European countries. The organisation and structures for how healthcare institutions are owned and run also vary. For example, in some countries leaders and managers of hospitals have great influence whereas in other countries the clinical chairs and physicians carry greater responsibility.

In many cases clinical doctors in collaboration with their colleagues have responsibility both for patients and for clinical research, as well as making decisions about which new knowledge to implement, ensuring that it is carried out and checking that it is done.

In some countries new clusters of people with a mixed medical and administrative background have been developed to form national and local authorities. These work with assessment experts to evaluate the literature, usually in collaboration with experts in the medical field in question, based on a full systematic literature review. These assessments form the basis for HTA evaluations, guideline production and sometimes also reimbursement decisions by other bodies. This group of people handles the research results, the writing of guidelines and the audit of outcomes.

4. Recommendation Rec(2001)13 and explanatory memorandum. Strasbourg. ISBN 92-871-4788-4. Internet: <http://www.arztbibliothek.de/mdb/edocs/pdf/literatur/coe-rec-2001-13.pdf>

1. Introduction

Knowledge generation, translation and clinical decision-making

'Knowledge translation' is defined by the Canadian Institutes of Health Research (CIHR) as a dynamic and iterative process that includes the synthesis, dissemination, exchange and ethically sound application of knowledge to improve health, provide more effective health services and products and strengthen the health-care system. One model of this 'Translational Pipeline' according to Khoury et al. 2007⁵ is described in Figure 2. The definition has been adapted by different organisations such as the World Health Organisation (WHO). The common element among these different terms is a move beyond the simple *dissemination* of knowledge into actual *use* of knowledge. Knowledge creation (e.g., through research), knowledge distillation (e.g., through the creation of guidelines) and knowledge dissemination (e.g., through publication in journals and in presentations) are not enough on their own to ensure the use of knowledge in decision-making.

All groups of decision-makers, including clinical doctors and researchers, healthcare providers, patients, informal care-givers, managers and policy-makers, do not make sufficient use of evidence from research to make informed decisions. This is apparent in both developed and developing countries, in primary and specialities care and in care provided by all disciplines. Increasing awareness of the gaps in translating knowledge to action has led to efforts to change behaviour, practices and policy. Introducing a change in behaviour is a complex process requiring evaluation. This includes the identification of barriers to change (for example lack of integrated health information systems) and targeting all those involved in making decisions. Efforts have to be made to improve health outcomes by using effective interventions and to close the gaps in translating knowledge to practice. These initiatives must include all aspects of care, including access to and use of valid evidence, patient safety strategies and organisational and systems issues⁶.

Patient/public-doctor relationship

When considering issues of clinical decision-making, the perspective of the patient and public is important. The sorts of questions patients ask are not necessarily identical to those asked by clinicians or researchers:

5. Khoury MJ, Gwinn M, Yoon PW, et al. The continuum of translation research in genomic medicine: how can we accelerate the appropriate integration of human genome discoveries into healthcare and disease prevention. *Genet Med* 2007; 9: 665-74
6. Straus SE, Tetroe JM, Graham ID. Knowledge translation is the use of knowledge in healthcare decision making. *J Clin Epidemiol*. 2011; 64 (1): 6-10

patients want to know what is wrong with them, what will happen, what can be done to help, and what the pros and cons are of the options available. During such discussions it is important that potential benefits and risks of treatment options are clearly communicated. There are several resources now available to support the discussions that are needed^{1,7,8,9,10,11,12,13}

It is also important to acknowledge that different people have different expectations. Some wish only to be treated and cured and not be given detailed information. Others will come with a broad knowledge obtained from the internet and other sources, preferring to arrive at treatment decisions in collaboration with their doctors. Doctors should try to ensure that their conversation style is appropriate. The area is complicated and whilst patient autonomy should be respected, shared decision-making needs to be encouraged.

Where are the challenges?

The process of generating a new idea, testing it through research then bringing it into clinical practice is undoubtedly complex. The process from the development of guidelines to implementing new clinical practice is in itself highly complex and there is a great variation in how this process is organised throughout the countries of Europe. There are however many steps where quality improvement of the overall process can be identified and is needed. Organisation and decision-making is influenced by many non-scientific factors related to local and governmental policy, cost-effectiveness and other economic aspects such as insurance and industry as well as cultural traditions and national wealth. There are many stakeholders who should be taken into account.

7. Sense about Science. Factsheet: Systematic Reviews. [www.senseaboutscience.org.uk/index.php/site/about/429/Evans and Thornton](http://www.senseaboutscience.org.uk/index.php/site/about/429/Evans%20and%20Thornton) 2009

8. Sense about Science. Making Sense about Statistics (2010). <http://www.senseaboutscience.org.uk/index.php/site/project/484/>
9. Evans I, Thornton H, Chalmers I (2010). Testing treatments: better research for better healthcare. London: Pinter and Martin. Download text free at: www.jameslindlibrary.org/testing-treatments.html

10. Schwarz L, Woloshin S, Welch HG. Know your chances: understanding health statistics. Berkeley: University of California Press (2008).

11. Edwards A, Elwyn G, Atwell C. et al. Shared decision-making and risk communication in general practice. Report to the 'Health in Partnership' programme, UK Department of Health. www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4082332 (2004)

12. Thornton H. Statistical illiteracy is damaging our health. Doctors and patients need to understand numbers if meaningful dialogues are to occur. *Int J Surg* 2009;7:279-284.

13. Thornton H. Communicating to citizens the benefits, harms and risks of preventive interventions. *J Epidemiol Com Health* 2010;64:101-102

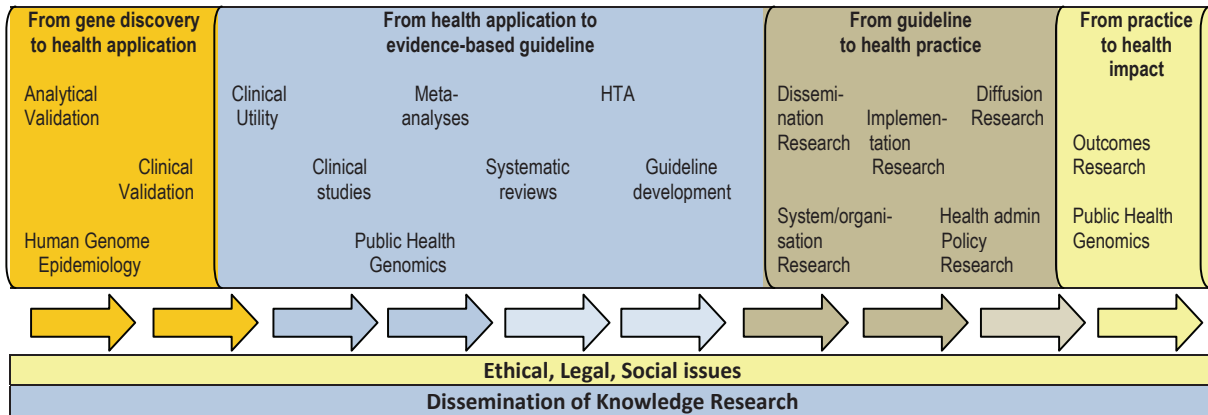


Figure 2. The Translational Pipeline (Inspired from Khoury *et al.* 2007)

Key stakeholders

Group 1:

- Academic research (basic to patient-oriented research)
- Learned societies
- Universities
- Healthcare providers/hospitals: Healthcare professionals, i.e. clinicians, primary care practitioners, medical specialists including medical ethicists
- Teachers (undergraduate and postgraduate medical training, as well as for continuous professional development)

Group 2:

- Methodologists, systematic reviewers, healthcare professionals
- Health economists
- HTA and guideline agencies
- Policy-makers and healthcare systems

Group 3:

- National and EU funding agencies and research councils
- National and EU regulators
- Ministries
- Ethics committees

Group 4:

- Patients and general public
- Patient organisations
- Philanthropic organisations

Group 5:

- Journal editors and peer reviewers
- Media: internet, journals, medical journalists, etc.

Group 6:

- Private sector:
 - Pharmaceutical industry
 - Medical devices industry

2. Knowledge Generation

Clinical research can be looked upon as a broad term including basic-oriented research, disease-oriented research with animal models, i.e. translational research, patient-oriented research and outcome research. The terminology is varied across Europe and the rest of the world, but in spite of this it is important to stress that all aspects of biomedical research are necessary. In particular basic-oriented research considers problems that are important to generate knowledge but may perhaps not be immediately relevant for practical applications in patient care. Clinical research is described by others only as research protocols involving patients. For all involved in this research area the important thing is that the whole spectrum of research is essential, from basic, through translational to patient-oriented research and back again.

Research results of importance for clinical practice may therefore originate from all kinds of research. It is important to ensure the best condition for this knowledge-generating research. However, regardless of how new knowledge is generated it needs to be systematically and objectively evaluated before a decision is made about whether it should influence daily clinical practice.

Patient-oriented research relies on and is carried out for the benefit of the public. For this reason it should be supported, directly or indirectly, by public health authorities. These should help to identify needs and questions and set priorities. Public funds should be used to support clinical research in order to ensure its unbiased independence in the interest of public health and should also serve to establish and support multinational cooperative research networks which play an important role in identifying treatment effects.

Although randomised trials, systematic reviews and meta-analyses of trials are adequate methods for addressing questions about the feasibility, effectiveness and short-term harm of interventions, other kinds of research may be required to address other kinds of questions¹⁴. The concept of personalised medicine will further challenge currently available research methodologies.

A wide variety of research is relevant to informing decisions and choices in clinical care and policy. In some cases, treatment effects – wanted and unwanted – are dramatic and randomised trials are not needed to detect them¹⁵. More frequently, **controlled trials** are needed to detect relatively modest but nevertheless important effects of treatments. **Observational studies** are needed

when rare side effects of treatments are suspected and they are also used, for example, to assess disease prognosis and the performance of screening and diagnostic tests. The evaluation of surgical performance and outcomes at times needs alternative prospective designs, such as **interrupted time series studies** and **registry studies**. In cases when randomised trials are not feasible or cannot properly account for factors that depend on operators, teams and settings, such as operators' learning curves, variations in the quality of research settings and perceptions of equipoise¹⁶, **qualitative studies** are needed, for example, to document the experiences of patients and clinicians. **Health economic evaluations** and **studies of initiatives for quality improvement and safety** can provide important evidence for developing, prioritising and running health services. Each of these and other types of study are required to meet the need for a wide range of information.

Regardless of the study type, however, patients, clinicians and policy-makers need access to all the evidence relevant to a particular clinical question, assembled systematically using scientifically defensible methods. Study designs must be chosen carefully to ensure that research delivers value for money. Four successive stages at which the production and dissemination of clinical evidence can be derailed have been identified: the choice of research questions; the quality of research design and methods; the adequacy of publication practices; and the quality of reports of research (see Figure 3). It is unethical to conduct and report research inadequately, and it is also wasteful: indeed, the authors argue that the dividends from tens of billions of dollars of investment in research are lost every year because of correctable problems.

Each of the stages at which research can be wasted is examined below.

Questions must be relevant to clinicians, patients and decision-makers

There is often poor engagement of end-users of research – patients, clinicians, policy-makers – with the framing of research questions and the design of research studies¹⁷. The avenues of communication between researchers and end-users are often not well developed. Often, researchers and clinicians are the same. Researchers communicate with other researchers, and (ideally) clini-

14. Rawlins M. De testimonio: on the evidence for decisions about the use of therapeutic interventions. *Lancet* 2008; 372:2152-61

15. Glasziou P, Chalmers I, Rawlins M, McCulloch P. When are randomised trials unnecessary? Picking signal from noise. *BMJ* 2007; 334:349-351

16. McCulloch P, Altman DG, Campbell WB et al. No surgical innovation without evaluation: the IDEAL recommendations. *Lancet* 2009; 374:1105-12

17. Tallon D, Chard J, Dieppe P. Relation between agendas of the research community and the research consumer. *Lancet* 2000; 355:2037-40

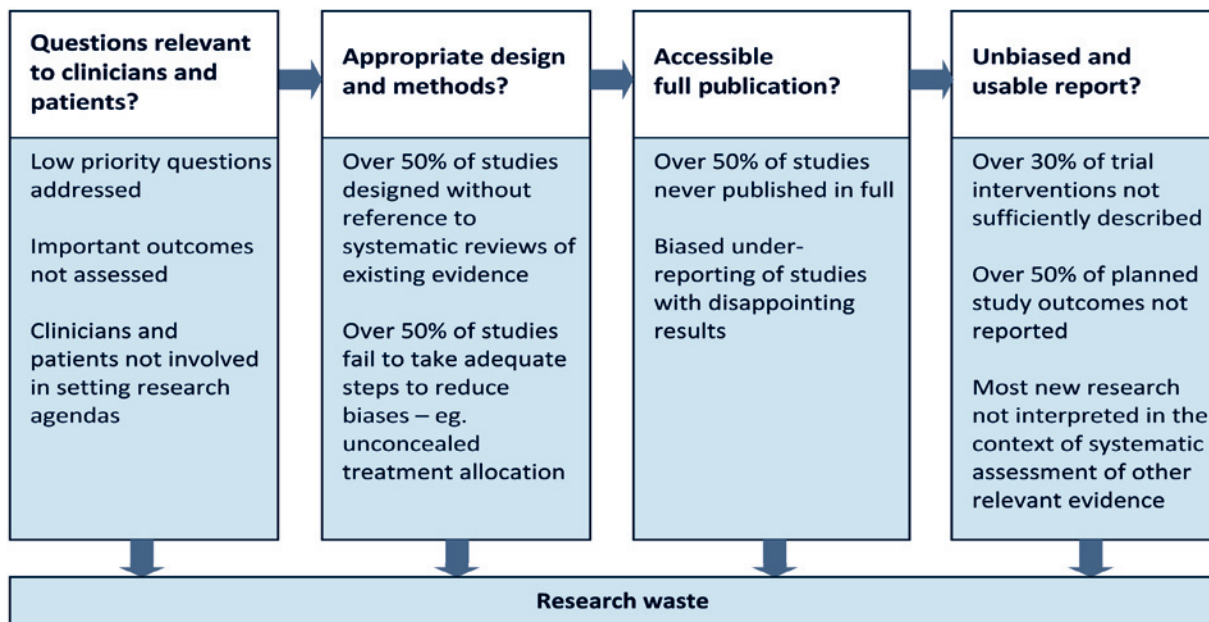


Figure 3. Stages of waste in the production and reporting of research evidence relevant to clinicians and patients
 Source: Chalmers I, Glasziou P (2009). Avoidable waste in the production and reporting of research evidence. *Lancet* 374:86-89.

icians and patients communicate with each other¹⁸. Too rarely however, is there an exchange between these two worlds. Patients and other stakeholders should be more involved in shaping research agendas and specific questions¹⁹ (see also Chapter 7). In Spain the relationship among researchers, clinicians and patients has been fostered by the Centers for Biomedical Network Research (CIBER), for example on Rare Diseases²⁰ and by evidence-based healthcare programmes set up at the initiative of the Carlos III Health Institute.²¹

In the UK, the organisation INVOLVE has been established by the Department of Health to promote patient and public involvement in research in order to improve the way that research is prioritised, commissioned, undertaken, communicated and used.²²

There are initiatives to identify and publish uncertainties about the effects of treatments²³, and to bring

patients and clinicians together to prioritise those they agree deserve most urgent research²⁴. The National Institute for Health and Clinical Excellence (NICE), UK database of research recommendations, for example, has been derived from patients, professionals and researchers taking national health priorities and outlining the evidence gaps after a systematic review of the evidence. NICE already links in to the main research funders and after a slow start this is now bearing fruit²⁵.

The UK Database of Uncertainties about the Effects of Treatment (UK DUETs) publishes uncertainties about the effects of treatment that cannot currently be answered by up-to-date systematic reviews of existing evidence. UK DUETs draws on three main sources to identify uncertainties: patients', carers' and clinicians' questions about the effects of treatment; research recommendations arising from systematic reviews and clinical guidelines; and ongoing research, both systematic reviews in preparation and new primary studies.

The forthcoming Standard Protocol Items for Randomized Trials (SPIRIT) statement is an evidence-based checklist of the items that should be addressed in trial protocols and hence it has the potential to improve research at the design stage.²⁶

18. Edwards a, Elwyn G, Atwell C. et al. Shared decision making and risk communication in general practice Report to the 'Health in Partnership' programme, UK Department of Health. www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4082332 (2004)

19. Thornton H. Patients and health professionals working together to improve clinical research: where are we going? *European Journal of Cancer* 2006; 42:2454-2458, plus Appendix A.

20. www.ciberer.es/index.php?option=com_content&task=view&id=12&Itemid=28

21. www.isciii.es/htdocs/en/redes/redes_presentacion.jsp

22. www.invo.org.uk

23. www.library.nhs.uk/duets

24. www.lindalliance.org

25. www.nice.org.uk/research/index.jsp?action=rr

26. www.equator-network.org/resource-centre/library-of-health-research-reporting/reporting-guidelines-under-development/

2. Knowledge Generation

Other bodies aimed at involving all stakeholders include the UK Clinical Research Collaboration²⁷, which brings together the National Health Service (NHS), research funders, industry, regulatory bodies, Royal Colleges, patient groups and academia in a UK-wide environment that facilitates and promotes high quality clinical research for the benefit of patients, and the Office for Strategic Coordination of Health Research (OSCHR)²⁸, whose mission is to ‘facilitate more efficient translation of health research into health and economic benefits in the UK through better coordination of health research and more coherent funding arrangements to support translation’.

It is worth noting that identifying evidence gaps is one thing but framing a potentially answerable research question another. Indeed sometimes the process is so complex that the question changes from the one that was asked in the first place²⁹. Irrelevant research questions are often asked because insufficient effort has gone into reviewing existing evidence, sometimes with the result that public resources are wasted on unnecessary or poorly designed research. Systematic reviews of existing evidence – an ordinary published systematic review, a Cochrane report or an HTA report³⁰ – are needed as a basis for agreeing and refining which questions should be addressed in new research^{31,32}.

Basic research must be of high quality

Another issue is the limited relevance and quality of some basic research in biomedical fields, for example animal research. This matters because such research is often relied upon to develop research questions for clinical research.

A meta-review of systematic reviews of studies concluded that animal experimentation should be refocused³³. Animal models have been instrumental in studying damage, in developing therapies and in

understanding gene function, among others, in many different fields from cancer to deafness^{34,35}.

However, a survey about the quality of experimental design, statistical analysis and reporting of animal research³⁶ revealed a number of issues, particularly reporting omissions. Building on these results, the authors have developed a set of reporting guidelines to assist transparent and complete reporting of animal research³⁷.

Clinical study designs and methods

There is much research published in the literature which is of low quality^{38,39}. That most systematic reviews reject a high proportion of retrieved studies because they are of inadequate quality is just one illustration of this continuing challenge. These concerns mostly relate to published studies, many more studies may be started but end up either not completed or not reported.

There are a number of factors that contribute to the continuing production of low quality research papers. Clinical education includes too little training in critical appraisal of research; there is too little input from expert methodologists at the stages of designing and reviewing research; incentives for primary research ignore the need to use and improve on existing research on the same question; the regulation of research has become unwieldy⁴⁰; and there is biased under-reporting of completed research⁴¹.

It is also an issue that trials are often performed on very selected patients without co-morbidity, in contrast to real life, in which several drugs may be given concurrently. This makes the external validity and thereby generalisability of the results poor. Patients in clinical trials should be more representative of the population to which the results will be applied. For example the consumption of drugs is higher in patients over 65 but clinical trials often do not include this age group.

27. www.ukcrc.org/

28. www.nihr.ac.uk/about/Pages/about_oschr.aspx

29. Thornton H, Edwards A, Elwyn G (2003). Evolving the multiple roles of ‘patients’ in healthcare research: reflections after involvement in a trial of shared decision-making. *Health Expectations* 6:189-197

30. Sense about Science (2009). Factsheet: Systematic Reviews. www.senseaboutscience.org.uk/index.php/site/about/429/Evans and Thornton 2009

31. Lau J, Schmid CH, Chalmers TC. Cumulative meta-analysis of clinical trials builds evidence of exemplary clinical practice. *Journal of Clinical Epidemiology*. 1995; 48:45-571

32. Horn J, de Haan RJ, Vermeulen RD et al. Nimodipine in animal model experiments of focal cerebral ischemia: a systematic review. *Stroke* 2001; 32:2433-8

33. Pound P, Ebrahim S, Sandercock P, Bracken MB, Roberts I. Where is the evidence that animal research benefits humans? *BMJ* 2004;328: 514-7

34. <http://www.eumodic.org/>

35. <http://www.informatics.jax.org/>

36. Kilkenny C, Parsons N, Kadyaszewski E et al. Survey of the quality of experimental design, statistical analysis and reporting of research using animals. *PLoS One* 2009; 4(11):e7824.

