Embedding trials in evidence-based clinical practice
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CHAPTER 11

SUMMARY AND GENERAL DISCUSSION
This thesis presents a number of research projects centered on ‘evidence-based medicine’ (EBM). In the projects reported here, we focused both on the generation of evidence, through clinical trials, and the integration of evidence from solid research into clinical practice.

This thesis consists of two parts. Part 1 focuses on improving recruitment of the necessary number of patients in clinical trials, as this is a major problem while evaluating the effectiveness of interventions in health care. To improve our understanding of patient recruitment, we tried to identify obstacles and facilitators for successful recruitment. Part 2 of this thesis focuses on improving integration of evidence-based decision making in clinical practice. We identified barriers for EBM teaching in practice, developed an EBM Teach the Teacher course, and evaluated methods to assess EBM in clinical practice.

In Chapter 1 we introduced the rationale for this thesis. ‘Evidence-based medicine’ (EBM), defined in 1992 by Gyatt as “the integration of individual clinical expertise with the best available external evidence from systematic research”, is considered the cornerstone of decision making in current clinical medicine. As the way in which we intuitively derive knowledge from experience can lead to biased decisions, we need valid evidence from high quality clinical trials.¹

PART 1: IMPROVING RECRUITMENT OF PATIENTS IN CLINICAL TRIALS

In Chapter 2 the rationale and design of our project “IMproving PArticipation of patients in Clinical Trials” (IMPACT) were presented. To better understand barriers and facilitators for successful recruitment in trials from different levels, we planned two cohort studies (Chapter 3 and Chapter 4) and a case-control study (Chapter 5).

Chapter 3 depicted factors that influence successful recruitment in trials, based on an analysis from a cohort of 1,129 trials registered in the Netherlands Trial Register with a planned completion date between 2005 and 2010. We analyzed 386 trial questionnaires, reporting on a total recruitment target of 42,412 participants in multiple specialties, both in industry and non-industry sponsored trials. Two thirds (66%) of the trial coordinators stated that recruitment was more difficult than anticipated. In less than half (43%) of the trials 80% or more of the targeted number of patients had been recruited at the planned completion date, while a mere 53% had reached the targeted sample size at the
completion date. Only 52% of the trials had been reported in the peer reviewed literature within two years after the completion date. Unfortunately we failed to identify a consistent pattern of characteristics associated with slow recruitment.

Chapter 4 described the results of a web-based questionnaire sent to the local researchers of centres that had recruited in total 14,808 patients for 17 multicentre trials performed in the Consortium for Obstetrics and Gynaecology in the Netherlands. We studied whether factors motivating centre decisions about participation in trials, the research orientation of the department, and the (perceived) logistical support by research personnel were associated with recruitment. In univariable analysis, participating in trials because “expecting others to recruit in return for their studies” was associated with higher recruitment scores, while participating “because it is expected from us” was associated with lower scores. Higher recruitment scores were seen in centres regularly initiating research and in tertiary care centres. Weighted recruitment scores were higher in centres in which research staff was more frequently available.

In Chapter 5 we reported findings from 21 semi-structured interviews with pregnant women invited to a randomized trial in obstetrics. We studied two groups: those who participated (n=12) and those who had declined participation (n=9). We interviewed patients from 8 different trials. Contribution to scientific research was for 5 of 12 participants the main motive for participation in the trial, while 5 mentioned to have participated because the intervention was not available outside the trial. Key motives for non-participation (n=9) were a negative association or dislike of the intervention, either because it might do harm (n=6) or for practical reasons (n=3). We identified seven main themes that influenced decisions on participation. We noted that uncertainty about scientific research and/or the intervention was reported to be of considerable importance. Patients’ understanding of scientific research was generally low. A personal, complete and well-timed dialogue may facilitate a balanced decision on trial participation.

Chapter 6 presented a questionnaire survey sent to clinicians in all departments of Obstetrics and Gynecology in the Netherlands. We observed that recruitment for multicenter clinical trials was associated with better knowledge about the trial results; overall, clinicians who had recruited were on average 1.8 times more likely to know the trial results, compared to clinicians who had not recruited (95% confidence interval (CI) 1.7 to 1.9; range between 1.1 and 3.3 across individual studies). Recruitment for a trial was
also significantly associated with implementation of study results, though the effect was small, with a summary relative risk of 1.1 (95% CI 1.02 to 1.19).

PART 2: IMPROVING EVIDENCE-BASED MEDICINE IN CLINICAL PRACTICE

Many courses on evidence-based medicine (EBM) are offered nowadays, but optimally integrating EBM teaching in clinical practice remains a challenge. Teach the Teacher (TTT) EBM courses, aimed at educating clinical EBM teachers, could help to improve teaching quality and to set a standard for EBM teaching.