37. Kilkenny C, Browne WT, Cuthill IC et al. Improving biomedical research reporting: the ARRIVE guidelines for reporting animal research. *PLoS Biol* 2010; 8 (6): e1000412

38. Altman, DG. The scandal of poor medical research. *BMJ* 1994;308:283-4

39. von Elm E, Egger M. The scandal of poor epidemiological research. *BMJ* 2004;329: 868-9

40. Frewer LJ et al. Has the European Trials Directive been a success? *BMJ* 2010; 340:c1862

41. Song F, Parekh S, Hooper L et al. Dissemination and publication of research findings: an updated review of related biases. *Health Technol Assess* 2010; 14(8): 1-193

Funding bodies should require grant proposals to build on systematic reviews of existing evidence

For example, advice to applicants for the UK Medical Research Council (MRC) global health trials programme says, 'Where a recent review does not already exist, applicants are encouraged to conduct a systematic review of the available evidence, and preferably a pilot or feasibility study, before applying for a grant for a large scale, late phase, definitive trial'.⁴²

However, well-conducted systematic reviews require resources and specialist expertise that are not available to all researchers. Medical libraries often include information specialists with good ability to help formulate questions and retrieve relevant literature. With the advent of most journals being electronically available, the work of many hospital-based information specialists needs to be developed.

Implement a risk-based approach for clinical trials

A risk-based approach for the regulation of investigator-driven clinical trials and a streamlining of the procedures for obtaining authorisation for clinical trials should be developed by improving the EC Clinical Directive 2001. The EMRC Forward Look 'Investigator-Driven Clinical Trials' has, together with many other actions, led to the establishment of an OECD Global Science Forum working group on clinical medical research. This group aims to develop recommendations to facilitate international clinical trials.

Improve incentives and training for patient-oriented clinical research

There is a high percentage of medical doctors who are not well trained in the methodology of clinical research and who do not have adequate methodological support or infrastructure. In addition the training of medical doctors in MD/PhD programmes in the field of clinical research has to be improved.

Moreover, current incentives in fellowships and career paths are weighted towards primary research, even if this is of low relevance in practice. More emphasis should therefore be placed on initial training of researchers in critical appraisal and systematic reviews, rather than on designing and conducting new primary research. The systematic reviews needed to underpin new research questions should be carried out to appropriate, evidence-based, minimum standards, such as those defined by the Cochrane Collaboration, and then fully reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses⁴³ (PRISMA) statement.

42. www.mrc.ac.uk/Fundingopportunities/Grants/Trialgrant/Globalhealthtrials/MRC004151

43. www.prisma-statement.org, <http://www.equator-network.org/resource-centre/library-of-health-research-reporting/reporting-guidelines/systematic-reviews-and-meta-analysis/>

Traceability of clinical research

Thorough and transparent registration of clinical trials and reporting of their results are particularly important. For several scientific, ethical and practical reasons many sponsors, funders and publishers of biomedical science now mandate the prior registration of clinical trials in publicly accessible online registries. It will help researchers and the public to see which studies are on the horizon. This is especially important for patients so that they can find which ones they might be eligible for.

To ensure consistent reporting across all trial registries the WHO has developed a minimum dataset and criteria for registries accepted by WHO and the International Committee of Medical Journal Editors (ICMJE). The WHO web portal serves as a metaregister and provides links to the WHO approved national and regional trial registries.⁴⁴

Furthermore, because many trials are not (or are not fully) reported in formal publications, rapid and standardised reporting of registered trials' main results is now mandated too. The US Food and Drug Administration (FDA) Amendments Act 2007 requires the registration of the designs, results, and harms for all phase II-IV trials of products needing FDA approval.

Since 2004 all interventional drug trials are to be registered in the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database of the European Medicines Agency (EMA). Data on phase II-IV trials (as well as Phase I paediatric trials and trials outside the European Economic Area (EEA)) registered with EudraCT became open for the general public and freely accessible in the first quarter of 2011. A publicly available database on results of these trials is still under construction. Generally, trial registration should be mandatory for all types of clinical trials in humans, not only drug trials, as between 40% and 50% of clinical research involves e.g., surgical methods, other procedures, medicinal products or psychotherapy. The results of all trials, including non-interventional trials, should be published.

Editors have also played their part and the ICMJE has, since 2005, refused to consider papers reporting unregistered trials and continues to encourage other biomedical journals to follow suit. Although all of these policies currently apply specifically to clinical trials there is increasing interest in registering all health research, including observational studies, as in Sweden and Spain.

Although most research funding agencies expect and demand some commitment or effort on the part of grant holders to disseminate the findings of their research, there does not appear to be clarity between funding

44. www.who.int/ictrp/

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agencies as to what this should entail. Moreover, the expectations and guidance provided to researchers vary from one funder to another.⁴⁵

Researchers need clearer guidance on how best to disseminate findings. Research funders are well placed to influence this activity. Given the current emphasis on reducing the 'gaps in translation' and on the need to deliver tangible returns on the substantial investment in research, funders should be encouraging their grant holders to adopt a more structured and theoretically informed approach to their research dissemination at the grant application stage.⁴⁶

Unbiased, usable reporting of research

Biased reporting

A recent HTA review confirmed that studies with significant or 'important' results were more likely to be published than those with non-significant or 'unimportant' results, and that publication bias seemed to occur mainly before presenting findings at conferences and submitting manuscripts to journals⁴⁷. The authors recommend several ways to combat the non-publication of 'negative' findings including prospective registration of studies, disclosure of data from unpublished studies, searching for and inclusion of unpublished studies, assessment of risk of publication bias in systematic reviews, and dissemination of research through archiving and data deposition as well as through formal publication in journals. They also noted other forms of dissemination bias, such as database bias, duplicate publication bias, citation bias, and media attention bias. Editors have a great responsibility in avoiding duplicate data publication and also citation bias. There is also plenty of evidence that biased reporting of research is associated with commercial funding of studies. For example, Lexchin and colleagues reviewed 30 studies that analysed research sponsored by a pharmaceutical company and that compared methodological quality or outcomes with studies with other sources of funding. They found systematic bias favouring products made by the companies funding the research, mediated by several mechanisms such as the selection of inappropriate comparators in trials and publication bias⁴⁸. Kirkham

45. Wilson PM, Petticrew M, Calnan MW, Nazareth I. Why promote the findings of single research studies? *BMJ* 2008; 336:722

46. Wilson PM, Petticrew M, Calnan MW, Nazareth I. Does dissemination extend beyond publication: a survey of a cross section of public funded research in the UK. *Implement Sci* 2010; 5:61

47. Song F, Parekh S, Hooper L et al. Dissemination and publication of research findings: an updated review of related biases. *Health Technol Assess* 2010; 14(8): 1-193

48. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003; 326: 1167-1170

and colleagues⁴⁹ examined the prevalence of outcome reporting bias and its impact on Cochrane reviews and offered a nine point classification system for missing outcome data in randomised trials. This bias occurs when only a subset of the originally recorded outcome variables is selectively reported. The authors found that nearly a fifth of statistically significant meta-analyses of the review primary outcome were biased in this way and a quarter would have overestimated the treatment effect by 20% or more. The consequences of publication bias can be serious: according to Turner and colleagues (2008)⁵⁰ the effect of antidepressants is overestimated (between 20 and 50%) if only publications are taken into consideration.

Unusable reporting of research

Biased reporting and under-reporting of research are important issues, but so is inadequately detailed reporting. All of these points can make research hard to interpret and use. For instance, reporting clinical trial interventions only in general terms such as 'low salt diet' or 'exercise programme' and comparators such as 'usual care' provides information that is too vague for anyone to implement the results⁵¹. If journals cannot provide space to report interventions and other key aspects of study design fully enough to make the research reproducible, researchers could use free access repositories, separate from any publications, to report details of treatments, tests, or instruments studied. Furthermore, editors could require new studies to begin and end with references to systematic reviews of other relevant evidence.⁵²

Breaches of publication ethics are an important issue too. Plagiarism, duplicate publication and lack of transparency over authorship are all too common ways in which the research record can be distorted. Outright scientific fraud is only occasionally exposed, but its true frequency and its overall impact on the evidence base are impossible to judge.

Ways to improve research reporting

The International Committee of Medical Journal Editors' (ICMJE) uniform requirements for biomedical manuscripts⁵³, individual journals' advice to authors,

49. Kirkham JJ, Dwan KM, Altman DG et al. The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. *BMJ* 2010;340:c365.

50. Turner EH, Matthews AM, Linardatos E et al. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med* 2008; 17;358(3):252-60

51. Glasziou P, Meats E, Heneghan C, Shepperd S. What is missing from descriptions of treatment in trials and reviews? *BMJ* 2008;336:1472-1474

52. Clark S, Horton R. Putting research into context – revisited. *Lancet* 2010;376:10-11

53. <http://www.icmje.org/>

peer review by clinicians and methodologists, and editing all play their part in improving the reporting of published research. More than 4,000 journals worldwide are members of the Committee on Publication Ethics (COPE) and have undertaken to follow COPE's code of conduct and follow its guidance on handling cases of publication misconduct.⁵⁴

One particularly important and independent initiative to improve the transparency and completeness of research reporting and publication is the EQUATOR Network⁵⁵. This is an openly accessible online network that promotes the development of guidance and provides checklists for fully reporting a wide range of different biomedical research study designs⁵⁶. Most of this guidance, such as the Consolidated Standards of Reporting Trials⁵⁷ (CONSORT) statement, is for reporting completed research properly in publications and at conferences. Researchers should be trained to communicate 'numbers' clearly, according to the evidence for the best methods available^{58,59}.

Open access publication

The publishing landscape is changing. A profusion of new journals is appearing, many with low thresholds for acceptance of articles. One possible advantage is that industry is publishing more data that would not previously have been disseminated, particularly from studies considered to be insufficiently interesting for traditional journals. But the model of publication requiring the author to pay a fee for peer review could be argued to be bad for science. There is evidence of 'e-bias' in that well-resourced institutions, industry notably, can afford these charges more than publicly funded researchers⁶⁰.

The next frontier is the sharing of the full datasets generated by research, making them accessible so that readers and other researchers can judge the quality of and make further use of the data. However, data deposition, curation and mining pose technological challenges; reinterpretation and reuse of data without pre-specified hypotheses have methodological risks; and data sharing poses risks to patients' privacy. Consent for publication

54. <http://publicationethics.org/>

55. www.equator-network.org/

56. Simera I, Moher D, Hirst A et al. Transparent and accurate reporting increases reliability, utility, and impact of your research: reporting guidelines and the EQUATOR Network. *BMC Med.* 2010; 26:8:24

57. <http://www.consort-statement.org/home/>

58. Gigerenzer G, Gaissmaier W, Kurz-Milcke E et al. Helping Doctors and Patients Make Sense of Health Statistics. *Psychological Science in the Public Interest.* 2008; Volume 8, Number 2. 53-96

59. Thornton H. Communicating to citizens the benefits, harms and risks of preventive interventions. *J Epidemiol Com Health* 2010; 64:101-102

60. Jakobsen AK, Christensen R, Persson R et al. And now, e-publication bias. *BMJ* 2010; 340:c22

of appropriately anonymised raw data should, ideally, be sought from participants in clinical research and datasets that contain three or more indirect identifiers, such as age and sex and should be reviewed by an independent researcher or ethics committee before being submitted for publication⁶¹.

Drug and device evaluation

The evaluation of drugs and devices for use in health-care systems is another kind of knowledge generation, one that is not always conducted in an unbiased and transparent way and is often poorly reported. It has been argued that as pharmaceutical companies evaluate their own products it is unsurprising that the resulting evidence is sometimes biased in favour of the interests of the industry.⁶² The authors suggest four ways in which governments could alter the balance of their support in favour of patients and health services: involving patients in shaping the therapeutic research agenda, making transparency in drug evaluation a legal requirement, requiring and resourcing independent evaluation, and requiring proof of added value for all new drugs.

Mechanisms and resources should be established to allow independent evaluation of drugs. Some European agencies have already begun to do this, including the Italian Agency for Drugs (AIFA), the Spanish drug regulatory agency, and the English National Institutes of Health Research. The Italian initiative has legal backing: all drug companies operating in Italy are required by law to pay 5% of their promotional expenses to the agency to support independent clinical research on the efficacy of orphan drugs, comparisons of drugs for the same indication, observational outcome studies and pharmacovigilance.

Greater transparency in evaluation of drugs is needed too. Garattini and Bertele⁶³ have noted that the recent move of the European Medicines Agency (EMA) to the Health and Consumer Policy Directorate (DG Sanco), rather than the Enterprise and Industry Directorate, could provide an opportunity for more openness. They call on EMA to require that for all new drug applications there should be evidence of benefit in studies that use clinical end points over an adequate length of time and greater transparency about evidence used to make decisions. They propose a Europe-wide network for post-marketing pharmacovigilance with the results being evaluated by a different body from that which granted the marketing

61. Hrynaszkiwicz I, Norton ML, Vickers AJ, Altman DG. Preparing raw clinical data for publication: guidance for journal editors, authors, and peer reviewers. *BMJ* 2010; 340:c181

62. Garrattini S, Chalmers I. Patients and the public deserve big changes in the evaluation of drugs. *BMJ* 2009; 338: 804-06

63. Garattini S, Bertele V. Europe's opportunity to open up drug regulation. *BMJ* 2010; 340:c1578

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authorisation ensuring that newly approved medicines have better efficacy or safety than those already available. They also recommend that the European Commission raises the budget for investigator-driven clinical trials to remove dependence on industry funding, and that it funds independent studies in addition to data produced by drug companies and explores further the clinical potential of drugs with no commercial appeal but of potential public health value.

The EMA perspective

As EMA is part of the European Civil Service it cannot make policy or enact changes in the law. It provides material and a scientific advice service, in collaboration with other in-house sections, with individual regulatory agencies of EU Member States, with academia throughout the EU and with FDA. It already requires stringent proofs of short- and long-term benefit in studies submitted for advice, especially ensuring designs that lead to both scientifically and clinically meaningful results.

Around 40% of the applications for marketing authorisation by pharmaceutical companies to EMA in 2009 had a negative outcome, indicating that the regulators have started to adopt a robust and appropriately critical posture in defence of public health.

Moreover, EMA decisions are informed by evidence, some of which is available on the EMA website.

EMA supports the notion of non-industry funded studies, presumably supplementing those already funded by national grant-giving bodies such as the UK Medical Research Council (MRC) or the Max Planck Institute in Germany. However, it submits that the acquisition of a grant-awarding function has its own resource implications and that the frame of reference for such a function should be tightly drawn.

Evaluation of existing technologies and methods

Many technologies including medical devices come into use without having been appropriately evaluated. This is understandable given that it is often difficult to carry out a large scale evaluation on a new technology before it has been introduced (for example medical devices, new diagnostic technologies). Nevertheless evaluations are important and mechanisms should be sought for evaluating untested technology after an appropriate interval, examining the technology's merits and cost effectiveness.

Demonstration of added value for all new drugs

Current drug licensing requires that new drugs be shown to be better than placebo, but not that they be shown to be better than existing treatments with demonstrated beneficial effects. Phase III head-to-head trials are needed to assess comparative effectiveness and address questions of relevance to patients – ideally conducted by investigators who are independent of industry. Given the public cost of 'industry-funded' drug trials, research ethics committees and other regulators should assess what value proposed new commercial research is likely to yield for the (unavoidable) public investment of resources. In addition it is important to consider the ethical aspects such as abuse of participant time, trust and altruism in agreeing to participate in trials of little or no value, where sufficient research may have already been done.

Toxicological and clinical information and pharmacovigilance

Toxicological and clinical information should be made public. Although disclosure of documentation concerning production and drug technology could help competitors, there is no reason to hide data on toxicology and clinical evaluation. This information is essential to understand why a new drug has been approved or a new indication granted. Therefore a European pharmacovigilance system should be implemented. Proposed models for future pharmacovigilance include actively looking for toxicity rather than relying on spontaneous reporting. The proactive approach requires research projects to investigate severe adverse reactions such as gastrointestinal bleeding, prolonged QT interval, rhabdomyolysis, hepatitis, renal insufficiency and dependence. Programmes should focus on the signs of toxicity for specific drugs or classes of drugs. In addition, companies should be obliged to present meta-analyses of both beneficial and adverse events in the regular safety update reports they submit to the EMA. The EMA should establish a new pharmacovigilance committee, separate from the Committee for Human Medicinal Products (CHMP). Decisions to restrict the use of a drug or to withdraw it from the market must be taken by an independent group devoted to pharmacovigilance. The medicinal products committee already has a heavy workload and may be resistant to withdrawing a drug that it has approved.

According to EMA, the EMA CHMP assessment is transparent because the benefit-risk assessment is published extensively in the European Public Assessment Reports (EPAR). The EPAR is not written under the supervision of the company, the only right the company has is to request removal of confidential information mainly related to manufacturing.

Increased role for primary care physicians

Far more patients see a general practitioner (GP) than go to a hospital. GPs could provide much more data for healthcare research than they currently do. Involvement of family doctors in research will not only generate good data but will give these professionals more of a stake in the guidelines that arise from the research, making it more likely that the research findings influence practice. Primary care physicians should be trained to be made more aware of the contribution they can make. Research units for primary care physicians have been established in countries including Norway, Denmark, the Netherlands and Germany in order to increase research activity in this area (see also chapter 5).

Research funding, education and training

It has been announced that the EC Clinical Trials Directive 2001/20/EC will be revised and the EC FP7 health has decided to use about 30% of its funding for clinical research. This is a clear improvement for independent patient-oriented clinical research.

Challenges, however, remain. Independent funding from public funds and charities in the field of patient-oriented clinical research could still be increased – it should be considered as an investment to increase healthcare quality and decrease healthcare spending. It was demonstrated in 2008 by the UK MRC, Wellcome Trust and Academy of Medical Sciences report, ‘Medical Research: What’s it worth?’ that investment in medical research gives a return of 39% in the subsequent years, in perpetuity⁶⁴. This ‘interest rate’ of 39% per year is extremely high, and the report and its results should be made more widely known to all citizens of Europe and to all decision- and policy-makers.

Establish a pool of European funding

One way of getting better value for money would be to establish a pool of pan-European funding for multi-centre, multinational clinical research where evidence gaps are present to drive peer-reviewed research into evidence-based medicine. This could be done through establishing networks of existing national competent institutions in addition to the many excellent networks that currently exist. One funding model could be for countries to legislate to set aside a percentage of GDP for industry-independent research. One way of ensuring publicly funded research is to compel hospitals to carry out research, as is the case in Norway for example, or

64. Health Economics Research Group, Office of Health Economics, RAND Europe. Medical Research: What’s it worth? Estimating the economic benefits from medical research in the UK. London: UK Evaluation Forum; 2008

to have dedicated grants to investigator-driven clinical trials as in UK, Sweden and Germany.

Education and infrastructure

All clinicians should be trained in appraising research and recognising methodological flaws and biases and training in research methods should be improved for those doing research apprenticeships. In addition, the number of methodologists should be increased. The 2007 EMRC White Paper also called for specific measures to reinforce the training of medical doctors in science, and the setting up of more MD/PhD programmes and defined career tracks for young researchers leading to permanent positions⁶⁵. In addition ethical committees should be better trained in the review of trial protocols to ensure that studies will provide useful results.

Education and knowledge about how to carry out research and use research results is an important tool to implement evidence-based medicine. There are differences among the levels of education provided by universities across Europe for undergraduate medical education. Education in medicine is the responsibility of the healthcare system, as is lifelong continuous medical education once specialist competencies have been obtained. Several important and influential organisations strive to strengthen education in this field, including bodies such as the European Union of Medical Specialists (UEMS); the Standing Committee of European Doctors (CPME); and the Permanent Working Group of European Junior Doctors (PWG).

Education and knowledge about how to carry out research and use research results is not only important for doctors, but also other healthcare professionals such as nurses, physiotherapists, midwives, nuclear medicine technicians, pharmacists, bioengineers, physicists, chemists and other academics, who all play an important role in generating research results and using these results for the benefit of patients.

Education about guidelines in the undergraduate and continuous medical education of specialists should be strengthened.

There is also a great diversity between countries in Europe relating to hospital buildings and infrastructure, equipment, levels of safety and cleaning etc, all of which are important for the efficient running of the healthcare system.

Major issues

Better design, conduct and reporting of research

- There is a lack of methodologically well-educated

65. Billig, H., Blakemore C, Bouillon R et al. 2007. EMRC White Paper. Present Status and Future Strategy for Medical Research in Europe. Publication of the European Science Foundation.

2. Knowledge Generation

medical doctors in the field of systematic reviews and clinical research.

- Trials are often not correctly powered to achieve useful results.
- There is a lack of studies testing different diagnostic and therapeutic strategies.
- New studies are often not reported in the context of systematic reviews of the existing literature.

Publication of results and peer review

- Clinical trial protocols are only rarely registered or published.
- Many negative results are not published so there is no clear indication of the real efficacy and safety of a given treatment. The USA has an obligation to publish results in a trial register, but there is no similar requirement in Europe.
- Reporting bias is a major issue for interpreting research results and there is poor awareness, use and implementation of reporting guidelines by authors, reviewers and editors. Many journal reviews focus on expert judgments about contributions to knowledge rather than methods and usability.
- In many cases there is space restriction in journals for reporting of details of performance and results of trials.
- The peer review system is currently under scrutiny and needs significant improvement: reviewers often do not have the relevant knowledge and experience in critical evaluation and have competing interests.
- It is difficult to publish in some key journals due to the selection process favouring 'fashionable' subjects and what is and is not important for a particular journal.

Research Funding, education and training

- There is not enough funding for independent clinical research and comparative effectiveness research, and funding is often based on ideas with low scientific priority.
- Grant proposals are often not based on systematic evaluation of the existing evidence.
- The administrative process for the application of national and European funding projects is very complex.
- The application process, especially for international clinical trials, is very complex.
- Education and training for clinical researchers are not well developed.

Better evaluation of drugs

- In many cases the evaluation of new drugs is not transparent and the evaluators are not independent. The proof of added value of a new drug is often missing.

Better regulation of medicines

- The pharmacovigilance system is insufficient and has

to be improved.

- Toxicological and clinical information about medicines is often not made public.

Recommendations

Better design, conduct and reporting of research

- Improve evaluation of applications for clinical research grants e.g., by involving researchers and clinical specialists with good knowledge of Health Technology Assessment (HTA).
- Increase the number of methodologists in healthcare research, therefore emphasising initial training for doctors in critical appraisal, in recognising methodological flaws and biases and the need for systematic reviews rather than carrying out primary research. Train researchers to communicate 'numbers' properly and clearly, according to evidence of best methods for doing so.
- Ensure that investigator-driven clinical trials are carried out with an appropriate number of patients to produce statistically reliable results.
- More studies testing different diagnostic and/or therapeutic strategies are needed particularly comparing pharmacological with non-pharmacological interventions.
- Require – by incentives and regulation – registration and publication of protocols for all clinical trials at inception.

Publication of results and peer review

- *Registration of studies*
 - Legal obligation to register and publish all results with an FDA-like law with freedom of information;
 - NIH-type database of all results accessible on the internet by patients and clinicians; Obligation for industry to provide information about all outcomes of clinical trials, in a publicly accessible database for clinical trials extended to industry;
 - For EC-funded clinical trials, one of the requirements should be the sharing of results and one single place in Europe (European Trial Register) where data output of clinical trials should be made available.
- Increase author and journal awareness of and training in reporting guidelines, such as CONSORT and STARD statements⁶⁶. Support timely open access to full results on completion. Supplement peer review of studies with review by methodologists and end-users.
- Journal editors must require new studies to be set in the context of systematic assessments of related studies and authors have to conclude to what their study has added.
- Support web-based free access repositories – sepa-

66. www.stard-statement.org – www.consort-statement.org

rate from any publications – so that clinicians and researchers have details of the treatments, test, or instruments studied.

- Provide well-defined methods with the requirement that the outputs be published, e.g., mandatory in the EudraCT database.
- All studies should be reported transparently. Balance of journal referees means that all disciplines and approaches have to be taken into consideration.
- Ways need to be found to allow new ideas into the literature for access by everyone, i.e. open access initiatives – with fewer restraints and handled in a more open manner: *PLoS One* is an interactive open access journal for the communication of all peer-reviewed scientific and medical research.

Research Funding, Education and Training

- Processes to increase the use and implementation of HTA reports in administrative processes, including budget work on all levels, must be initiated. Loops should be started where evidence-based disinvestment of less effective and obsolete technologies create financial resources that can be given to new technologies with documented effectiveness according to evidence-based principles.
- Increase the public funding of independent patient-relevant clinical research. This would benefit the governments and citizens of European countries. Europe needs an initiative similar to the US Comparative Effectiveness Research (CER) Programme.
- Women and men should have equal access to research careers.
- Research funding bodies should require – and support – grant proposals to build on systematic reviews of existing evidence and for authors of reports of studies to state how their research has reduced the uncertainty on that topic.
- Simplify and harmonise the administrative procedures of the European system for the submission and management of European projects. Europe needs better coordination to avoid duplication in clinical studies and to achieve a critical mass and better competitiveness.
- Implement the conclusions of the Forward Look ‘Investigator-Driven Clinical Trials’: streamline procedures for obtaining authorisation for investigator-driven clinical trials; adopt a ‘risk-based’ approach to the regulation of investigator-driven clinical trials.
- Improve the education, training and career structure for scientists involved in patient-oriented clinical research. Develop a European training programme such as MD/PhD to improve the quality and education of clinical investigators. Promote a research career as a scientific MD/PhD. Link clinical pathway to get a specialisation degree with a PhD programme in clinical research.

Better evaluation of drugs

- Make transparency in drug evaluation a legal requirement. Mandatory, prospective publication of trial protocols should be required by law.
- Require proof of added value for all new drugs, with regulatory authorities to require drug companies to have at least one pivotal phase III trial conducted by independent scientific organisations.

Better regulation of medicines

- A European pharmacovigilance system should be implemented. Programmes should focus on the signs of toxicity for specific drugs or classes of drugs.
- EMA should establish a new pharmacovigilance committee, separate from the Committee for Human Medicinal Products (CHMP). Decisions to restrict the use of a drug or to withdraw it from the market must be taken by an independent group devoted to pharmacovigilance.
- Make toxicological and clinical information public. Companies should be obliged to present systematic reviews and meta-analyses of both beneficial and adverse events in the regular safety update reports they submit to the EMA.

Key stakeholders

Group 1:

- Academic research (basic to patient-oriented research)
- Learned societies
- Healthcare providers/hospitals: Healthcare professionals, i.e. clinicians, primary care practitioners, medical specialists including medical ethicists
- Teachers (undergraduate and postgraduate medical training, as well as for continuous professional development)

Group 3:

- National and EU funding agencies and research councils
- National and EU regulators
- Ministries
- Ethics committees

Group 4:

- Patients and general public
- Patient organisations

Group 5:

- Journal editors and peer reviewers
- Media: internet, journals, medical journalists, etc.

Group 6:

- Private sector:
 - Pharmaceutical industry
 - Medical devices industry

3. Knowledge Interpretation

Evidence-based medicine

Evidence-based medicine (EbM) seeks to use the best scientific evidence to inform clinical decision-making. It has been defined as “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient”. It means “integrating individual clinical expertise with the best available external clinical evidence from systematic research”⁶⁷ (see Figures 4 and 5).

Evidence-based practice is “the integration of clinical expertise, patient values, and the best research evidence into the decision-making process for patient care. Clinical expertise refers to the clinician’s cumulated experience, education and clinical skills. The patient brings to the encounter his or her own personal and unique concerns, expectations, and values. The best evidence is usually found in clinically relevant research that has been conducted using sound methodology”.⁶⁸

Cochrane Collaboration

The Cochrane Collaboration⁶⁹ is an international, independent, not-for-profit organisation of over 28,000 contributors from more than 100 countries, dedicated to making up-to-date, accurate information about the effects of healthcare readily available worldwide. The Collaboration is organised in 92 entities, including Collaborative Reviews Groups, Centres and Methods Groups. 59 of these entities are located in Europe and offer a strong network for various aspects of knowledge collection, synthesis and dissemination. Contributors work together to produce systematic reviews of healthcare interventions, known as Cochrane Reviews, which are published online in the Cochrane Library⁷⁰.

The Cochrane Collaboration has a central role that is internationally recognised for the generation of world-wide systematic reviews. It has a leadership position in review initiation and methodological development such as software, search tools and bias evaluation tools. Its key position is also vital because it has now generated over 5,000 Cochrane reviews and about 2,000 systematic review protocols of the highest quality. They are contained in the Cochrane Library, together with the largest collection of controlled trial information (more than 600,000) and other contributions like HTA reports and health economic abstracts. Review quality is linked to two major elements: a strict conflict of interest policy and the regular updating of reviews.

67. Sackett DL, Rosenberg WM, Gray JA et al Evidence-based medicine: what it is and what it isn't. *Clin Orthop Relat Res.* 2007; 455:3-5

68. Sackett DL. Clinical epidemiology. what, who, and whither. *J Clin Epidemiol.* 2002; 55(12):1161-6

69. www.cochrane.org

70. www.thecochranelibrary.com

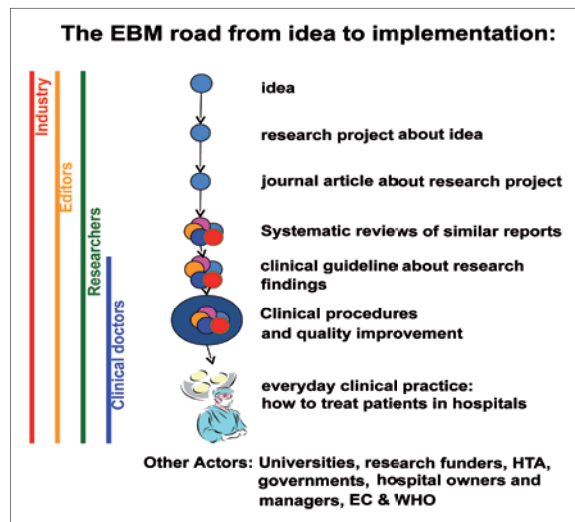


Figure 4. A simplified model describing the process of evidence-based medicine – but which in reality is often more complex and ‘non-linear’

Health Technology Assessment

According to the INAHTA (International Network of Agencies for Health Technology Assessment⁷¹), health technology assessment (HTA) systematically evaluates properties, effects, and/or impacts of existing or new healthcare technologies. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. The results of HTA are mostly published as reports, and often implemented through clinical practice guidelines. One important method used for HTA is EbM.

The main purpose of HTA is to inform technology-related policy-making in healthcare. HTA contributes to answering questions from decision-makers in areas and organisations related to health policy and/or practice and to inform decisions relating to national, regional or local healthcare systems. Such decisions may relate to the procurement, funding or appropriate use of health technologies and also to disinvestment in obsolete or ineffective technologies.

Those responsible for or associated with requests for assessments are the primary targets and the main focus for HTA. However, the influence of HTA on other decision-makers through provision of information will often also be important.

There are now around 50 agencies worldwide that assess health technologies, and more than half of them are based in Europe⁷² (accessed 20 June 2010). The importance of HTA has increased internationally since

71. www.inahta.org

72. www.inahta.org



Figure 5. The EbM Triad

the 1970's. This is reflected by the expanding membership of INAHTA, a non-profit umbrella organisation established in 1993. Other important organisations involved in HTA research are the scientific international societies Health Technology Assessment International (HTAI⁷³), the Guidelines International Network G-I-N⁷⁴ and the International Society for Pharmacoeconomics and Outcomes Research⁷⁵. An international Masters programme in health technology assessment and management, ULYSSES⁷⁶, is also now offered.

In 2008, with funding from the European Commission and member states, the European network for Health Technology Assessment (EUnetHTA) was established to aid collaboration between the many relevant European bodies⁷⁷.

The European Patients' Forum (EPF), one of the network's stakeholders, pointed out in May 2010 that there is much work to be done before HTA adequately reflects patients' priorities: "In general terms, this is happening only in an *ad hoc*, piecemeal fashion across the Member States, with some reservations in a number of countries on the added value of involving patients. On the other hand, with some exceptions, there is generally limited knowledge and know-how across the broad EU patient community on the science and the policy rationale behind HTA and mechanisms to get involved effectively"⁷⁸.

The level at which HTAs should operate – pan-European, national or regional – is open to debate. There is a general view that HTAs should be at least national, and that health economy evaluations should be included in assessments. In many countries, healthcare is organised and financed regionally, making regional HTA work important. Pan-European economic evaluations are likely to be difficult to translate across national boundaries because of the widely differing economic environments

73. www.htai.org/

74. www.g-i-n.net

75. www.ispor.org/

76. www.ulyssesprogram.net/careers.html

77. www.eunethta.net/Public/About_EUnetHTA/ (accessed 20 June 2010)

78. www.patientsorganizations.org/attach.pl/1142/983/EPF%20Seminar%20on%20HTA%20programme.pdf

across Europe. There is a widely held view that university hospitals should be competent in HTA evaluations. There is also a debate to be held about whether HTA should be an inherent part of guidelines.

Examples of national HTA institutions:

HTA UK: the UK Health Technology Assessment programme is part of the UK's National Institute for Health Research. The HTA Programme harvests research questions and passes them to panels to prioritise, then commissions research to address the most important uncertainties. It also supports investigator-led studies. HTA-funded trials and systematic reviews are almost 100% published, partly because all of the programme's studies must be published in its own HTA Reports, and that a proportion (5-10%) of funding is withheld until publication. It has had a number of notable successes. For example it commissioned a trial to determine if Bell's Palsy responded better to steroids or to antiviral therapy. A clear-cut conclusion was reached that steroids are helpful and antivirals are not⁷⁹.

Another HTA study examined the use of compression stockings in stroke units to prevent deep vein thrombosis. The results were disseminated through the website clinicaltrials.gov, and the results led to changed practice within 24 hours of their release⁸⁰.

IQWiG: the Institute for Quality and Efficiency in Healthcare in Germany was set up in 2004 to help ensure quality and efficiency in the German healthcare system. The Institute produces independent, evidence-based reports on healthcare issues such as drugs, non-drug interventions (e.g. surgical procedures), methods for diagnosing and screening, treatment guidelines and disease management programmes. In addition IQWiG provides easily understandable health information for patients and the general community. The sole contracting agencies are the Federal Joint Committee (G-BA) and the Federal Ministry of Health (BMG). IQWiG can also tackle topics on its own initiative (general commission). IQWiG publishes all results in the form of freely accessible reports, rapid reports and working papers, thereby addressing both scientists and stakeholders in healthcare as well as the general public. It makes knowledge available, with the aim of enabling everyone to make informed decisions.

79. Sullivan FM, Swan IR, Donnan PT et al. A randomised controlled trial of the use of aciclovir and/or prednisolone for the early treatment of Bell's palsy: the BELLS study. *Health Technol Assess.* 2009; 13(47) 1-130

80. Dennis M, Sandercock PA, Reid J et al. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. *Lancet.* 2009, 6;373(9679):1958-65

3. Knowledge Interpretation

Reimbursement

An important issue is the concept of “reimbursement” where in some countries HTA organisations decide which new treatments should obtain reimbursement and thereby be paid for from the public purse. This, too, is organised differently across Europe. The reimbursement system may be influenced by the government wishing to keep health expenditure down, by commercial companies who wish to sell their products and by patients who wish to have what they believe to be the best treatment. Physicians and medical researchers also influence the system through their own preference for particular treatments. They are however sometimes accused of influencing the system due to conflicts of interest through connections with the industry, for example. Little hard data exist on the size and importance of this bias, but it is debated and it casts suspicion on the doctor-patient relationship.

Education and training

Given the importance of EbM, HTA, health economics and the use of guidelines and quality improvement tools, these should be included early in the training *curriculum* of health professionals. Students should learn the essential tenets of evidence-based healthcare and quality improvement and thereafter there should be continued education in these topics.

Major issues

- Many technologies come into use without having been fully evaluated.
- There is not enough awareness and there is a lack of education and training among healthcare professionals in the field of EbM, HTA and quality improvement.

Recommendations

- Untested technologies should be systematically evaluated before deciding whether they should be introduced into routine healthcare.
- The methods of EbM, HTA and health economics should be included early in the training *curriculum* of health professionals.
- A new model should be considered where HTA reports are written by a team of involved clinicians with support from HTA experts and quality control processes.

Key stakeholders

Group 1:

- Academic research (basic to patient-oriented research)
- Learned societies
- Universities
- Healthcare providers/hospitals:
Healthcare professionals, i.e. clinicians, primary care practitioners, medical specialists including medical ethicists

Group 2:

- Methodologists, systematic reviewers, healthcare professionals
- Health economists
- HTA and guideline agencies
- Policy-makers and healthcare systems

4. Knowledge Implementation in Clinical Practice

Several ways to address the 'knowing-doing gap'

A huge amount of medical research is carried out every day, producing vast quantities of data. Getting this information to healthcare professionals and patients is a challenge.

One key way of getting new information to healthcare professionals is through issuing clinical guidelines. This is discussed in greater detail below.

Information technology is used to disseminate data, of which the Cochrane Library⁸¹ is an excellent example of best practice.

There is a need to identify the current best practices in the use of IT to disseminate knowledge to:

- identify existing tools
- evaluate existing tools
- develop new tools

There is an increasing demand for efficiency in healthcare. Medical opportunities are growing more rapidly than the budgets for healthcare, creating a widening gap between the need from a public health perspective and what can actually be afforded (see Figure 6). This makes it more important than ever to ensure that only the most effective and cost-effective technologies are used and that inefficient or ineffective diagnostics and treatments as well as those with poor cost-effectiveness are discarded.

The new '-omics' technologies such as genomics and proteomics, are expected to herald a new paradigm in healthcare, the concept of personalised medicine. This will introduce new challenges in the area of implementing new knowledge.

Clinical guidelines

Clinical guidelines are an important tool that can be used to implement medical knowledge in clinical practice.

Definition: The standard definition of Clinical Practice Guidelines (CPGs) is that of Field and Lohr⁸²: "systematically developed statements to assist practitioners and patient decisions about appropriate healthcare for specific circumstances". Clinical guidelines aim to describe appropriate care based on the best available evidence as well as on systematic and transparent consensus processes⁸³. Guidelines help healthcare professionals

81. www.thecochranelibrary.com

82. Field MJ, Lohr KN (Eds), 1990. Clinical Practice Guidelines: Directions for a New Programme, Institute of Medicine, Washington, DC: National Academy Press

83. Council of Europe 2002. Developing a Methodology for Drawing up Guidelines on Best Medical Practices. Recommendation Rec(2001)13 and explanatory memorandum. Strasbourg. ISBN 92-871-4788-4. Internet:<http://www.arztbibliothek.de/mbd/edocs/pdf/literatur/coe-rec-2001-13.pdf>

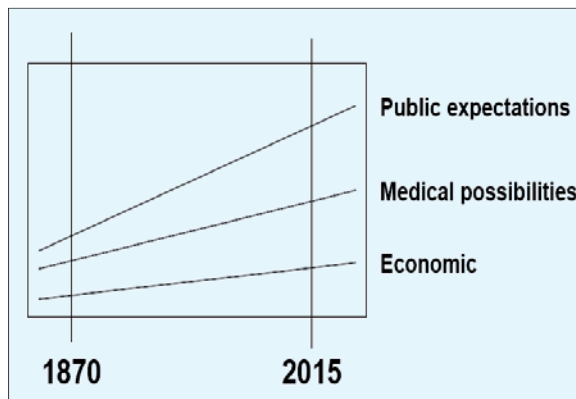


Figure 6. The gap between needs from public health perspective and what can be afforded

in their work, but they do not replace their knowledge and skills.

Aims: Good clinical guidelines aim to improve the quality of healthcare and to reduce inappropriate variation in healthcare practice. They can change the process of healthcare and improve people's chances of getting better.

Clinical guidelines can be used to:

- provide recommendations for the treatment and care of people by health professionals
- develop standards to assess the clinical practice of individual health professionals
- help educate and train health professionals
- help patients make informed decisions

Who develops the guidelines?

How the system of guideline production is organised varies between European countries. Before guidelines can be produced, systematic reviews including critical appraisal of the evidence must be undertaken. Guidelines can be produced locally in a hospital department, by a cluster of hospitals working together or at a national level, as in Germany, Finland and the Netherlands where it is a task of the scientific academies and professional societies. The national academies or scientific learned societies produce guidelines on a national basis where experts in each sub-specialty scrutinise the available research in an area, extract the relevant knowledge and match it with their knowledge from everyday clinical practice. Most guidelines are produced in multidisciplinary teams, often supported by methodological experts. A set of recommendations to be included in the guidelines can then be agreed upon, based on a combination of evidence from research and consensus.

Such guidelines are also made at a European level by European academies/scientific learned societies.

4. Knowledge Implementation in Clinical Practice

Here, experts in a given discipline from Europe, sometimes including colleagues from elsewhere, collaborate to develop a mutually acceptable guideline. Often the European guidelines state what is 'best practice' and also mention what can be done if availability of equipment and knowledge is not optimal. Sometimes international guidelines are produced by international bodies, such as the World Health Organisation (WHO).

Guidelines are also produced by central agencies:

Examples of national guideline-producing bodies

Germany: The umbrella organisation of the scientific medical societies in Germany (AWMF) publishes mono- and multidisciplinary developed evidence-based clinical guidelines with primary focus on specialist care⁸⁴. For use within disease management programmes, the German Agency for Quality in Medicine ÄZQ coordinates the development and implementation of multidisciplinary tools of the National Disease Management Guidelines Programme: i.e. Guidelines, Patient Guidelines, Practice Aids and Quality Indicators⁸⁵.