In the project described in Chapter 7 we evaluated the availability and content of existing TTT EBM courses. Through country specific EBM networks and infrastructure we identified 16 courses that could be labelled as TTT courses: 4 in Hungary, 4 in the Netherlands, 4 in the United Kingdom, and 4 in Germany. Of these, 15 out of 16 were taught by academic specialists and 11 by methodologists or statisticians. Seven of the course organizers highlighted the need for help in providing practical examples of successful techniques for teaching EBM in clinical practice, 7 for help with a curriculum for trainers to train healthcare workers, and 7 help with funding of TTT courses.

Chapter 8 presented an evaluation of a web based educational course for clinical trainers, designed to teach EBM principles in everyday practice with confidence. The course consisted of e-learning modules that defined the learning objectives and incorporated video clips of practical and effective EBM teaching methods, aimed to seize opportunities for teaching in six different clinical settings. In a group of 56 clinical tutors, in different specialties across six European countries, 47 (84%) moderately improved their score on a questionnaire to measure learning achievement after the course, from an average of 69 (SD 10) to 77 points (SD 12) (p<0.0001).

Improving knowledge on how to teach EBM does not automatically translate in more or better EBM teaching in clinical practice. In Chapter 9 we identified and compared barriers for teaching EBM in clinical practice in various European countries, using a questionnaire completed by 120 clinical EBM teachers from 11 countries. On a 7 point Likert scale, anchored at “1: not at all” on the one end and “7: an insurmountable barrier” at the other, “lack of time” received the highest score (median 5). Moderate barriers (median 4) were “lack of requirements for EBM skills” and “a top down health care management structure”.

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In Germany, Hungary and Poland reading and understanding articles in English received higher barrier scores than in the other countries.

Self-reported barriers and facilitators can be of help in identifying strategies to improve practice. To measure whether such strategies have an effect on actual behavior, a valid and reliable assessment method is needed. In Chapter 10 we presented a systematic review of original studies that described the development or use of tools to assess Evidence-based Practice behavior in healthcare professionals. We identified 172 such studies: 117 questionnaires, 10 interviews or focus groups, 9 observational studies, and 27 chart evaluations, while 9 other studies used a combination of methods. Psychometric properties of the questionnaires used were reported in about half of the studies. In 7 studies, assessing a single EBM step, and in 6 studies that assess a combination of EBM steps with a questionnaire, validity and reliability of the instrument were both reported. One of these questionnaires assessed all five steps of EBM. We concluded that valid and reliable methods are available, but the specific aims of the assessment should guide the choice of an instrument for assessing EBM behavior in practice.
IMPLICATIONS FOR PRACTICE AND SUGGESTIONS FOR FURTHER RESEARCH

The studies summarized in this thesis and comparable projects by others have shown that recruiting a sufficient sample of patients and improving evidence-based clinical decision making are complex, context dependent processes.\textsuperscript{2-6} In general, we found that patient recruitment and EBM seem to flourish better when sowed in fertile ground: an environment where recruitment for trials and working evidence-based are (culturally) embedded in clinical practice and accepted, or even expected, by opinion leaders and clinical trainers.\textsuperscript{3,7} Yet a fertile ground in itself is not a sufficient condition for clinicians to change from a more authority based culture to a culture where the rationale underlying decisions is critically appraised and openly discussed. Inviting patients to participate in trials presupposes the courage to admit that the medical community currently does not know what is best, while EBM directly or indirectly challenges the traditional authority of trainers and clinicians.\textsuperscript{3} A large number of implementation strategies have been tested so far, but we can still improve our understanding of the drivers and constraints for changing clinicians’ behavior.

HOW CAN WE CHANGE BEHAVIOR?

Despite the availability of many methodologically sound studies our understanding of the processes involved in changing the behavior of healthcare professionals has not led to the definition of fail-proof interventions.\textsuperscript{8} A general consensus has emerged that there is no one ‘magic bullet’ for changing professional practice, and that interventions must be targeted at many levels to reach long lasting results, recognizing that the effects of improvement strategies will be context dependent.\textsuperscript{6,9} The variability in effectiveness of interventions, which sometimes work in one setting, but not in another one, is not fully understood.\textsuperscript{6} A comprehensive plan, targeting a range of problems and barriers to change, with strategies aimed at different levels - professional, team, patient, and organization- seems most likely to achieve long lasting changes in clinical behaviour.\textsuperscript{6,10}