Finland: Current Care Guidelines in Finland are developed by the Finnish Medical Society Duodecim whose members include over 90% of Finnish doctors and medical students⁸⁶.

Netherlands: The Dutch umbrella organisation of medical specialist societies supports mono- and multidisciplinary guideline development, similar as in Germany. The Dutch umbrella organisation of healthcare insurers has a role in monitoring the guidelines.

United Kingdom: The National Institute for Health and Clinical Excellence (NICE) provides guidance, sets quality standards and manages a national database to improve people's health and prevent and treat ill health. It develops guidelines and guidance which are made available at the NHS Evidence – National Library of Guidelines. NICE has four national collaborating centres (NCCs) to help develop the clinical guidelines by harnessing the expertise of the royal medical colleges, professional bodies and patient/carer organisations.

There is increasing consensus about the need for centrally programming of guidelines to reduce duplication of effort and to increase the efficient use of investments in guideline development⁸⁷.

84. www.leitlinien.net

85. www.versorgungsleitlinien.de

86. www.duodecim.fi

87. Institute of Medicine (IOM) report *Knowing What Works in Healthcare: A Roadmap for the Nation*, 2008

The USA has a specialist-based guideline system and often there is good collaboration between European and US guideline authors, who are typically part of the same research community. The National Guideline Clearinghouse™ is a comprehensive, web-based database of evidence-based clinical practice guidelines edited by the Agency for Healthcare Research and Quality (AHRQ). This agency is financed by the US Department of Health and Human Services.

At international level the Guidelines International Network G-I-N⁸⁸ aims to improve the quality of healthcare by promoting systematic development and use of clinical guidelines. The network has the world's largest international guideline library. Regularly updated with the latest information of the G-I-N membership it contains more than 7,200 documents (as at November 2010). Founded in 2002 G-I-N has grown to around 150 organisational and individual members, with 75 members in Europe⁸⁹.

Guideline production models – the debate

From the discussions during the workshops that formed the basis of this Forward Look it is apparent that there is a diversity of opinion – and indeed strong feeling – about who is best placed to produce practice guidelines: a central guideline-producing agency (sometimes government-funded as in France and the UK, or funded by healthcare professional organisations as in Finland and Germany), doctors regionally or locally, or learned societies on a national basis. An even more important subject is what data should form the basis for guideline production. Guidelines must be based on systematic literature review preferably in the format used in, for example, HTA reports. It is important to acknowledge these differing views and to have an honest and open debate on the issues. The debate may result in the evolution of a new solution for the development of a next generation, mutually agreeable model for guideline production with clinicians, researchers and learned societies working in close collaboration with central organisations.

Denmark provides a good example of how collaboration between clinical experts, researchers, HTA experts and national authorities can yield a beneficial outcome. Recently the different experts were charged with designing new guidelines for cancer diagnosis. After much intensive debate, within two years a mutually agreeable set of guidelines were produced and have now been

88. www.g-i-n.net

89. Ollenschläger G, Marshall C, Qureshi S, et al. Board of Trustees 2002, Guidelines International Network (G-I-N). Improving the quality of healthcare: using international collaboration to inform guideline programmes by founding the Guidelines International Network (G-I-N). *Qual Saf Health Care*. 2004; 13(6):455-60

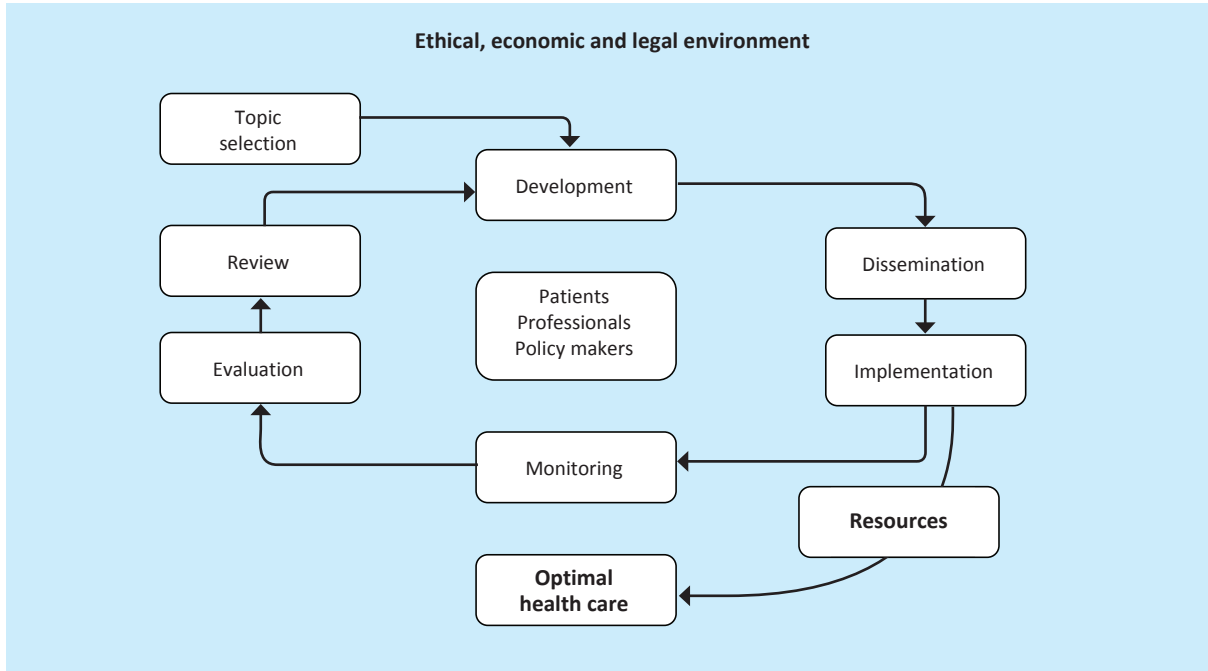


Figure 7. Process of guideline production and use (Council of Europe 2001)

implemented. The guidelines have been well received and have had a dramatic influence on cancer diagnosis in Denmark⁹⁰.

One of the relevant topics dealing with guideline quality, beside the issue of coordinating bodies and authorship, is the question of whether the development process follows internationally accepted methods for guideline production or not. According to the Council of Europe Recommendations from 2001 (see also Figure 7):

- Guidelines should be produced by multiprofessional groups in a systematic, independent and transparent fashion, using appropriate quality criteria.
- End-user involvement through a wide review and/or testing of the pilot version is necessary before adopting a guideline for implementation.
- If guidelines are adapted from other countries or areas, they must be re-edited and reviewed or tested for applicability in the new environment.

We need to develop a new ‘best practice’ on how to proceed in the future. In this spirit of open debate, the relative merits of the approaches of clinicians/learned societies versus central agencies are discussed briefly below.

90. Stauss J, Franzius C, Pfluger T et al. Guidelines for 18F-FDG PET and PET-CT imaging in paediatric oncology. *Eur J Nucl Med Mol Imaging*. 2008; 35(8):1581-8

Clinicians and learned societies should produce guidelines:

As mentioned above, learned societies and academies are in many cases responsible for writing practice guidelines. Academies and learned societies are often regarded as ideal for guideline writing by the medical community, as those involved as guideline authors are working clinicians and researchers, actively involved in patient treatment. They can thereby better understand how to treat patients with the many complexities due to subgroups of diseases combined with the diversity of biology. Clinical trial protocols are performed in well-defined patient populations, with many patients excluded from these trials. The research results therefore have to be understood in that context, and often results have to be “translated” into the relevant clinical situation. Guidelines reflecting this are naturally preferred by clinicians.

The concept of reflexivity – being cognisant of how ‘upstream factors’ such as study design, methodologies or our own subjective experiences might influence and shape research outcomes and conclusions drawn from biomedical data – is important for the learned societies in their process of guideline writing. Hands-on clinicians and researchers have the potential and competencies to evaluate the available evidence if adequately supported e.g., by HTA or EbM experts; they must however be unbiased and uninfluenced by industry and their own

4. Knowledge Implementation in Clinical Practice

private financial interests to act as “honest brokers of knowledge transfer”.

Pros: The guidelines’ authors are medical practitioners who have everyday working knowledge of their patients, have views about what works in reality and have a thorough knowledge about clinical practice and research in their area enabling them to exercise their professional expertise and judgment to the best effect.

Cons: Clinicians and medical researchers are potentially open to conflicts of interest due to influence by industry and perhaps also a bias towards augmenting their own influence and possibility of increasing their private income. They are often not well methodologically trained.

Central organisations should produce guidelines:

Pros: The authors are not influenced by the above mentioned potential conflicts of interest regarding industrial connections and bias towards augmenting their own power. Further, they have a thorough knowledge of methods for assessing research data and literature.

Cons: They are not all working healthcare practitioners with clinical experience; if they are physicians they may not have the relevant up to date clinical competencies and therefore they may be regarded as out of touch with what is feasible in everyday clinical practice. Potential conflicts of interest can arise in terms of being paid by the government and, for some organisations, with a more or less explicit goal to keep health expenditure down. There is a view among some opponents of centrally produced guidelines that the organisation could have a further conflict of interest in that it may wish to augment the importance of its own area to maintain and strengthen its influence.

These points are raised not to stoke antipathy but to acknowledge that different and strongly held opinions exist, and that sound arguments are available on both sides.

Research implementation

Despite substantial global investment in the commissioning of health service research and clinical guidelines to support decision-making, evidence suggests that whilst the transfer of research to practice is possible, its success can be variable. There is now extensive evidence that there is a gap between the healthcare that patients receive and the practice that is recommended^{91,92}. In both primary and secondary care there are unwarranted

variations in practice and in the resulting outcomes which cannot be explained by characteristics of the patients^{93,94,95}. Implementation research has been defined as the scientific study of methods to promote the uptake of research findings for the purpose of improving the quality of care. Implementation is now recognised as a complex process, highly dependent on context, and interactions between multiple, interconnected factors at the level of individuals, groups, organisations and wider health systems^{96,97,98,99}. Despite this, research efforts have historically been concentrated on the search for a ‘magic bullet’ mainly through the utilisation of randomised controlled trials to assess the effectiveness of specific interventions used in strategies to change individual behaviours.

Successive overviews of systematic reviews by members of the Cochrane Collaboration’s Effective Practice and Organisation of Care group (EPOC)¹⁰⁰ have suggested that a range of interventions can be successful in changing professional behaviour in some circumstances, but the reasons why interventions work in some circumstances but not in others remain unclear^{101,102,103}.

Small to moderate improvements in clinical practice have been reported across a range of interventions including the dissemination of printed educational materials, audit and feedback, interactive educational meetings, opinion leaders, educational outreach (performance

93. Sheldon TA, Cullum N, Dawson D, Lankshear A et al. What’s the evidence that NICE guidance has been implemented? Results from a national evaluation using time series analysis, audit of patients’ notes, and interviews. *BMJ* 2004; 329:999

94. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients’ care. *Lancet*. 2003; 362(9391):1225-30.

95. Grol R, Wensing M. What drives change? Barriers to and incentives for achieving evidence-based practice. *Med J Aust*. 2004; 180(6 Suppl):S57-60.

96. Ferlie EB, Shortell SM. Improving the quality of healthcare in the United Kingdom and the United States: a framework for change. *Milbank Q* 2001; 79:281-315

97. Lomas J. Retailing research: Increasing the role of evidence in clinical services for childbirth. *Milbank Q* 1993; 71:439-475

98. Centre for Reviews and Dissemination. Getting evidence into practice. *Effective Health Care* 1999; 5:1

99. Greenhalgh T, Robert G, MacFarlane F, Bate P, Kyriakidou O. Diffusion of innovations in service organizations: systematic review and recommendations. *Milbank Q* 2004; 82:581-629

100. www.epoc.cochrane.org/

101. Oxman AD, Thomson MA, Davis DA, Haynes RB. No magic bullets: a systematic review of 102 trials of interventions to improve professional practice. *CMAJ* 1995; 153:1423-31

102. Grimshaw JM, Shirran L, Thomas RE, Mowatt G, Fraser C, Bero L, et al. Changing provider behaviour: an overview of systematic reviews of interventions. *Medical Care* 2001, 39 (Suppl 2):2-45

103. Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, Whitty P, Eccles MP, Matowe L, Shirran L, Wensing M, Dijkstra R, Donaldson C. Effectiveness and efficiency of guideline dissemination and implementation strategies. *Health Technol Assess* 2004; 8(6):1-72

91. Asch SM, Kerr EA, Keeseey J, Adams JL et al. Who is at greatest risk for receiving poor-quality healthcare? *N Engl J Med*. 2006; 354(11):1147-56

92. McGlynn EA, Asch SM, Adams J et al. The quality of healthcare delivered to adults in the United States. *N Engl J Med*. 2003; 348(26):2635-45

feedback) and reminder systems. Many implementation research studies have used combinations of more than one intervention, but the evidence suggests that multifaceted interventions do not consistently provide bigger effects than single interventions. Depending on the context, small effects, particularly if shown to be cost-effective, may still be regarded as worthwhile.

Based on the best available evidence, no strong recommendations can be given regarding the best way to implement medical research in clinical practice. Thus, health professionals need to use considerable judgment about which interventions are most likely to be effective in any given circumstance and also need to consider the feasibility, costs and benefits that any intervention is likely to yield.

Given that the evidence base is incomplete, the challenge is to move beyond intervention studies to conduct research that considers the nature of the processes by which health technologies are adopted and sustained and the particular context and setting in which implementation occurs.

In the UK, the Clinical Effectiveness Research Agenda Group has made recommendations for developing an implementation research agenda that addresses these issues from research funding infrastructure and capacity building, theoretical and methodological development through to sustainability and impact¹⁰⁴. Also in the UK, the National Institute of Health Research is funding a number of long-term Collaborations for Leadership in Applied Health Research and Care (CLAHRCs) between universities and surrounding NHS organisations. These have been established to create and embed approaches to research, its dissemination and implementation to enhance the effectiveness and efficiency of clinical care.

Finally as healthcare resources are finite there remains a need to consider the costs and benefits of investment in strategies to improve the research implementation and uptake. Implementation efforts compete with other healthcare programmes for limited healthcare resources, it is therefore important to determine whether implementation activity is actually worthwhile^{105,106,107}.

104. Eccles MP, Armstrong D, Baker R, Cleary K, Davies H, Davies S, Glasziou P, Iltott I, Kinmonth AL, Leng G, Loga S, Marteau T, Michie S, Rogers H, Rycroft-Malone J, Sibbald B: An implementation research agenda. *Implement Sci* 2009; 4:18
105. Fenwick E, Claxton K, Sculpher M. The value of implementation and the value of information: combined and uneven development. *Med Decis Making*. 2008; 28:21–32
106. Mason J, Freemantle N, Nazareth I, Eccles M, Haines A, Drummond M. When is it cost-effective to change the behaviour of health professionals? *JAMA* 2001; 286:2988–92
107. Hoomans T, Severens JL, Evers SM, Ament AJ. Value for money in changing clinical practice: should decisions about guidelines and implementation strategies be made sequentially or simultaneously? *Med Decis Making*. 2009; 29:207-16

Another example of stimulating implementation research is the Implementation Fellowship Programme, funded by the Dutch Organisation for Health Research and Development (ZonMw). The aim of the programme is to broaden and deepen the insight in the implementation of effective innovations and to disseminate knowledge.

It is important that there should be an increase in the use and implementation of HTA reports and guidelines in administrative processes including budget work on all levels. Loops should be initiated where evidence-based disinvestment of less effective and obsolete technologies creates financial resources that can be given to new technologies with documented effectiveness according to evidence-based principles.

Quality improvement and audits

A critical component in quality improvement is the phase of maintenance, follow-up and refinement of novel implementations. One important strategy in this respect is the field of audit and feedback that has been developed over recent years. This can comprise retrospective self-reports, patients' reports and chart review or medical record review. A recent report from the Federal Public Service, the Health Evidence Network and the European Observatory on Health Systems and Policies has addressed this important issue and has scrutinised the available literature in the area. The early evidence, while not yet conclusive, is that these audit systems improve the quality and safety of healthcare.

One issue that needs to be taken into account when developing any system of audit is the administrative burden that it will impose on professionals. A less time-consuming audit system with intelligent use of IT systems might be the solution for the future. Developmental costs of these IT solutions should be taken into account.

Quality indicators

Quality indicators can provide valuable information about healthcare performance. However, generating good quality indicators is a challenge. A quality indicator is only as good as the data that are used to develop it and as such, indicators must be constructed carefully. Benchmarking systems have been developed in many areas but an editorial¹⁰⁸ states that comparing hospital mortality ratios is of little use, as the data are not comparable so the resulting comparisons are not valid. As an example, myocardial infarction mortality can differ between rural and urban hospitals due to unmeasured confounders. Thirty-day mortality on the other hand can be a better indicator.

108. Black N. Assessing the quality of hospitals. *BMJ* 2010 20;340:c2066.

4. Knowledge Implementation in Clinical Practice

Similarly, survival rates for cancer treatment among countries are frequently used as a parameter for healthcare quality. However this is a complicated area as population habits have influence on mortality and morbidity. A common example is the Danish low survival rates for cancers, where it has been argued that Denmark's higher smoking and alcohol consumption compared to the other Nordic countries is the reason for poorer health outcomes. However, a recent report on the survival of patients with lung cancer in Denmark demonstrated a marked and significantly higher mortality for the same population including confounders in hospitals where modern diagnostics with PET/CT was not used for staging lung cancer. So the populations' bad habits cannot alone be responsible for the generally poor Danish outcome.

Developing good quality indicators is therefore a challenge and it is vital that professionals can have faith in their value. One way of achieving this is to ensure that the professionals are involved in developing the quality indicator and feel that they have a degree of ownership. In Germany, for example, quality indicators are increasingly developed together with the production of guidelines by multidisciplinary guideline groups¹⁰⁹.

Registries

Good disease registries are a rich and important source of information and their number should be increased in Europe. They provide a powerful way to assess the implementation and effectiveness of guidelines and treatment outcomes. However there remain serious challenges surrounding the establishment and use of data from registries, centring largely on ethical and legal issues. The combination of disease and death registries, electronic patients' records and biobanks are emerging with large demands for IT capacity and new methodologies. It is vital that this is further developed so that Europe can become a leading player in the field of developing the tools for the new concept of personalised medicine.

Patient safety and quality handbook

In some specialities and in some hospitals and countries there is an especially strong focus on patient safety and how this can be continually improved. Since the pivotal edition of the BMJ in 2000¹¹⁰ this area has developed rapidly. A quality handbook with guidelines is often combined with guidelines on key aspects of patient safety and in good systems there are policies for how

to update both guidelines on treatment of diseases and guidelines on patient safety. For example the field of nuclear medicine is regulated by a directive from the EC because of the use of radiopharmaceuticals and isotopes. Departments are requested to have a quality handbook with guidelines and feedback loops including surveys of safety procedures, cases of unwanted side effects. The system is easy to use and operates in departments all over Europe. This could form a model system for other departments and specialities.

Major issues

- Clinicians receive much of their information from industry and thereby from a biased source.
- The majority of medical doctors and many researchers are not well trained in systematic assessment of medical knowledge.
- Sometimes research results are introduced in clinical practice although the results are not robust and may be insufficiently assessed. Sometimes robust data are not introduced in clinical practice due to a number of barriers.
- The growing accumulation of the body of evidence is an issue. Reviews need to be written and updated but this is sometimes regarded as a challenge if this task is not financed. Some specific speciality fields are not recognised, and for these areas the knowing-doing gap is especially wide.
- The Internet has changed the relationship between patient and physician due to the information being widely available, with most information being of poor quality. In general practice the time is very short between research being published/being selected by the media/patient asking GP about it.
- Guidelines are often too narrowly focused because they have been produced by specialists and not by a multidisciplinary team including other healthcare professionals such as nurses, allied health professionals and patients.
- Guidelines may be influenced by bias – due to interests of drugs companies and other conflicts of interest. In many countries economic considerations and cost-effectiveness issues need to be taken into account when guidelines are produced.
- Guidelines are often made for treatment of patients, but are not suitable for patients to read, as they are not understandable by laypeople.
- Problems may arise and errors introduced if guidelines are being translated from one language to another and from one healthcare system to another.
- The same criteria for drawing up guidelines are not used across Europe. There are acknowledged guidelines for guidelines, but they are not used in all European countries.

109. Kopp IB, Geraedts M, Jäckel WH et al. The German programme for disease management guidelines: evaluation by use of quality indicator. *Med Klin.* 2007; 102(8):678-82

110. Nolan TW. System changes to improve patient safety. *BMJ.* 2000; 320(7237):771-3

- Guidelines may not reach the end-user and might not get to practitioners in a timely way. New information is arising all the time and a slowly produced guideline can become outdated.
- Guidelines are sometimes not based on full systematic reviews.
- Often guidelines may not be used because those people for whom they are intended do not feel ownership.
- Normative guidelines may be impossible to use in clinical practice.

Recommendations

- Clinicians and clinical researchers should be involved in the assessment of the medical technologies they want to introduce.
- To reduce duplication of effort, guideline development and updating should be programmed centrally on a national level and for some topics, such as infectious diseases, also on an international level.
- Learned societies together with national bodies have an important role in getting the information out to the clinicians in hospitals and GPs to reduce the influence of the pharmaceutical industry.
- Training, education and knowledge management in healthcare should be strengthened – with special respect to evidence-based healthcare, using effective educational methods, such as problem-based learning, academic detailing.
- The concepts, development and usage methods of guidelines and of other quality improvement tools should be introduced in the medical *curriculum* at the pre-graduate medical education stage with the goal of developing a structured career path for health workers engaged in both clinical and research activities.
- Hospitals and other healthcare practices should, in their annual reports, write about their use of clinical guidelines, which guidelines they use and how they are updated, implemented and how they ensure that they are followed.
- Improve the awareness for the need of systematic reviews for all medical specialties and improve the funding for systematic reviews. Use better IT and databases for collection and dissemination of data.
- Educate the general public about evidence-based medicine, health technology assessment and guidelines.
- IT-based open access databases should be made available for both professional and lay persons. Databases for professionals should include guidelines and open access to journal articles. The Wellcome Trust proposal for a European repository linked to guidelines might be the solution. A data collection and overview of all available guidelines in countries in Europe and globally should be provided. We have to assure that internet sites with quality information are available for patients, i.e. in collaboration with the guidelines as the “best practice” example from Finland where the academies both write guidelines for healthcare and also shorter guidelines dedicated to patients.
- The same criteria and methods in drawing up guidelines should be used across Europe. In other words there should be guidelines for guidelines. The use of international quality criteria of guidelines, described in AGREE II (Appraising Guidelines for Research and Evaluation), should be encouraged¹¹¹.
- Guidelines should be generated by multidisciplinary teams including physicians, nurses, learned societies and other healthcare professionals, when relevant. Patients may be involved, also when relevant. Guidelines should be updated on a regular basis with explicit policies for this.
- It is important that guidelines are independent of bias. Any interests should be declared by the guideline authors.
- Lay versions of guidelines should be produced so that patients can have access to the information in ways that are comprehensible to them.
- Care should be taken with the language used in guidelines, especially if guidelines are translated from one language to another. Effort should be made to ensure that guidelines are comprehensible and unambiguous to everyone who will use them.
- Once guidelines have been produced they need to be ‘marketed’ to ensure that they get to the people for whom they are intended. Therefore guidelines need to get to clinicians and practitioners in a timely way – new information is arising all the time and a guideline slowly produced can become outdated. For this reason there need to be mechanisms for updating guidelines as new data come to light.
- Guidelines should be based on critical evaluation of internationally published data that can be applied nationally. In those countries where economic considerations preclude the implementation of a guideline, the guideline should be re-assessed in the light of the economic issues.
- Guidelines are more likely to be accepted and used by professionals if they have had a role in the guidelines’ development – where there is a sense of ‘ownership’.
- Guidelines should be recommendations for good clinical practice. Normative and ethical considerations should be made explicit, allowing adaptation to daily practice in local hospital settings.

111. <http://fhswedge.csu.mcmaster.ca/pebc/agreestrust/>

4. Knowledge Implementation in Clinical Practice

Key stakeholders

Group 1:

- Learned societies
- Healthcare providers/hospitals:
Healthcare professionals, i.e. clinicians, primary care practitioners, medical specialists including medical ethicists

Group 2:

- HTA and guideline agencies
- Policy-makers and healthcare systems

5. Perspectives from General Practice

General practitioners (GPs) encounter in principle the total population. Countries that have a strong focus on primary care have better health at lower costs and also greater equality in health¹¹². Rules and rates for referral from primary to secondary care differ among countries. In Europe, several countries including Norway have list-based primary care. In Norway 70-90% of all health problems presented to GPs will not be referred to secondary care.

Medical research is, however, only to a modest degree guided by and based on questions relevant for general practice. As a consequence, specialist-driven research results may be difficult to implement in primary care (see Box: Clinical everyday scenario and Figure 8).

General practice

For the sake of characterising the general practice population quite roughly, a four-category model has been introduced¹¹³. Patients have a subjective experience of good health or of degrees of bad health, and based on the biomedical approach to humans, doctors are presumed to be objective when distinguishing diseased from non-diseased persons (Figure 9).

Category 1 (“the truly healthy”) constitutes patients who both feel healthy and who are also told, by their GPs, that “nothing is wrong with you”.

Category 2 (“the imagined ill”) consists of people seeking help because of suffering. The GP cannot, however, find objective signs that provide adequate explanations. Examples are patients with addiction, chronic pain, or fatigue.

Category 3 (“the truly ill”) encompasses persons with organ diseases, they feel ill and the doctor can identify objective signs of disease, for example myocardial infarction in a patient with chest pain.

Category 4 (“the imagined healthy”) consists of persons who feel healthy but in whom asymptomatic signs or risk factors for future diseases are identified.

For many patients several categories may apply. But of course this model is a construction for the purpose of conceptualising the problems that occur in a medical approach that mainly focuses on objectivity in the understanding of diseases and illnesses.



Figure 8. Clinical everyday scenario in general practice

Implementation of medical research

The category of the “truly healthy” is steadily diminishing. Biomedical norms and current definitions tend to “move” people from category 1 to 4. Two causes can be identified. First, even if people feel healthy, medical tests can identify risk markers for future diseases. Scientists continuously define risk factors in an ever-increasing number and speed¹¹⁴. In addition, the number of “non-diseases” that may be addressed in the GPs’ office is increasing¹¹⁵.

For the category of the “imagined ill” – comprising all types of illnesses labelled as functional disease in somatic medicine and somatoform disorder in psychiatry – the healthcare system often fails to offer adequate help. Patients may even perceive that their health problems are ignored and that they themselves are disregarded as human beings¹¹⁶. When human suffering seems to be medically unexplainable – which consequently engenders a large number of acronyms (MUD, MUPS, CSS, BDD, etc) in medical terminology – this may reflect a “dysfunctional” medical theory and research approach, focusing on objectively observable, general, group-based, and fragmented knowledge, ignoring the impact of subjectivity and of personal experience on disease development¹¹⁷.

Patients with organ dysfunction are exposed to an increasing amount of technology. New technology is

112. Barbara Starfield (Professor at Johns Hopkins University), keynote lecture entitled “Primary care/specialty care in the era of multimorbidity” at the 19. Wonca world congress for family Doctors, Cancun, Mexico, May 2010. Link to lecture: www.globalfamilydoctor.com/index.asp?PageID=11401

113. Hetlevik I. Evidence-based medicine in general practice: a hindrance to optimal medical care? *Scand J Prim Health Care* 2004;22:136-140

114. Skolbekken JA. The risk epidemic in medical journals. *Sos Sci Med* 1995;40:291-305

115. Smith R. In search of “non-disease.” *BMJ* 2002;324:883-5

116. Salmon P, Peters S, Stanley I. Patients’ perceptions of medical explanations for somatisation disorders: qualitative analysis. *BMJ* 1999;318:372-6

117. Kirkengen AL. The lived experience of violation. How abused children become unhealthy adults. Bucharest: Zeta Books, 2010

5. Perspectives from General Practice

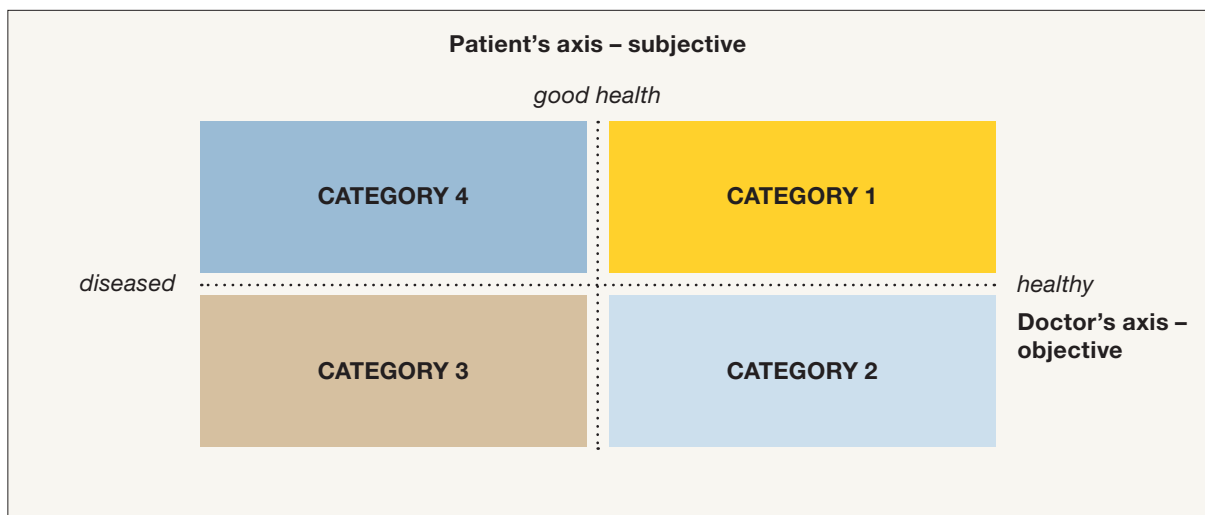


Figure 9. Four-category model for patients in general practice

often added to the existing in order to enhance diagnostic and therapeutic precision. A patient with heart disease may for example be regarded as under-treated unless he or she receives several drugs, particularly for this heart disease, regardless of possible additional diseases. Since the effect of each drug has been studied separately in clinical trials where, most often, patients with co-morbidity have been excluded, the effectiveness of each drug is unpredictable when implemented in general practice as well as in specialist care. This kind of health problem, defined as allocated in one organ at a time, may allow a follow-up in organ-oriented specialist care. In general practice, however, where all organs literally come as embodied in one person, such an approach is highly problematic.

Persons in the “risk” category are most often unaware of having risk factors for future diseases before they are told by their GP. They are “imagined healthy”, so to speak. GPs are, however, not defining the premises that establish this category. These are conceptualised by the medical profession as a whole. All definitions of medical risks are based on epidemiological studies, whereupon these risk definitions – the measurement levels on which GPs are supposed to act – are implemented in clinical guidelines to be used in general practice. There has, however, been little debate within the biomedical community about the pragmatic and ethical aspects of this activity¹¹⁸. For example, implementation of the 2003 European guidelines on cardiovascular disease (CVD)

118. Getz L, Kirkengen AL, Hetlevik I, Sigurdsson JA. Individually based preventive medical recommendations – are they sustainable and responsible? A call for ethical reflection. *Scand J Prim Health Care* 2005;23:65-7

prevention¹¹⁹ would label 76% of Norwegian adults 20 years and older (including 90% at the age of 50 and 50% at the age of 25) as having unfavourably high cholesterol and/or blood pressure levels¹²⁰. In addition most people would be labelled to be at high risk of fatal CVD from age 40¹²¹. Furthermore, the widely held presumption that ‘the net will close’ around a manageable group of individuals if several risk factors are jointly considered, has been shown to be flawed¹²². The recommendations in more recent European guidelines for prevention of CVD¹²³ would, if applied in a strict manner, destabilise the Norwegian healthcare system¹²⁴. The Norwegian

119. De Backer G, Ambrosioni E, Borch-Johnsen K, et al.: European guidelines on cardiovascular disease prevention in clinical practice. Third joint task force of European and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of eight societies and by invited experts). *Eur Heart J* 2003; 24:1601-10

120. Getz L, Kirkengen AL, Hetlevik I et al. Ethical dilemmas arising from implementation of the European guidelines on cardiovascular disease prevention in clinical practice: A descriptive epidemiological study. *Scand J Prim Health Care* 2004;22:202-8

121. Getz L, Sigurdsson JA, Hetlevik I et al. Estimating the high risk group for cardiovascular disease in the Norwegian HUNT 2 population according to the 2003 European guidelines: modelling study. *BMJ* 2005;331:551-4

122. Petursson H, Getz L, Sigurdsson JA, Hetlevik I. Can individuals with a significant risk for cardiovascular disease be adequately identified by combination of several risk factors? *J Eval Clin Pract* 2009;15:103-9

123. Mancia G, De Backer G, Dominiczak A, et al.: Guidelines for the management of arterial hypertension: *Eur Heart J* 2007; 28(12):1462-1536

124. Petursson H, Getz L, Sigurdsson JA, Hetlevik I. Current European guidelines for management of arterial hypertension. Are they adequate for use in primary care? *BMC Family Practice* 2009, 10:70

population is considered one of the world's most long-lived and healthy by international comparison – served by more GPs than in any other country worldwide. In short: there are not enough GPs in Norway to manage the workload associated with the recommendations for individual prevention of CVD among healthy persons.

Challenges

Three major challenges can be identified for general practice with regard to implementation of medical research results

- Medical risk
- Medically unexplained disorders
- Co-morbidity

Medical risk

Identification of indicators associated with future diseases is in principle unlimited within medical research. Blood pressure, serum cholesterol, blood glucose, body mass index, and bone density are just a few examples. Predictive gene tests are likely to increase this number.

As a result, GPs may end up as 'manipulators of fragments' within the healthy population, an activity with an inherent potential for health damage.

The focus on biomedical fragments becomes obvious in the European clinical guidelines for CVD prevention, which are based on more than 800 references; none of these refers to the extensive empirical documentation that existential experiences such as integrity violations and powerlessness have substantial pathogen impact^{125,126}.

Non-adherence to clinical guidelines in general practice is well documented¹²⁷ and there even seems to be resistance to guideline development and implementation strictly according to the rules of EbM¹²⁸. GPs who do not adhere to guidelines may have – in several aspects – valid reasons¹²⁹.

125. Kirkengen AL, Getz L, Hetlevik I. A different cardiovascular epidemiology. *Tidsskr Nor Lægeforen* 2008;128:2181-4

126. Marmot M. BMA presidency acceptance speech: fighting the alligators of health inequalities. *BMJ* 2010;341:c3617

127. Hetlevik I. The role of clinical guidelines in cardiovascular risk intervention in general practice. Dissertation for the degree of dr.med. Trondheim: Department of public health and general practice, Norwegian University of Science and Technology, 1999

128. Fretheim A. Implementing change: the Rational Prescribing in Primary Care (RaPP) study. Dissertation for the degree of dr.med. Oslo: Institute of general practice and community medicine, University of Oslo, 2007

129. Hetlevik I, Getz L, Kirkengen AL. General practitioners who do not adhere to guidelines – do they have valid reasons? *Tidsskr Nor Lægeforen* 2008;128:2218-20

Medically unexplained disorders

Pain, addiction, fatigue and several other so-called 'functional' conditions represent serious challenges for GPs and for wider society. These states of impaired health often result in frequent referrals to secondary care, where, most often, no adequate explanation based on the traditional biomedical approach can be provided. Consequently, the problems – in other words "the problematic patients" – are returned to primary care¹³⁰.

Co-morbidity

Medical doctors are traditionally trained to focus on separate diagnoses in accordance with the International Classification of Diseases (ICD).

This approach is further supported by the disease-specific structure and content of clinical guidelines, sometimes criticised as "the silo approach"¹³¹.

It is well documented that chronic illnesses and diseases have a tendency to cluster in the same person – as in Helen (see Box: Clinical everyday scenario below). To adhere to current clinical practice guidelines in caring for an older person with several co-morbidities may have undesirable effects¹³².

Both researchers and clinicians call for a better understanding of co- and multi-morbidity^{133,134,135}.

Diseases are considered to have multifactorial, complex origins which also include genetic and epigenetic factors. Pathogenetic stressors often co-occur^{136,137} and mutually reinforce each other in complex webs of causation^{138,139}. The fact that detrimental and interacting stressors, such as poverty, unemployment, neglect, vio-

130. Barker KK. The fibromyalgia story. Medical authority and women's worlds of pain. Philadelphia: Temple University Press, 2005

131. Parekh AK, Barton MB. The challenge of multiple comorbidity for the US healthcare system. *JAMA* 2010; 303:1303-4

132. Boyd CM, Darer J, Boulton C et al. Clinical practice guidelines and quality for older patients with multiple comorbid diseases: implications for pay for performance. *JAMA* 2005; 294(6):716-24

133. First MB. Mutually exclusive versus Co-occurring diagnostic categories: The challenge of diagnostic comorbidity. *Psychopathology* 2005; 38:206-10

134. Ulvestad E. Chronic fatigue syndrome defies the mind-body-schism of medicine. *Med Health Care and Philos* 2008; 11:285-92

135. Valderas JM, Starfield B, Sibbald B, Salisbury C, Roland M. Defining comorbidity. *Ann Fam Med* 2009; 7:357-63

136. Mazzocchi F. Complexity in biology. Exceeding the limits of reductionism and determinism using complexity theory. *European Molecular Biology Organization (EMBO) Report* 2008;9:10-14

137. Doll WE, Trueit D. Complexity and the healthcare professions. *J Eval Clin Pract* 2010; 16:841-8

138. Kiecolt-Glaser JK. Stress, food, and inflammation: psychoneuroimmunology and nutrition at the cutting edge. *Psychosom Med* 2010; 72:365-9.

139. Shankardass K, McConnell R, Jerrett et al. Parental stress increases the effect of traffic-related air pollution on childhood asthma incidence. *Proc Natl Acad Sci USA* 2009; 106:12406-11.

5. Perspectives from General Practice

lence and threats, unfavourable lifestyle options/choices tend to be more prevalent in lower social classes is likely to explain much of the well-documented social gradients in health^{140,141}.

Internationally, there has been an increasing interest in chronic, metabolic dysregulation as a basic, pathogenetic factor for a variety of diseases. This idea is most explicitly expressed in the theory of *allostatic load*. Here, various stressors accumulate to load an individual's metabolism¹⁴². If this load surpasses the individual's ability to adjust and recover, the situation is termed *allostatic overload*. Over time, *allostatic overload* will render the individual susceptible to diseases and illnesses. The theory of *allostatic overload* thus offers a new causal perspective on clusters of disease and on co- and multi-morbidity. It also challenges the traditional medical research methodology where subjectivity is considered a confounder and source of error, and thus systematically avoided.

Clinical everyday scenario in general practice:

Helen, aged 60 (not identical to the woman in the picture), is a woman with limited formal education. The list of diagnoses in her medical records comprises: obesity (BMI>30), hypertension, diabetes type 2, depression, asthma, chronic widespread pain, dermatitis, hypothyroidism, recurrent airway infections, and a previous period with high consumption of addictive drugs. She is still a daily smoker, despite medical advice to quit. Helen began to visit her GP in her twenties due to widespread pain. Since then, she has been given several risk diagnoses (obesity, hypertension, diabetes type 2) and likewise several diagnoses confirming organic diseases (asthma, dermatitis). Her pain, however, has persisted.

Helen has during the years had a large number of specialist consultations for her pain – and received several “risk diagnoses” – with no relevance for her health problem. Since individuals may be diseased in their own way – and not as “an average” person – the need to study the development of personalised life histories must be emphasised.

Major issues

- Medical knowledge gained in secondary care may not be compatible with primary care and therefore not implementable.
- Definitions of medical risk hold a potential to define everybody as in need of medical control and to destabilise healthcare systems if implemented.
- Objective medical research results do not provide adequate explanations regarding functional diseases.
- Co- and multi-morbidities represent considerable challenges for the individual, the healthcare system, and the society-at-large.
- EbM may be a hindrance to optimal medical care in general practice by over-emphasising information from randomised controlled trials, meta-analyses and systematic reviews and may often exclude patients with complex and multiple conditions.

Recommendations

- Medical research should be context-oriented and in accordance with the level of its implementation, in other words appropriate knowledge for primary care must be gained at this level.
- Medical knowledge ought to mirror, in a comprehensive and consistent way, the converging findings from a variety of disciplines, documenting the interconnectedness between human biology and biography.

Key stakeholders

Group 1:

- Academic research (basic to patient-oriented research)
- Learned societies
- Healthcare providers/hospitals: Healthcare professionals, i.e. clinicians, primary care practitioners, medical specialists including medical ethicists
- Teachers (undergraduate and postgraduate medical training, as well as for continuous professional development)

Group 4:

- Patients and general public
- Patient organisations

140. Marmot M. Harveyan Oration. Health in an unequal world. *Lancet* 2005;368:2080-94

141. Seeman T, Epel E, Gruenewald T et al. Socio-economic differentials in peripheral biology: cumulative allostatic load. *Ann N Y Acad Sci.* 2010; 1186:223-39

142. McEwen BS, Wingfield JC. The concept of allostasis in biology and biomedicine. *Horm Behav.* 2003; 43(1):2-15

6. Patient and Public Involvement in Research

Patient and public involvement (PPI) in clinical trials is founded on the belief that a collaborative approach to testing treatments is vital if the uncertainties that matter most to patients are to be reduced¹⁴³.