The existing evidence suggests that interventions targeted at specific obstacles to change are more effective than generic interventions.\textsuperscript{6} Bosch and colleagues concluded that there is often a mismatch between the level of identified barriers and the type of interventions selected for an improvement strategy.\textsuperscript{11} Better tailoring of strategies to the identified level of being a barrier, should deserve more attention. Michie and colleagues developed a theoretical, consensus-based framework that could
be used to select obstacles when designing an implementation strategy. They identified twelve domains to explain behavior change: knowledge, skills, social or professional role and identity, beliefs about capabilities, beliefs about consequences, motivation and goals, memory, attention and decision processes, environmental context and resources, social influences, emotion regulation, behavioral regulation and nature of the behavior.\(^9\) Multiple concurrent interventions targeted on different domains should be selected, preferably with a specific goal of overcoming one or more of the barriers.\(^{11}\) However, methods used to identify impediments and tailor interventions to address them need further development.\(^{12}\)

**HOW SHOULD WE INTEGRATE RECRUITMENT OF PATIENTS INTO CLINICAL PRACTICE**

It is difficult not to agree on the large potential that exists for improving recruitment for trials at clinical sites.\(^4\) Unfortunately, we failed to identify a consistent pattern of trial characteristics associated with successful recruitment, though this failure is in line with previous, comparable attempts published in literature.\(^2,5\) This suggests that we should discontinue our search for simple, generally applicable predictors or ‘magic bullets’ that can guarantee success or failure in enrolling a sufficient number of patients.

A source of inspiration for alternative approaches could be the strategies that have been developed for improving implementation of evidence-based health care interventions in clinical practice. Several such strategies work with a series of plan-do-check-act cycles, in which one monitors whether a thoroughly designed recruitment plan, tailored to the trial, recruiting institute, patient population and expected obstacles, achieves the defined target. If not, one adjusts it further, as needed.\(^{13}\) McDonald and colleagues, propose the use of a business model approach and marketing techniques for recruitment in clinical trials. The model seems promising, but more examples of its application in practice are needed.\(^{14}\)

Expected obstacles could be derived from interviews and focus groups with patients and health professionals, ran before the study is developed, and from pilot studies. A review by Fletcher and colleagues on improving recruitment activity of clinicians in randomized controlled trials identified the use of qualitative methods to identify and overcome barriers to clinician recruitment activity as the most promising intervention.\(^{15}\) Further improving our knowledge about the processes of trial recruitment could further facilitate identification and elements that should be taken into account. Additionally, we should build strategies to convince and remind both health professionals and the general public of the value of research for practice. Familiarity and awareness of clinical research in the
general population could be enhanced by national public campaigns to improve awareness of clinical research.\textsuperscript{16,17}

The problems in recruiting participants also invokes a discussion on whether or not recruitment should be a shared societal responsibility, with obvious and unavoidable consequences for all clinicians and healthcare organizations. In our view, running and participating in trials should no longer be viewed as an optional activity, in one can opt in, but as an inescapable consequence of being a health professional and an absolute necessity for delivering quality care. Running trials and integrating trial results into clinical practice would then also be a responsibility for professional organizations, nationally and internationally. The rewards for participation in trials would then also change, from scientific recognition through authorship of articles, the now dominant form, to an essential element in the salary of individuals and the budget for healthcare organizations. The current opt-in system of inviting patients to trials could be replaced by an opt-out system for low risk evaluation research, based on the societal benefits of such a system. Such a change has already been proposed and tested in 2005 by Junghans and colleagues, where an opt-in system resulted in lower response rates and a biased sample.\textsuperscript{18} An opt-out system would not only improve participation rates, but could also lower the burden of patients, by shifting some of the responsibility of the often difficult decision making process about trial participation from patient to physician.\textsuperscript{19} Bernabe and colleagues argued that an opt-out procedure in minimal risk phase IV studies could be ethically acceptable.\textsuperscript{20} Crombie added to this discussion that “research should be undertaken only when there is a high likelihood of producing valid findings. Ethics requirements which result in invalid research may themselves be unethical”.\textsuperscript{21} The use and further investigation of such a system is also recommended by Al-Shahi Salman, in order to increase the value in biomedical research.\textsuperscript{22}

Patients could be informed about this general policy as soon as they enter the hospital, and are invited to sign a general informed consent about the use of data and efforts to improve quality. Such a system, has been pilot tested under federal regulations for clinical trials in pediatric medicine that are judged by the Institutional Review Board to reduce or have no effect on patient risk.\textsuperscript{23}