Patients may be involved in the sense that they are invited to participate as **“passive trial participants”** (formerly described as “subjects”), or may be involved **actively as co-researchers in the research process itself**, working alongside other health professionals throughout in either a part, or throughout the entire trial, from formulation of hypothesis through to reporting, dissemination and promotion^{144,145}.

Either way, their contribution is as vital as it is varied. In addition, patients’ carers and other “ordinary citizens” (“the public”) may also be usefully and productively involved in the research process.

Contributions from collaborating patients and citizens can be formal or informal; as individuals or in groups; using various methodologies (as appropriate) to provide insight into the best way to choose and develop research questions. Such patients will have a desire to see that findings resulting from such activity are clearly, accurately and promptly reported, disseminated and used.

The James Lind Alliance¹⁴⁶ takes the partnership further: it brings patients, their carers and clinicians together to identify and prioritise treatment uncertainties for research.

“Passive” patients being invited to participate in trials will be affected by:

- their understanding of the trial/trial concepts/randomisation and their perception of the need for research;
- the attitude of the trial team and the ability of their team to communicate effectively and to satisfy the prospective patient’s information requirements;
- their own values and preferences and their perception of mismatch of experience with expectation.

Advantages and disadvantages of active patient and public involvement

These are some of the **advantages** that have been identified that can accrue from active involvement of patients and the public in research:

Patients can identify mismatches between research that gets done and research they would like to see done; i.e. agenda setting. They can help to provide a patient view within a research team that can illuminate what it is like to be involved, thereby helping to design trials that are “patient friendly” and workable. Patient input can throw light on the feasibility and acceptability of a particular trial design. A group affected by the disease in question will have experience that can contribute to identifying what might be feasible and what might not be feasible.

Patients can help refine the question, prioritising and highlighting important factors; add to them; eliminate non-important ones and can help make a complex trial protocol comprehensible to lay people. They can thus improve the readability, quality and style of information for potential participants – the “trial information leaflet”.

Mutual learning occurs within a group of lay and health professionals working on a particular topic. They can help with dissemination of trial results to patients and carers through their information and support group channels.

Patient and public involvement can lead to improved recruitment. They can importantly provide encouragement for the continuation of a trial to its completion – arguing the case against stopping a trial prematurely and can have links to networks that can help publicise a trial: the quicker it recruits, the quicker the results will be available. Patient and public involvement bring a sense of broad ownership of the concept and design of a trial, can help build better relationships between lay and professional and can provide the balance that is needed in the design of trials with difficult ethical considerations presenting the submission to an Ethics Committee. They increase the diversity of values that should underpin a good quality research question. Those who participate together in shared research find that it is satisfying and satisfactory.

Communication and education

Language use

Semantics are important. Words used to define those involved people who are not health professionals should be carefully chosen to accord in the context in which they are employed (“patient”; “patient and public”; “user”; “participant”; “active patient participant”; “passive patient participant”; “people”; “lay people”; “citizen”; etc. and **very** occasionally “subject”). This is suggested, not only for the sake of clarity and accuracy, but also to convey more clearly the attitudinal and conceptual aspects. “Subjects” has become outmoded and unacceptable, denoting a former subjugated role – someone prone to

143. Evans I, Thornton H, Chalmers I. Testing treatments: better research for better healthcare. London: British Library, 2006

144. Thornton H, Edwards A, Elwyn G. Evolving the multiple roles of ‘patients’ in healthcare research: reflections after involvement in a trial of shared decision-making; Health Expect. 2003; 6:289-197

145. Thornton H. Patients and health professionals working together to improve clinical research: where are we going? European Journal of Cancer 2006; 42:2454-2458

146. www.lindalliance.org

6. Patient and Public Involvement in Research

accept diktats from on high – and increasingly unsuited to the new doctor/patient relationships in healthcare prevailing today in many cultures. “Subject” is far removed from the concept of equality of collaborative input possibilities currently observed in some societies.

Use of confidential patient data

Any encounter/consultation between a patient (or a member of the public) and a doctor or other health professional will involve recording and storage of personal data. This occurs both in “usual practice” and “in research” or given voluntarily for databank collection i.e. the Biobank Project. In each case, the subsequent uses to which these data may be put are varied and likely to be at least partially unknown at the time of obtaining the data and seeking consent for its use. These further uses include general epidemiological research, public health research, “follow-on” research in a specific disease area, genetic research, etc.

Decisions about use of such data should be by informed community decisions, not made solely by the expert scientific, medical, political bodies or other agencies – either individually or together. Decision-makers should include the beneficiaries of such research e.g., the community as a whole.

But it is essential that opinions about secondary uses of confidential patient data are not sought from an uninformed lay public, unaware of the potential problems, general ramifications and scope of the efforts to safely generate, store and make available this rich seam of data for mining without breaching individual patient confidentiality.

The results of a UK NHS (Connecting for Health¹⁴⁷) Survey undertaken in 2008 and 2009 clearly illustrate the problems of attempting to conduct and report on a public national survey about the secondary use of patient data.

Advantages of Patient Involvement

Fostering this mutual aim of undertaking high quality research in partnership will result in a powerful, united voice for progress. This united voice will be able to call for high quality research endeavours that reduce the numerous uncertainties about treatments; about new technologies; about preventive strategies and other tools (e.g., guidelines, web-based resources). This collaboration of knowledgeable and well-trained health professionals and involved lay people can campaign strongly to ensure that resources (both human and financial) are not wasted on futile, unnecessary or poorly conceived and executed

research. They will clamour for high quality, meaningful research that follows best practice; makes use of available tools and checklists (EQUATOR, CONSORT, PRISMA, etc.) and seek to ensure that the products of such research are systematically reviewed; adequately and fully reported; and promptly and efficiently made available for use by clinicians and other health professionals, and patients and public, with the sole aim being the improvement of healthcare for all people.

This steady process of intelligent, non-wasteful knowledge building is a responsibility that does not rest solely with the medical and scientific community – it must be shared by the whole community. Only by jointly and fully shouldering this responsibility can any rights begin to be claimed.

Major issues

- Although patients are the principal “end-user” 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 addressed including people’s attitudes and levels of awareness.

Recommendations

- 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 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 education and as part of their continuing professional development.
- Patient groups must be independent and without affiliation to industry.

147. <http://www.connectingforhealth.nhs.uk/>

Key stakeholders

Group 1:

- Academic research (basic to patient-oriented research)

Group 3:

- National and EU funding agencies and research councils

Group 4:

- Patients and general public
- Patient organisations
- Philanthropic organisations

Group 5:

- Journal editors and peer reviewers
- Media: internet, journals, medical journalists, etc.

7. Diversity Across Europe

The WHO definition of Europe includes 53 countries where the healthcare systems vary markedly. There are wealthy countries with a high Gross domestic product (GDP) and a high percentage of GDP directed towards healthcare, and there are less privileged countries with healthcare systems striving to deliver an appropriate service in spite of serious economic constraints.

Some countries have “free available medicine” as in the UK and the Nordic countries where the same healthcare is provided to all citizens for free at the point of delivery, funded through the taxation system. Other countries have a combination of a public and a private healthcare system. Public healthcare can be paid directly by the state or region/Länder/provinces through tax, or partly via private or public insurance companies.

Central and Eastern European countries (CEEC)

CEEC are facing the same problems as those faced by their Western European counterparts, but the problems are more acute and extreme. Most clinical trials are run by industry and rarely by academia. Patient-oriented research is lagging behind basic research. There is a strong need to support the paradigm shift towards more application of the *-omics* into therapeutic and diagnostic innovations and public-private partnerships (PPP) will be necessary to meet these challenges.



8. Recommendations

This chapter summarises all recommendations from the different parts of this report (knowledge generation, knowledge interpretation, knowledge implementation in clinical practice, perspectives from general practice and patient involvement). The eight main recommendations which were chosen by the participants are listed below in a box in this chapter and in the executive summary.

Patients

- Involve patients in developing research agendas, and in funding, planning and reporting of research. Ways and best practice of involving patients should be identified (for example through patient organisations or lay councils).
- Educate the general public about evidence-based medicine, health technology assessment (HTA) and guidelines. Ways and best practice of educating the public should be identified (for example by providing lay versions of guidelines so patients have access to comprehensible information, and by including teaching of statistical thinking in school *curricula*).

Quality

- More studies should be performed to test different diagnostic and/or therapeutic strategies aiming at developing practical guidelines (particularly comparing or associating pharmacological with non-pharmacological interventions).
- Improve evaluation of applications for grants for clinical research, e.g., by also involving researchers and clinical specialists with good knowledge of health technology assessment.
- Untested diagnostic and/or therapeutic strategies or pharmacological and non-pharmacological interventions should be systematically evaluated after an appropriate interval, before introduction in routine healthcare.
- Ensure that trials are ‘correctly powered’ (appropriate number of patients to produce statistically reliable results).
- Studies should be reported transparently:
 - Mandatory, prospective publication of trial protocols should be required by law – transparency in drug evaluation should be a legal requirement.
 - All clinical studies should be registered in trial registers before ethical approval is sought.
 - Research output should always be published (e.g., mandatory in the EudraCT database).
 - Journal editors must require that new studies are set in the context of systematic assessments of related studies; that authors’ conclusions state what their study has added; that methods are well defined and described; and ensure that peer review of studies is

supplemented with review by methodologists and end-users.

- Journals should offer balanced reviewing: referees with all disciplines and approaches should be taken into consideration; scientists should have the possibility to suggest a peer reviewer (possible with some journals) and have direct contact with referees to discuss their views (e.g., email or chat style).
- Proof of added value for all new drugs, diagnostic and/or therapeutic strategies or pharmacological and non-pharmacological interventions should be required (regulatory authorities could require to have at least one pivotal phase III trial conducted by independent scientific organisations).
- Pharmacovigilance should be implemented.
 - The European pharmacovigilance system should be implemented with programmes focusing on signs of toxicity for specific drugs or classes of drugs.
 - The EMA should establish a new pharmacovigilance committee, separate from the Committee for Human Medicinal Products (decisions to restrict the use of a drug or to withdraw it from the market must be taken by an independent group devoted to pharmacovigilance).
 - Toxicological and clinical information should be made public (regular safety update reports submitted to EMA should include systematic reviews and meta-analyses of both beneficial and adverse events).
- A new model should be considered where HTA reports are written by a team with the involved clinicians and with support from HTA experts and information specialists and with formalised quality control processes.
- Learned societies together with national bodies have an important role in getting the information out to the clinicians in hospitals and GPs in order to reduce the influence of the pharmaceutical industry.

Education

- Improve and strengthen education, training and career structure for health workers and scientists involved in patient-oriented clinical research (how to perform research, to use research, to write guidelines, to use the guidelines, to secure their implementation in every day practice, to practice evidence-based healthcare), aiming for the promotion and development of a European training programme with the goal of developing a structured career path including both clinical and research activities (for example, MD/PhD programme to improve the quality and education of clinical investigators).
- Specifically:
 - Increase numbers of methodologists in healthcare research, therefore emphasise initial training for

8. Recommendations

doctors in critical appraisal, in recognising methodological flaws and biases and the need for systematic reviews.

- The methods of EbM, HTA and health economics should be included early in the training *curriculum* of health professionals or even medical students.
- The concept and writing of guidelines should be introduced in the medical *curriculum* in undergraduate medical education.
- Increase author and journal training in reporting guidelines, such as CONSORT and STARD statements¹⁴⁸.
- Studies should address why women do not choose certain careers in some countries, and studies should look at how to implement a successful career adaptable to a normal lifestyle.

Publication

- Implement a legal obligation to publish all results with an FDA-like law with freedom of information, NIH-type database of all results accessible on the internet by patients and clinicians, obligation for industry.
- Require – by incentives and regulation – registration and publication of protocols for all clinical trials at inception.
- Support free access repositories – separate from any publications – so that clinicians and researchers have details of the treatments, tests, or instruments studied.
- Ways need to be found to allow new ideas into the literature for access by everyone, i.e. open access initiatives, less number restraints and handled in a more open manner: a good example is *PLoS One* – an interactive open access journal for the communication of all peer-reviewed scientific and medical research.
- IT-based open access databases should be made available internationally for both professional and lay persons. These databases should include guidelines and open access to journal articles.
- Better use of IT and databases for collection and dissemination of data.
- Internet sites with quality information should be made available for patients.

Funding

- Increase the public funding of independent patient-relevant research and investigator-driven clinical trials. This would benefit the governments and citizens of European countries. Europe needs an initiative similar to the US Comparative Effectiveness Research (CER) Programme.

148. www.stard-statement.org – www.consort-statement.org

- Improve awareness of the need for systematic reviews for all medical specialties, and improve the funding for systematic reviews.
- Research funding bodies should require – and support – grant proposals to build on systematic reviews of existing evidence and for authors of reports of studies to state how their research has reduced the uncertainty on that topic.
- Simplify and harmonise the administrative procedures of the European system for the submission and management of European projects. Europe needs better coordination to avoid duplication in clinical studies and to achieve a critical mass and better competitiveness.
- For EC-funded clinical trials, one of the requirements should be the sharing of results and one single place in Europe (European Trial Register) where data output of clinical trials should be made available.
- The research agenda might comprise a global study on the position and legal issues surrounding guidelines.
- Implement the conclusions of the Forward Look ‘Investigator-Driven Clinical Trials’: streamline procedures for obtaining authorisation for clinical trials; adopt a ‘risk-based’ approach to the regulation of clinical trials.
- Processes to increase the use and implementation of HTA reports in administrative processes, including budget work on all levels, must be initiated. Loops should be started where evidence-based disinvestment of less effective and obsolete technologies create financial resources that can be given to new technologies with documented effectiveness according to evidence-based principles.

Guidelines

- The same criteria and methods in drawing up and using guidelines should be used across Europe. In other words there should be guidelines for guidelines¹⁴⁹.
- It is important that guidelines are independent of bias –

149. **Germany:** National Disease Management Guideline Programme. Methods Manual (Methoden-Report. 4. Auflage), 2010. Available from: <http://www.versorgungslinien.de/methodik/reports>

Netherlands: CBO. Guideline Development, 2007. Available from: <http://www.cbo.nl/thema/Richtlijnen/Richtlijnontwikkeling/>

Spain: Guia Salud. Guideline Methodology, 2010. Available from: <http://portal.guiasalud.es/web/guest/metodologia-gpc>

United Kingdom (England and Wales): NICE. Guideline Manual, 2009. Available from: <http://www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelinedevelopmentmethods/GuidelinesManual2009.jsp>

United Kingdom (Scotland): SIGN. Guideline Developer’s Handbook, 2008. Available from: <http://www.sign.ac.uk/guidelines/fulltext/50/index.html>

and not influenced by the interests of drug companies, medical device manufacturers, or individuals sponsored by such companies, for example. Any interests should be declared by the guideline authors.

- Guidelines should be based on full systematic literature review with critical evaluation of internationally published data according to the principles for Health Technology Assessment. In those countries where economic considerations preclude the implementation of a guideline, the guideline should be re-assessed in the light of the economic issues.
- Clinical practice guidelines should be generated by multidisciplinary teams including physicians, allied health professionals, methodologists, patients and public. Guidelines should be updated on a regular basis with explicit policies for this.
- Guidelines should be implemented in hospitals and general practice. Hospitals should, in their annual reports, write about their use of clinical guidelines, which guidelines they use and how they are updated, implemented and how they ensure that they are followed.
- Care should be taken in the language used in guidelines especially if guidelines are translated from one language to another. Effort should be made to ensure that guidelines are comprehensible and unambiguous to everyone who will use them.
- Once guidelines have been produced they need to be 'marketed' to ensure that they get to the people who are intended to use them.
- Guidelines need to reach clinicians and practitioners in a timely way – new information is arising all the time and a slowly produced guideline can become outdated. For this reason there need to be mechanisms for updating guidelines as new data come to light. IT clinical decision support and surveillance can be useful.
- Guidelines are more likely to be accepted and used by professionals if they have had a role in the systematic literature review with critical evaluation of published data and the development of corresponding guidelines – so that there is a sense of 'ownership'.
- Guidelines should be recommendations for good clinical practice and not considered normative. They should be adapted to the daily practice at the hospital.

9. Implementation Plan

Stakeholder groups

For a successful and sustainable implementation of the recommendations, we need to target specific groups of stakeholders.

Group 1:

- Academic research (basic to patient-oriented research)
- Learned societies
- Universities
- Healthcare providers/hospitals: Healthcare professionals, i.e. clinicians, primary care practitioners, medical specialists including medical ethicists
- Teachers (undergraduate and postgraduate medical training, as well as for continuous professional development)

Group 2:

- Methodologists, systematic reviewers, healthcare professionals
- Health economists
- HTA and guideline agencies and Cochrane Collaboration
- Policy-makers and healthcare systems

Group 3:

- National and EU funding agencies and research councils
- Ministries
- National and EU regulators
- Ethics committees

Group 4:

- Patients and general public
- Patient organisations
- Philanthropic organisations

Group 5:

- Journal editors and peer reviewers
- Media: internet, journals, medical journalists, etc.

Group 6:

- Private sector:
 - Pharmaceutical industry
 - Medical devices industry, etc.

The stakeholder group categories cover different activities in health research, and there is a certain overlap between different groups.

Figure 10 illustrates which stage of the knowledge process each of the groups has an interest in and which recommendations are relevant to the groups.

Activity plan

The first activity is the widespread dissemination of this Forward Look report, with endorsements and recommendations from all EMRC Member Organisations.

Dissemination will be made through press statements, press conferences, articles and so on. This is seen as an essential first step. The Forward Look will be sent to Member Organisations, key political figures in nations and the EU, including commissioners, members of parliament and national government ministers as well as to key political stakeholders and research councils outside Europe, e.g., NIH (USA) and CIHR (Canada), and to regulatory agencies as well as to HTA and EbM agencies. The implementation of the recommendations will be discussed and elaborated in more detail within the different stakeholder groups.

The following recommendations are not ranked. The list represents a summary of all recommendations in the report.

1. Strengthen European work, collaboration on, coordination in and funding of systematic reviews of existing evidence, comparative effectiveness research, health technology assessments and clinical practice guidelines.

The implementation of this recommendation needs all six stakeholder groups. Funding, collaboration and coordination should be improved at the European level. A pan-European interdisciplinary working group should be implemented which aims at developing implementation strategies. These have then to be advertised and spread throughout Europe. Existing groups and networks should be integrated. One important implementation step could be to develop a common international declaration for researchers, publishers and agencies to use or to work with EbM, HTA and clinical guidelines.

2. Foster transparency and require evidence on comparative effectiveness and costs of drugs and other new technologies to demonstrate added value before approval.

The implementation of this recommendation needs the input of national competent authorities, EMA and industry (groups 2, 3 and 6) and could necessitate a change of national or European regulations. As a first step, a working group should be established with representatives from HTA agencies, EbM specialists, regulators and industry to discuss concrete suggestions on how to change the process of an approval for a new medicinal product so that an added value can be demonstrated.



Figure 10. Relevance of recommendations to the different stakeholder groups

3. **Improve education and training of and career structure for health professionals.**

Models and best practice of MD/PhD training as well as for postgraduate training in clinical research and research implementation within the different countries of Europe should be developed with key stakeholders mainly from groups 1 and 2 as a first step. These should help to disseminate and establish best practice models and to strengthen European training programmes.

4. **When relevant, inform patients and the public about the prioritisation, funding, planning, conduct and reporting of clinical comparative effectiveness research and evidence-based medicine.**

To improve the involvement of patients in research, strategies should be discussed in interdisciplinary groups with patient representatives, researchers, funding agencies and media (groups 1-5).

5. **Support and facilitate methodologically sound, high-quality clinical research inspired by gaps and uncertainties identified in systematic reviews that answers the needs of patients, health professionals and society.**

This recommendation again necessitates a broad discussion with representatives from the six stakeholder groups – the implementation should be anchored within our Member Organisations. One main activity

could be to develop dissemination and implementation strategies to improve quality in the different stages of medical research within Europe.

6. **Promote rigorous reporting of all clinical studies.**

7. **Strengthen shared national and international open access databases on protocols, data, reports, systematic reviews and health technology assessments.**

For these two recommendations, a broad discussion will be necessary – between researchers, methodologists, funding agencies and representatives from industry. The implementation of open access and databases could be again strengthened via our Member Organisations. Existing well-established local or national solutions could be used as best practice models.

8. **Generate through multidisciplinary teams and with patient involvement, high-quality evidence-based clinical practice guidelines according to common standards and criteria.**

For this activity the key stakeholders are identified as researchers, learned societies, healthcare providers, clinicians, EbM experts, methodologists and patients. One important activity could be to develop incentive systems for using and implementing evidence-based practice at medical care level, through

9. Implementation Plan

national European guidelines or even regulations. This could again be anchored via those Member Organisations interested and the relevant learned societies. Existing well-established local or national solutions could be used as best practice models.