\textbf{HOW SHOULD WE INTEGRATE EBM TEACHING INTO PRACTICE?}
Based on a review of the literature, Coomarasamy and Khan concluded that EBM teaching
should be moved from classrooms to clinical practice, if one wants to see genuine improvement in relevant patient outcomes.\textsuperscript{24} Young and colleagues argued, based on a meta-review, that EBM teaching and learning strategies should not only be clinically integrated, but also multifaceted and including assessment.\textsuperscript{25} In these processes, evaluation and assessment remain quintessential. Different methods for assessment of either teaching or non-teaching interventions have been developed, focusing on knowledge, skills or actual EBM behavior.\textsuperscript{26,27} Although valid and reliable instruments are available to measure the effect of teaching on knowledge and skills, the ultimate goal of EBM teaching is to improve patient outcomes, by changing behavior of the health professionals.

Our review on original studies that described the development or use of tools to assess EBP behavior in practice resulted in a variety of methods to assess EBM behavior: questionnaires, interviews or focus groups, observational studies or chart evaluations.\textsuperscript{27} Before one can select the optimal method for assessment, one has to be explicit about the objectives of such an assessment, and on what EBM should mean in practice.\textsuperscript{28} In our survey, TTT EBM course organizers highlighted the need for help in defining the curricula. How and with whom to build EBM curricula was also identified as an issue in a review for policy recommendations on how to improve EBM.\textsuperscript{29} A possible explanation for this might be that (clinical) EBM teachers are scattered over various (hospital) departments.

To our knowledge, there is at present no standard in medicine or in medical education about what we may expect from healthcare professionals when they are working evidence-based, and when we would qualify a health professional as working evidence-based in an adequate fashion. A survey amongst European EBM course organizers showed that most organizations welcomed a standardized European qualification in EBM.\textsuperscript{30} The Sicily statement (2005) postulates that “all health professionals need to understand the principles of Evidence-based Practice (EBP), recognize EBP in action, implement evidence-based policies, and have a critical attitude to their own practice and to evidence. Without these skills, professionals and organizations will find it difficult to provide “best practice”.”\textsuperscript{31} Despite this broad definition, EBM training and assessment focuses often on searching and critical appraisal of original studies.\textsuperscript{27,30} We feel one can question whether these goals are the most relevant and attainable ones for trainees. Glasziou for instance showed, based on work from Kibbon et al and Hersh et al, that answers from students and doctors improved after a searching task, compared to before searching, but in 7 to 14 percent of cases answers went from right to wrong. In another 36 to 48 percent of cases initially wrong
still wrong, after searching. As training of healthcare professionals largely takes place in clinical practice, the question is who should teach EBM to trainees and, more importantly, who should be the role model for adequate EBM behavior in practice. Choudry et al. reported that 32 of 62 identified studies quality of care was lower for physicians with more years of experience, compared to more junior colleagues. This implies that more experienced clinicians may not necessarily be the best EBM role models. Constraints in resources and the complexity and vastness of the available evidence make it extremely unlikely that all healthcare professionals will become EBM experts, operating at a level in which they can identify and analyze the available evidence, evaluate validity and applicability of original articles, and apply the evidence appropriately in the care for individual patients. There is room for diversification in skills, in a structure where all healthcare professionals understand and encourage EBM, have basic knowledge and skills (followers), while a selected group of health professionals, trained as EBM experts, gather, synthesize and apply the available evidence into evidence-based practice recommendations. Ubbink and colleagues proposed such a policy, were EBM should be exerted at micro level, meso level and macro level, supported by professional, educational and managerial role models.

Yousefi-Nooraie and colleagues discussed these issues with 51 EBP teachers from 15 countries and arrived at a consensus conclusion, that formulating clinical questions, searching pre-appraised resources, introduction to systematic reviews and critical appraisal of studies about therapy should be covered in starter level EBP courses, while other critical appraisal topics and quantitative decision-making techniques should be left to more advanced levels. If clinicians rely on - and depend on - pre-appraised resources, such as guidelines, valid and reliable pre-appraised sources and guidelines are even more necessary. Shaneyfelt pointed out that, in general, an improvement of the quality of guidelines is needed. A qualification system for clinical EBM experts, with requirements or expectations of the level of EBM knowledge and skills, could possibly help to reach and maintain high quality pre-appraised resources.

After more than 20 years, EBM has reached the age of maturity, but to make it fully functional, it has to be embedded in a coherent structure for teaching, managing and rewarding health care professionals. Only then will it deliver the anticipated gains in healthcare quality and efficiency, to the benefit of present and future patients.
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