9. *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.*

For this activity the key stakeholders are identified as principally healthcare professionals, researchers, patients, EbM experts and methodologists. One important activity could be to develop incentive systems for using and implementing evidence-based practice at medical care level through national European guidelines or even regulations, anchored with interested Member Organisations. Existing well-established local or national solutions could be used as best practice models.

10. *Increase use and implementation of health technology assessment reports and clinical guidelines in administrative processes including financing of technologies.*

The key stakeholders are identified as representatives from HTA and guideline agencies, regulatory agencies and ministries. Within this group strategies should be developed to strengthen the role of HTA, EbM and clinical guidelines in administration.

10. Conclusions

Medical research has made a fundamental contribution to health and wellbeing over the past half century. Well-directed, high-quality research can answer important medical questions and can provide the evidence upon which decisions are made in practice. Nevertheless, it must be recognised that some research is carried out that is not of sufficient quality or is not relevant, and that practitioners often do not take all their decisions using evidence provided by research findings.

Research questions should be framed so that they address problems that are relevant to the end-users of research: patients and the public.

It is important not to waste resources on duplicating research – seeking to answer questions that have been already answered. This can be avoided by carrying out systematic reviews of the literature.

Research must be methodologically sound so that the answers it delivers can be viewed and used with confidence. The protocols and results of all clinical trials should be made publicly available and reported in an unbiased way and with adequate detail, so that all stakeholders can benefit from them.

There is a need for more studies on the comparative effectiveness of drugs and other technologies. Toxicological and clinical information should be made public.

Education and training for clinical researchers are not well-developed and there are insufficient numbers of professionals with expertise in methodology, or an understanding of evidence-based medicine, health technology assessment and health economics.

Clinical practice guidelines are one important way to implement research findings. Various models exist to produce guidelines, including those produced by scientific learned societies and those produced by central government agencies. The different approaches have advantages and disadvantages. There is little evidence relating to the best way to implement research in clinical practice. Therefore more research in this area is needed. For the future, systematic clinical practice guidelines of the highest quality is the way to go, to assure implementation of the right research results in clinical practice – so that EbM is used in each and every patient treatment, everywhere.

A further key to improve quality of care is through audit and feedback. Quality indicators can be valuable but need to be constructed with caution. Registries can also provide a rich source of information, and they can be used for generation of new research.

Primary care has a key role to play in both research and implementation, given that family doctors encounter almost the whole population, whereas fewer people go into hospital. Research results derived from special-

ist areas of medicine can be difficult to implement into general practice because people who see their family doctor often have a multiplicity of medical conditions that influence each other. There is a need to gain better knowledge through research relating to primary care.

We need greater involvement of the public at all stages of research, and healthcare professionals should be well-equipped to communicate about research – including about issues such as risk. Funding agencies should require researchers to report their plans for involving patients and the public in their research project.

The 10 recommendations in this Forward Look are our attempt to summarise the many relevant and important recommendations in this report – gathered and developed to improve the quality of research and to improve the quality of patient treatment and healthcare, for the patients and the public – here in Europe and globally.

10. Conclusions

The top recommendations to strengthen implementation of medical research in clinical practice are the following:

1. **Strengthen European work, collaboration on, coordination in and funding of systematic reviews of existing evidence, comparative effectiveness research, health technology assessments and clinical practice guidelines.**
2. **Foster transparency and require evidence on comparative effectiveness and costs of drugs and other new technologies to demonstrate added value before approval.**
3. **Improve education and training of and career structure for health professionals.**
4. **When relevant, inform patients and the public about prioritisation, funding, planning, conduct and reporting of clinical comparative effectiveness research and evidence-based medicine.**
5. **Support and facilitate methodologically sound high-quality clinical research inspired by gaps and uncertainties identified in systematic reviews that answers the needs of patients, health professionals and society.**
6. **Promote rigorous reporting of all clinical studies.**
7. **Strengthen shared national and international open access databases on protocols, data, reports, systematic reviews and health technology assessments.**
8. **Generate, through multidisciplinary teams and with patient involvement, high-quality evidence-based clinical practice guidelines according to common standards and criteria.**
9. **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.**
10. **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.**

Annexes

Annex 1

Committee Members, Speakers and Participants

Committee Members

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Strategic Workshops, 17-18 May 2010, Frankfurt (DE)

Workshop 1

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- Professor Bogdan Petrunov
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- Dr Thomas Pieber
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Workshop 3

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Annex 2

Glossary

It is important to share common definitions. In this Forward Look we define the terms as follows:

Biobank

Also known as a biorepository, a place that collects, stores, processes and distributes biological materials and the data associated with those materials.

Biomarker

A cellular or molecular indicator of exposure, health effects or susceptibility. Biomarkers can be used to measure internal dose, biologically effective dose, early biological response, altered structure or function, susceptibility.

Clinical guidelines

Clinical guidelines are recommendations on the appropriate treatment and care of people with specific diseases and conditions. They are based on the best available evidence and help healthcare professionals in their work without replacing their knowledge and skills.

Clinical research

Patient-oriented research conducted with human participants or on material of human origin involving interaction with human participants in order to discover what causes human disease, and how it can be prevented and treated. Clinical research can include: mechanisms of human disease; therapeutic interventions; clinical trials; or development of new technologies. Epidemiological and behavioural studies, outcomes research and health services research can also be part of clinical research.

Clinical trial authorisation (CTA)

Permission from the appropriate regulatory authorities to carry out a clinical trial.

Cochrane Collaboration

The Cochrane Collaboration is an international, independent, not-for-profit organisation of over 28,000 contributors from more than 100 countries, dedicated to making up-to-date, accurate information about the effects of healthcare readily available worldwide. Contributors work together to produce systematic reviews of healthcare interventions, known as Cochrane Reviews, which are published online in the Cochrane Library.

Cochrane Reviews

Cochrane Reviews are systematic reviews of primary research in human healthcare and health policy. They investigate the effects of interventions for prevention, treatment and rehabilitation. They also assess the accuracy of a diagnostic test for a given condition in a specific patient group and setting¹.

1. www.cochrane.org/cochrane-reviews

COPE

The Committee on Publication Ethics (COPE) is a forum for editors and publishers of peer-reviewed journals to discuss issues related to the integrity of work submitted to or published in their journals. It supports and encourages editors to report, catalogue and instigate investigations into ethical problems in the publication process (www.publicationethics.org).

EC Clinical Trials Directive

The European Union published in April 2001 the European Parliament and Council Directive 2001/20/EC regulating clinical trials with medicinal products. By May 2004, all Member States were requested to have the Directive implemented in national regulations.

Effectiveness

A measure of the extent to which a specific intervention, procedure, regimen or service, when deployed in the field in routine circumstances, does what it is intended to do for a specified population; a measure of the extent to which a healthcare intervention fulfils its objectives. Has to be distinguished from efficacy.

Efficacy

The ability of a drug to produce the purported effect as determined by clinical trials.

EMA

The European Medicines Agency, a body of the European Union responsible for the protection and promotion of public and animal health through the evaluation and supervision of medicines for human and veterinary use.

EQUATOR

(Enhancing the QUALity and Transparency Of health Research): The EQUATOR Network is an international initiative that aims to enhance the reliability and value of the published health research literature. It is directed by an international Steering Group that brings together leading experts in health research methodology, statistics, reporting and editorial work. The EQUATOR website² provides resources, education and training to facilitate good research reporting and assists in the development, dissemination and implementation of robust reporting guidelines. It also carries out research projects to further enhance these goals.

EudraCT

A database of all clinical trials commencing in the European Community from 1 May 2004 onwards.

EudraVigilance

A data-processing network and management system for reporting and evaluating suspected adverse reactions

2. <http://www.equator-network.org>

during the development and following the marketing authorisation of medicinal products in the European Economic Area.

Evidence-based Medicine

According to Dr David Sackett and colleagues at McMaster University in Ontario, Canada Evidence-based medicine is “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient. It means integrating individual clinical expertise with the best available external clinical evidence from systematic research.” (1996)

FDA

The US Food and Drug Administration, an agency of the United States Department of Health and Human Services responsible for regulating and supervising the safety of foods, dietary supplements, drugs, vaccines, biological medical products, blood products, medical devices, radiation-emitting devices, veterinary products and cosmetics.

Genomics

The study of the genome (the sum of the genetic material present in a particular organism) and its action.

G-I-N

The Guidelines International Network (G-I-N) is an international not-for-profit association of organisations and individuals involved in the development and implementation of clinical guidelines (www.g-i-n.net).

HTA

Health Technology Assessment (HTA) as a term was first used already in the seventies. Health Technology Assessment evaluates systematically whether a technology works (i.e. is effective), is cost-effective, how it compares to other technologies and which risks it is associated with. One important method applied for HTA is EbM. HTA also addresses ethical, organisational and economic aspects of the technology. HTA thus addresses the direct, intended consequences of technologies as well as their indirect, unintended consequences. The results of HTA are mostly published as a report.

Implementation

Implementation is a well-structured, systematic and planned process aimed at structural introduction of evidence-based innovations or evidently best practices into the practice of health professionals, their organisations or into the health service structure.

Interrupted time series studies

In an interrupted time series (ITS) design, data are collected at multiple instances over time before and after an intervention to detect whether the intervention has an effect significantly greater than the underlying secular trend.

Knowledge

Knowledge is defined as information that is assembled according to commonly accepted rules in an accountable way, which is interpreted to a common cause and publicly accessible. Although robust knowledge is wider than research, scientific research is accepted as the most reliable way to built on such knowledge. The overview or synthesis of integrated results of scientific research is often indicated as evidence, mostly made available as guidelines.

IMI

Innovative Medicines Initiative, a novel approach for research funding under the European Commission’s 7th Framework Programme. It aims to remove bottlenecks hampering the efficiency of the development of new medicines through public-private partnerships.

Meta-analysis

A statistical synthesis of the data from comparable studies, leading to a quantitative summary of the pooled results. The aim is to integrate the findings, pool the data, and identify the overall trends of results.

NICE

The National Institute for Health and Clinical Excellence (NICE) is a UK-based independent organisation responsible for providing national guidance on promoting good health and preventing and treating ill health³.

Pharmaco-economics

The application of the economic framework to the study of medicines use and effectiveness.

Placebo

An inert medication or procedure i.e. one having no pharmacological effect, but that is intended to give patients the perception that they are receiving treatment of their complaint.

Power

The number of patients enrolled in a study has a large bearing on the ability of the study to reliably detect the size of the effect of the study intervention. This is described as the ‘power’ of the trial. The larger the sample size or number of participants in the trial, the greater the statistical power.

Quality indicator

A quality indicator is a measurement used as a guide to monitor, assess and improve the quality of patient care, support services, and organisational functions affecting patient outcomes. There are three types of indicators: structure, process and outcome indicators.

3. www.nice.org.uk

Randomised clinical trial

An experiment in which participants in a population are randomly allocated into groups, usually called *study* and control groups, to receive or not to receive an experimental preventive or therapeutic procedure, manoeuvre or intervention. The results are interpreted by rigorous comparison of rates of diseases, death, recovery or other appropriate outcome in the study and control groups.

Registry

A patient registry is an organised system that uses observational study methods to collect uniform data and evaluate specified outcomes for a defined population, who have a particular disease, condition or exposure, to serve predetermined scientific, clinical or policy purposes (Gliklich RE, Dreyer NA, eds. Registries for evaluating patient outcomes agency for healthcare research and quality publication No.07-EHC001).

SOPs

Standard operating procedures: detailed instructions on what to do to achieve good clinical, laboratory and manufacturing practice.

Sponsor

An individual or organisation which initiates, manages and/or finances a clinical trial and takes the responsibility of the clinical trial.

Systematic Review

The application of strategies that limits bias in the assembly, critical appraisal, and synthesis of all relevant studies on a specific topic (Dictionary of Epidemiology, 2001).

Translational research

The conversion of basic research advances into products that can be tested on humans.

Future Outlook: Emerging Innovative Approaches for Effective Integration of Medical Research in Clinical Practice

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“Knowing is not enough, we must apply; willing is not enough, we must act.”

Johann Wolfgang von Goethe

1. Introduction

Unprecedented advances in biotechnology and medical research in Europe have led to mounting public expectations for innovative approaches to effectively link “research to action”. This requires connecting interdependent – but often disconnected – points situated along a lengthy science translation continuum that includes conception of a research hypothesis, generation of required research evidence and adoption of a new health intervention into clinical practice. Bridging the gaps between “what we know” and “what we do” is of substantial interest to supranational organisations such as the ESF-EMRC and the World Health Organisation (WHO). The WHO has issued, for example, the “World Report on Knowledge for Better Health”, including a discussion devoted to linking research to action¹. The latter report underscores the importance of turning scientific knowledge into actions that improve health and alleviate poverty worldwide.

The challenge of moving new biomedical findings in biomedicine into effective, affordable and safe medical products was also recognised by the US Food and Drug Administration (FDA) White Paper entitled “Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medicinal Products”². This report noted that “the applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic sciences. The new science is not being used to guide the technology development process in the same way that it is accelerating the technology discovery process”.

Indeed, such gaps in translation of research to health products have been observed in various medical specialties and therapeutic areas. In the case of genome-based medicine, no more than 3% of the published research on genomics applications focuses on the development of evidence-based guidelines or health systems delivery,

dissemination and diffusion research³.

What is the problem? In addition to much needed investments in translation research in biomedicine, are there emerging innovative approaches to expeditiously link research ideas and findings with tangible applications in the clinic and population health? The past few years have seen a conceptual shift towards the empirical study of health innovations as *ecosystems* with many “moving parts” and components that interact in more than one way^{4,5} (e.g., cooperation, competition, pre-competitive collaboration). Notably, innovations are shaped not only by advances in biotechnology and laboratory science but also by patient demands and other end-users of scientific knowledge and health products.

In the outlook discussion that follows, we first present a *structural architecture* of the translation research phases so that a “higher resolution map” can be established on the critical path from a new idea to health products in the clinic. Second, we present a *functional architecture* of the different phases of translation research. This pertains to knowledge translation (KT) strategies to effectively link research with practice and policy. Both the structural and the functional architectures can be usefully conceptualised as being complementary to understand the translation of research data to medical knowledge and health products.

2. Structural Architecture of Translation Research

The multidisciplinary research necessary to advance preclinical or basic science findings to clinical and population health applications is often named as translation research^{6,7}. This process has, however, multiple phases each of which might require engagement of different technologies, research methodologies, data analytical frameworks and stakeholders. Over the past few years, translation research has been classified into four distinct phases based on, for example, genomics and other areas

1. World Health Organization. World report on knowledge for better health. Geneva: WHO 2004.

2. Food and Drug Administration (US FDA). Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medicinal Products. 2004.

3. Khoury MJ, Gwinn M, Yoon PW, et al. The continuum of translation research in genomic medicine: how can we accelerate the appropriate integration of human genome discoveries into healthcare and disease prevention. *Genet Med* 2007; 9: 665-74

4. Guston DH. Innovation policy: not just a jumbo shrimp. *Nature* 2008; 454(7207): 940-1

5. Ozdemir V, Husereau D, Hyland S, et al. Personalized medicine beyond genomics: New technologies, global health diplomacy and anticipatory governance. *Current Pharmacogenomics and Personalized Medicine* 2009; 7(4): 225-230

6. Rohrbach LA, Grana R, Sussman S, et al. Type II translation: transporting prevention interventions from research to real world settings. *Eval Health Prof* 2006;29:302-33

7. Westfall JM, Mold J, Faqnan L. Practice-based research-blue highways on the NIH road map. *JAMA* 2007; 297: 403-6

of healthcare and prevention⁸. The successive phases of translation research acknowledge that there are often overlaps among each phase and that information flow among them can at times be nonlinear. The following four phases of translation research were proposed for genome-based medicine⁹ and might provide an example as an organisational framework for other medical specialties as well.

- Phase 1 translation (T1) research aims to advance a basic science discovery into a candidate health application (e.g., genetic test/intervention).
- Phase 2 translation (T2) research concerns the development of evidence-based guidelines for a health application.
- Phase 3 translation (T3) research aims to connect evidence-based guidelines with health practice, through delivery, dissemination, and diffusion research.
- Phase 4 translation (T4) research evaluates the “real world” health outcomes of a health application in practice.

Understanding these various phases and the inherent structural heterogeneity is essential: it can help us rapidly identify where the gaps are most prominent and by extension, precisely where future research investments in translation research are warranted and timely.

3. Functional Architecture of Translation Research: KT as a Key Component

Superimposed on the structural organisational framework on translation research, a functional architecture translates biomedical data to knowledge and clinical practice. Importantly, a functional architecture of translation research would take into account the concept of KT and factors (both technical and non-technical) that influence the existing gaps between knowledge generators (e.g., university academic researchers) and knowledge consumers (e.g., patients, insurers, policy-makers).

KT is defined as “the synthesis, exchange and application of knowledge by relevant stakeholders to accelerate the benefits of global and local innovation in strengthening health systems and improving people’s health”¹⁰.

8. Khoury MJ, Gwinn M, Yoon PW, et al. The continuum of translation research in genomic medicine: how can we accelerate the appropriate integration of human genome discoveries into healthcare and disease prevention. *Genet Med* 2007; 9: 665-74
9. Khoury MJ, Gwinn M, Yoon PW, et al. The continuum of translation research in genomic medicine: how can we accelerate the appropriate integration of human genome discoveries into healthcare and disease prevention. *Genet Med* 2007; 9: 665-74
10. World Health Organization. Bridging the “Know-Do” gap: report on meeting on knowledge translation in global health. Geneva: WHO; 2006. WHO document WHO/EIP/KMS/2006.2.

While KT is now recognised as an essential activity to bridge the gaps between research, policy and clinical practice of medical research, this was not always so. In the two decades after the Second World War, investments in science – beyond strategic government projects – led to the rise of bottom up basic science¹¹ without a firm emphasis on KT activities. Indeed, prior to the 1970s, research findings were, by and large, subject to “passive diffusion” from the laboratory to the clinic and society. In contrast, the advent of the evidence-based medicine in the 1970s used a “push strategy” for active translation, synthesis and dissemination of discoveries in science¹².

KT employs various complementary models to bring about coherent links among research, practice and policy (Figure 1). “Push” efforts are usually led by researchers, and other purveyors of research (e.g., communications staff). “User-pull” efforts involve consumers of research such as policy-makers, patients, clinicians or civil servants. “Linkage and exchange” efforts materialize when, for example, producers of research (e.g., scientists) develop a partnership with a user group for their research and discovery. Finally, an “integrated” strategy to link research to action involves large-scale knowledge translation platforms that incorporate multiple stakeholders across the translation continuum utilising elements of the push, pull and exchange approaches¹³. Canada has emphasised knowledge translation models that focus on linkage and exchange (among research, clinical practice and policy)¹⁴.

While each model for linking research to action and policy might offer an advantage in different contexts, a “translation platform” that allows bi-directional exchange and contact between scientists and policy-makers appears to strongly facilitate the use of research in policy-making based on a systematic review of 24 interview studies^{15,16}.

One example of the “linkage and exchange” model of KT is early public engagement in research priority setting between experts and end-users of scientific knowledge

11. Menand L. *College: the end of the Golden Age*. New York Review of Books 2001; 48: 44-7

12. Landry R, Amara N, Pablos-Mendes A, et al. The knowledge-value chain: A conceptual framework for knowledge translation in health. *Bull World Health Organ* 2006; 84(8): 597-602

13. Lavis JN, Lomas J, Hamid M, et al. Assessing country-level efforts to link research to action. *Bull World Health Organ* 2006; 84(8): 620-8

14. International Development Research Centre. *Knowledge translation: basic theories, approaches and applications*. Ottawa: IDRC; 2005

15. Innvaer S, Vist G, Trommald M, et al. Health policy-makers’ perceptions of their use of evidence: a systematic review. *J Health Serv Res Policy* 2002;7:239-44

16. Choi BCK, Pang T, Lin V, et al. Can scientists and policy-makers work together? *J Epidemiol Community Health* 2005; 59: 632-637

Future Outlook: Emerging Innovative Approaches for Effective Integration of Medical Research in Clinical Practice

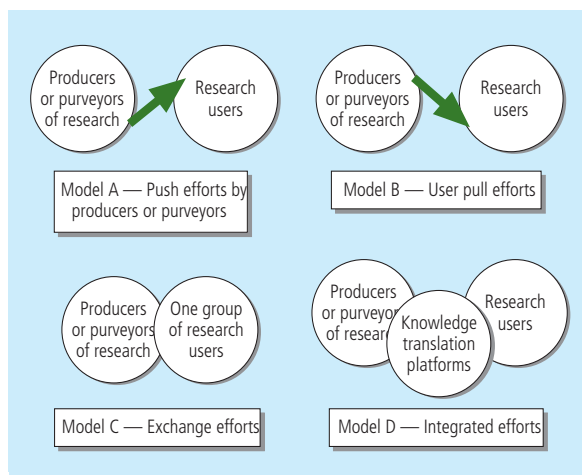


Figure 1. Models to link research to action according to WHO Bulletin

(e.g., patients). For example, the involvement of patients by researchers assessing treatments for rheumatoid arthritis showed that, for most patients, fatigue was the dominant symptom of concern contrary to what researchers had assumed (pain)¹⁷. It is noteworthy that such “upstream” public engagement concerning new therapeutic candidates or emerging biotechnologies can allow bi-directional exchange of expert knowledge and local evidence (e.g., patients’ personal experiences of illness) thereby shaping both scientific practice and uptake of scientific knowledge by end-users¹⁸. Recent direct-to-consumer availability of personal genomics tests further attests to the fact that the continuum of KT is not always straightforward and that it can have discontinuities. At least in the case of personal genomics tests, new health products (genomics tests) can bypass the health professionals by virtue of direct availability to patients¹⁹. In effect, this may challenge the old notions of expertise and definitions concerning who or which stakeholder(s) should be considered an expert.

17. Hewlett S, De Wit M, Richards P, et al. Patients and professionals as research partners: challenges, practicalities and benefits. *Arthritis Rheum* 2006; 55: 676–80

18. Kato K, Kano K, Shirai T. Science communication: significance for genome-based personalized medicine – a view from the Asia-Pacific. *Curr Pharmacogenomics Person Med* 2010; 8(2): 92–6

19. Prainsack B, Reardon J, Hindmarsh R, et al. Personal genomes: Misdirected precaution. *Nature* 2008; 456(7218): 34–5

4. Are We Asking the Right Questions?

Scientific methodologies and data analytical frameworks receive substantial attention in evaluations of scientific credibility. However, scientific rigour starts much earlier at the level of appropriate, objective and balanced framing of a research question. In other words, in discussions on linking research to action, we also need to consider if we are asking the right questions.

When presented with a new health intervention or diagnostic test, we are faced with two significant questions:

(1) Should we use a new health intervention given current information?

This first question deals with the evidentiary standards for adopting or rejecting the use of a new health product. A vast range of evidence from what is commonly referred to as the “knowledge pyramid” with increasing degrees of population and public health impact (e.g., basic science data, treatment guidelines, systematic reviews, etc). In the case of genomics diagnostics tests, a notable example is the independent Working Group of the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative²⁰. The latter Working Group considers multidimensional criteria including analytical and clinical validity, clinical utility and the ethical, legal and social issues related to a genomics application. A recent example from Canada is the Genetic testing Evidence Tracking Tool (GETT)²¹. This tool allows a) researchers to summarise the current evidence and to identify knowledge gaps for further research and; b) stakeholders to collect data related to a given molecular test and improve their decision-making process. Because population genomics knowledge can usefully inform public health practice and prevention²², independent working groups and decision-tools that evaluate and synthesise research evidence serve a much needed “filter-and-catalyst” function on the critical path from a research concept to clinical practice.

(2) Is further research justifiable when there is uncertainty surrounding the decision on adoption or rejection of a new health intervention?

This second question is often neglected but is of substantial importance – given that we often do *not* have

20. Teutsch SM, Bradley LA, Palomaki GE, et al. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative: methods of the EGAPP Working Group. *Genet Med* 2009; 11(1): 3–14

21. Rousseau F, Lindsay C, Charland M et al. IFCC Scientific Division Committee on Molecular Diagnostics. Development and description of GETT: a genetic testing evidence tracking tool. *Clin Chem Lab Med* 2010; 48(10): 1397–1407

22. Knoppers BM, Leroux T, Doucet H, et al. Framing genomics, public health research and policy: points to consider. *Public Health Genomics* 2010; 13(4): 224–34

an unequivocal answer to the first question above. New approaches such as the value of Information Analysis (VOI) aim to provide answers to this second question. VOI analysis informs decision-makers about the expected value of conducting more research to support a decision. VOI including its strengths and limitations are reviewed elsewhere for interested readers^{23,24}.

5. Theragnostics: Fusion of Therapeutics with Diagnostic Medicine

Personalised medicine has received much attention in the post-genomics era. However, personalised medicine is part of a larger shift in *therapeutics* as it increasingly engages with *diagnostic* medicine. Theragnostics is a new field of inquiry that combines these two strands of knowledge that have traditionally remained separate in the past^{25,26}. “Theragnostic medicine” thus aims to develop targeted health interventions – not only pharmaceuticals but also customised nutrition and vaccines – together with companion diagnostic tests that are envisioned to be used in tandem with a health intervention.

Insofar as KT and linking research to clinical practice are concerned, adequate attention is paid to “asymmetries” on the developmental path of these two strands of knowledge. For example, if a personalised health intervention and a companion diagnostic test are required, they need to be developed in real-time or at least coordinated in parallel. Theragnostic medicine relies on data-intensive sciences such as genomics and requires tool building, e.g., population biobanks, which can be creatively mined, further driving applied and conceptual innovations in medicine. Hence, theragnostics presents additional challenges to integrate research findings to clinical practice. Chief among these is to avoid the creation of a false hierarchical dichotomy between infrastructure tool-building science and subsequent discovery-oriented science; both are inseparable and rely on each other to materialise²⁷.

23. Yokota F, Thompson KM. Value of Information literature analysis: A review of applications in health risk management. *Med Decis Making* 2004; 24: 287-98

24. Claxton K, Eggington S, Ginnelly L, et al. A pilot study of value of information analysis to support research recommendations for NICE. Centre for Health Economics Research Paper 4. (2005).

25. Street JM, Dear JW. The application of mass-spectrometry-based protein biomarker discovery to theragnostics. *Br J Clin Pharmacol* 2010; 69(4): 367-78

26. Ozdemir V, Williams-Jones B, Glatt SJ, et al. Shifting emphasis from pharmacogenomics to theragnostics. *Nat Biotechnol* 2006; 24(8): 942-6

27. Ozdemir V, Armengaud J, Dubé L, Aziz RK, Knoppers BM. Nutriproteomics and proteogenomics: cultivating two novel hybrid fields of personalized medicine with added societal value. *Current Pharmacogenomics and Personalized Medicine* 2010; 8(4): 240-244

Precompetitive collaboration^{28,29}, defined as competitors sharing early stages of research that benefit all³⁰, is one potential approach to tool building for theragnostic medicine in the future.

6. Convening Function of the ESF-EMRC: Not to be Forgotten

Research ideas and findings transition through a complex path before they can be integrated into clinical practice. This path has both structural and functional architectures (as outlined above) that intersect and interact with a multitude of stakeholders. To this end, supranational organisations such as ESF-EMRC have an important role to play by remaining on the cutting edge of advances on this path. Notably, the convening function of ESF-EMRC across these complex sets of stakeholders and structural and functional architectures is essential to forge meaningful and sustainable linkages between research, practice and policy in Europe and on a global stage.

28. Altshuler JS, Balogh E, Barker AD, Eck SL, Friend SH, Ginsburg GS, Herbst RS, Nass SJ, Streeter CM, Wagner JA. Opening up to precompetitive collaboration. *Sci Transl Med* 2010; 2(52): 52cm26

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How Regulators Can Help

The European Medicines Agency (EMA)

Scientific advisory services

The EMA encourages interaction with companies depending on the key features and development status of the medicine or technology. These scientific advisory services are spread across the agency and are designed to speed up the development and availability of high quality, effective and acceptably safe medicines, for the benefit of patients¹.

- Innovation Task Force (ITF)
- SME Office (dedicated assistance for micro, small and medium-sized enterprises)
- Orphan Medicinal Product designation
- Scientific Advice and Protocol Assistance

Novel methodologies

The EMA qualification process is a new, voluntary, scientific pathway leading to either a Committee for Human Medicinal Products (CHMP) opinion or a Scientific Advice on innovative methods or drug development tools:

- **CHMP Qualification Opinion** on the acceptability of a specific use of the proposed method (e.g., use of a novel methodology or an imaging method) in a research and development (R&D) context (non-clinical or clinical studies), based on the assessment of submitted data;
- **CHMP Qualification Advice on future protocols and methods for further method development towards qualification**, based on the evaluation of the scientific rationale and on preliminary data submitted.

This qualification process addresses innovative drug development methods. It includes qualification of biomarkers developed by consortia, networks, public/private partnerships, learned societies or pharmaceutical industry for a specific intended use in pharmaceuticals R&D.

Scientific Advice organises expert meetings to inform of their advice and involves patients, academics, regulators and companies.

Telematics programme EU Telematics

The EMA is responsible for implementing EU Telematics strategy. This strategy is designed to increase efficiency and transparency across the European Medicines Regulatory Network and to make legally required electronic procedures as straightforward as possible.

EU Telematics are a central set of pan-European systems and databases and their use by stakeholders is only limited by legal or confidentiality requirements. The Telematics systems exchange information with the systems of external stakeholders and National Competent

1. http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000113.jsp&url=menus/about_us/about_us.jsp&mid=WC0b01ac0580028c2a

Authorities (NCAs), while staying separate from them. The systems help provide high quality information on medicinal products to the general public and support the monitoring of the post authorisation risk/benefit balance of medicines in the European Union.

Most of the systems listed below are already in place, though some (e.g., Eudra Data Warehouse), are still in development.

- **EudraCT**: database containing registrations of clinical trials.
- **EudraPharm**: database of authorised medicinal products.
- **EudraVigilance**: system monitoring the post-authorisation safety of medicines through safety reports.

EudraCT

EudraCT is the Community's electronic database of clinical trials. It contains information submitted by sponsors (commercial and non-commercial), in the Clinical Trials Application form. It informs NCAs of ongoing clinical trials in all member states, enabling an overview of multi-state trials. The system also alerts NCAs in the case of early interruption or termination for:

- safety reasons or a lack of efficacy;
- suspension or prohibition;
- the refusal of the NCA; or
- a negative opinion of an ethics committee in a given Member State.

EudraCT is envisaged as the base system upon which the information collection, storage, processing and publication requirements of Regulation no. 1901/2006 on Medicinal Products for Paediatric Use will be built. The database for paediatric clinical trials is under development.

Further information can be found on the EudraCT website.

New pharmacovigilance legislation by European Parliament

The EMA welcomes the adoption of the new pharmacovigilance legislation by the European Parliament. This is a major step towards the legislation coming into force, currently expected for mid-2012.

The new Directive and Regulation propose a number of changes that will strengthen the way the safety of medicines for human use is monitored in the EU.

The proposed changes include enhanced monitoring of the benefits and risks of medicines post-authorisation, replacement of the Pharmacovigilance Working Party with a Committee, and an increased level of transparency of safety information.

The Directive and Regulation are still awaiting adoption by the Council of the EU².

2. <http://www.europarl.europa.eu/en/pressroom/content/20100921IPR83194/>

Annex 5

Best Practice Example – Technologie- und Methodenplattform für die vernetzte Klinische Forschung (e.V.) TMF, Berlin, Germany

The TMF CPG Development Portal

Under one roof and accessible at any time: www.cpg-development.com

CPGs (clinical practice guidelines) as important decision support gather more and more importance in medical practice. But their quality and medical worthiness depend considerably on systematic and transparent development methodology. The latter, however, is very complex. The CPG development portal of TMF and Charité, Berlin, supports development and consensus building of CPGs, where large teams of experts efficiently work together over a long period.

The CPG development portal¹, conducted by TMF and based on the experience from numerous CPG developments, provides an internet-based infrastructure, which supports the development of high quality CPGs of level S3 (according to German classification). There, developers find a comprehensive assortment of well-proven and evaluated tools. Most of these can be combined according to individual needs.

Efficient communication

Well-functioning communication between all participants – anytime and anywhere – is a substantial prerequisite for fast, smooth CPG development. In most situations, the portal provides optimum solutions for communication:

- Mailing lists, fora and chat-rooms for communication within large groups
- News and calendars for exchange of important news and notifications
- Newsletters on login to inform about changes since last access

The only prerequisite for the use of the portal is access to the Internet (pocket devices are not supported so far). Then, it can be used with every up-to-date web browser, alternatively in German or English. Thus, international CPGs can equally be developed.

Information and documents – available just-in-time.

For CPG developers it is important to have access to all the documents and information required for all individual working steps at any time. An excellent organisation guarantees order and orientation within the document jungle. Equally important is the distribution of working results to other participants. For this purpose, the portal provides a manifold of functions, from shared workspaces to allocation and provision of difficult-to-access literature.

Optimised tools

Both fast access to information and efficient communication, together with numerous other tools, lead to a

significant reduction of development time and organisational overheads. A main focus is preparation, execution and evaluation of online voting. Extent, design and duration of a voting are largely user-defined. Skilfully applied, the effort for subsequent consensus conferences can be reduced comprehensively.

Furthermore, a specific text editor and a Wiki tool simplify the joint compilation of documents and other texts. At the same time, most of the tools support the automatic documentation of the development process, thus guaranteeing quality management.

Methodological and technical support

In addition, the team of the portal offers advice on preparation and realisation of CPG developments, supports users in the efficient search and appraisal of literature sources and provides support in conducting consensus conferences, e.g. by allocation of televoting systems.

Terms of use

The CPG development portal is conducted on behalf of TMF by the Competence network “Inflammatory Bowel Diseases” at the Department of Medicine I, Charité Universitätsmedizin Berlin, Campus Benjamin Franklin.

The portal is available for non-gratuitous use for interested CPG developers: the offer is directed to developers of individual CPGs, but also to medical societies with their complete CPG programmes. The charges depend on the number of participants and the extent of services used. Participants only need a computer (PC or Mac) with a browser and mail client installed.

To get a first impression of the scope of services offered, interested users can access a fictitious guideline development area of the portal by logging in on www.leitlinienentwicklung.de (German by default) or www.cpg-development.com (English by default) as a guest, using ‘visitor’ as username and password. In this environment, most of the portal services can be tested.

The team of the CPG development portal would be glad to answer all open questions and is available for any methodological or technical questions.

Contact:

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www.tmf-ev.de

1. www.cpg-development.com

Patient and Public Involvement

Brief history of Patient and Public Involvement in research (PPI)

Active “Patient and Public Involvement” (PPI) is not new: its history extends over many decades, perhaps beginning in the United States, then moving to the UK and Europe. It is currently developing at a different pace across Europe^{1,2} with the UK leading the way with initiatives, structures, systems, and in the provision of training for both lay and health professionals about how to become involved.

It is difficult to be precise about the origin of PPI but several early examples exist. **Rose Kushner** – a pioneer of patient involvement in the United States in the 1970s – was a freelance writer who also had breast cancer. She wrote a book, which was based on a thorough review of evidence of the effects of radical mastectomy. Her influence and attitude was such that she eventually reviewed new research proposals for the **US National Cancer Institute**.³ Her achievements helped inspire the work of the **US National Breast Cancer Coalition**.

Another early example of well-organised and influential involvement occurred in the 1980s in the United Kingdom in the perinatal field – the **Association for Improvement of Maternity Services** convened a meeting of interested voluntary organisations and patient groups to encourage them to support the Medical Research Council’s proposals for a randomised controlled trial of chorionic villus sampling in pregnancy. Representatives of these groups were involved in conducting and promoting this important trial.⁴

Another example is provided by well-organised groups of people with **AIDS** – first in the US and then in the UK – who challenged researchers’ approaches to conducting trials, which had overlooked patients’ preferred outcomes.⁵

In 1997, the **first international conference on breast cancer advocacy**, attended by people from 44 coun-

tries and six continents, took place in Brussels. It was led by the **US National Breast Cancer Coalition** and supported by organisations from Panama, Belgium, the UK, and Israel. This meeting helped shift the balance towards consumer participation, which was becoming a reality at that time.⁶ **The Cochrane Collaboration** (www.cochrane.org/) also took part in the meeting.

The **Consumers Advisory Group for Clinical Trials (CAG-CT)** was established in the UK in September 1994. This was a small **working group** of health professionals and patients established with the aim of initiating, facilitating and producing high-quality research that met the needs and interest of patients, the public and health professionals by advancing education in medical research methodology. Their aims were firstly: to work directly with the profession to look at research protocols, to help develop them and to help with patient information leaflets; and secondly: to advance public education about clinical trials.

The **UK government enquiry on Breast Cancer Services** was held in March 1995. Patient involvement in the whole research process had been advocated in the course of this enquiry.⁷ The Health Select Committee report on this enquiry devoted a section to “Involving patients in research.” On the basis of written and oral evidence, ministers recommended “that patient involvement at all stages of a trial, including the initial design, **is essential** and that initiatives such as the **Consumers Advisory Group for Clinical Trials** should be welcomed.”⁸ Ministers believed that their recommendations would help to improve the standard of care for women with breast cancer in the UK. They also hoped that “**as other specialties follow the lead, they may help to raise the standard of care for all cancer patients.**”

Subsequently, in the UK, the **Standing Advisory Group on Consumer Involvement in the NHS R&D Programme** was formed in April 1996 to advise the Central Research Development Committee on how to boost patient involvement in the UK NHS research and development programme. The group included representatives of consumer bodies, health professionals, managers, and information specialists. See: Review of Consumer/lay Participation in the R&D Agenda: Emerging issues so far. September 1996. (From Social Science Research Unit. Institute of Education, University of London.) This group was renamed ‘Consumers in Research’, and subsequently became **INVOLVE**.

6. Liberati A. Consumer participation in research and healthcare. *BMJ* 1997; 315:449.

7. Thornton H. Patients and health professionals working together to improve clinical research: where are we going? *Eur J Cancer* 2006; 42:2454-8, plus appendix A.

8. Health Committee. Third report. Breast cancer services. Vols I and II. 6 July 1995. Vol I, page lvi, para 205. London: Stationery Office.

1. European Overview of literature of patient involvement in clinical trials: (Aug.2008 – Sept.2009) <http://www.patientpartner-europe.eu/en/inventory/literature>

2. European Survey Report on good practices on patient involvement in clinical trials from the patient perspective (End 2008) <http://www.patientpartner-europe.eu/en/inventory/survey-patient-organisations>

3. Lerner BH. The breast cancer wars: hope, fear and the pursuit of a cure in twentieth century America. New York: Oxford University Press, 2003.

4. Chalmers I. Minimising harm and maximizing benefit during innovation in healthcare: controlled or uncontrolled experimentation? *Birth* 1986; 13:155-64.

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PPI in UK, Europe, US, Canada, Australia rapidly developed during the early 1990s.

National Institute for Health Research (NIHR). Professor Dame Sally Davies (UK Director General of Research and Development, Department of Health) is explicit about the centrality of PPI in research, describing it as ‘A Key Partnership’, stating that “People-focused research in the NHS simply cannot be delivered without the involvement of patients and the public.” “No matter how complicated the research, or how brilliant the researcher, patients and the public always offer unique, invaluable insights. Their advice when designing, implementing and evaluating research invariably makes studies more effective, more credible and often more cost effective as well.”⁹

- History is important. (Understand the Social and Cultural History).
- Databases are important: INVOLVE; INVOnet; etc.
- Important to maintain balance and equality.
- Evaluation of PPI: evidence now available¹⁰
- Measuring Impact¹¹

PPI in research now goes beyond involvement in clinical trials. For example, in the UK, an appointed group of 30 well motivated and informed lay members, the **Citizens Council of the National Institute for Health and Clinical Excellence**, is a formal committee of the Institute. It helps to develop the broad social values that should underpin NICE guidance. Each independent advisory committee or group that develop NICE guidance includes at least two (often more) lay people (patients, carers and members of the public) who, as committee members, ensure that patient, carer, and public views and experiences contribute directly to making NICE guidance recommendations. They consider clinical trial evidence but also other published research as well as evidence submitted by ‘stakeholders’, both professionals and patient, carers, and voluntary organisations. (www.nice.org.uk/page.aspx?o=citizenscouncil)

The **James Lind Alliance (JLA)** has been established to bring patients and clinicians together in ‘**Working Partnerships**’. Its aim is to identify the most important gaps in knowledge about the effects of treatments, within **Priority Setting Partnerships** to prioritise the unanswered questions that they agree are most important¹².

The JLA is seen as a valuable and important resource by their partners and funders, the UK National Institute for Health Research (NIHR), and the UK Medical Research Council (MRC).

In both of these examples, professional and lay members **focus together** on improving research processes and seeking fair systems that consider the needs of patients.

Since the recognition and acceptance of patient and public involvement, and the rapid accumulation of evidence regarding its worth,¹³ patient and public involvement has been implemented here in the UK and in Europe, the United States, Canada, and Australia. In the UK, the National Institute for Health Research (NIHR) is now established as part of the government’s strategy, “Best research for best health”. The NIHR wants patients and the public to be involved in all stages of research, and, together with its partners – the UK Clinical Research Collaboration and INVOLVE – has put structures in place to achieve and facilitate this.

Healthy development of the partnership between patients and the medical profession will depend on firm policy directives that encourage institutional collaboration to avoid wastage of resources and duplication of effort. It will be important to record and understand the social and cultural history of patient and public involvement, compile comprehensive databases, and undertake ongoing systematic reviews of the effect of public involvement if we are to make progress and maintain balance and equality within this new partnership.

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Annex 7

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