Embedding trials in evidence-based clinical practice
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CHAPTER 1

GENERAL INTRODUCTION
Decisions need to be made continuously in every day clinical practice, either explicitly or more implicitly. Implicit or intuitive decisions are often based on knowledge gained by experience. It is well known that the way in which we derive knowledge from experience could lead to conclusions that are systematically biased.\textsuperscript{1,2}

One could imagine, for example, that an adverse event that happened to a patient after an intervention, stays more firmly etched in the physician’s memory than the hundred times the same intervention was performed before, without any complication occurring. After the physician has applied an alternative intervention dozens of times, without any adverse events occurring, he might intuitively conclude that the new, alternative intervention is safer. Is this wrong?

No, in itself, it’s not. It is perfectly human. If we were be able to appropriately mark everything that happens around us, we would be able to process a huge amount of information now mostly unused. What can be problematic, is an intervention judged as helpful, based on the collective experience of multiple experts, but then proven to be ineffective, or even harmful, when appropriately tested in systematic research.\textsuperscript{3,4}

Overall, it seems unwise to rely exclusively on experience for important decisions in clinical medicine. New and existing interventions should be evaluated based on sound and solid trials of their effectiveness and potential harms. Clinical medicine should be a combination of personal wisdom and experience, amplified and corrected where needed by the rapidly growing body of evidence from scientific research. This integration of individual clinical expertise with the best available evidence and patients preferences, has been introduced as ‘Evidence-based Medicine’ (EBM) in 1992 by dr. Guyatt and his colleagues.\textsuperscript{5}
This thesis consists of a number of research project, centered on ‘evidence-based medicine’. We concentrated both on the generation of evidence, through clinical trials, and the integration of evidence from solid research into clinical practice.

Part 1 focuses on improving enrollment of patients in clinical trials, as this is a major problem encountered in the generation of scientific evidence. Part 2 focuses on the integration of evidence-based decision making in everyday clinical practice, by improving the teaching and evaluation of evidence-based clinical practice.

PART 1: IMPROVING ENROLLMENT OF PATIENTS IN CLINICAL TRIALS

The randomized trial is worldwide considered as the best instrument to evaluate the effectiveness of medical interventions, and, as such, it is a cornerstone in EBM. Optimal and affordable care, both from an individual and from a societal perspective, requires valid and reliable randomized trials, recruiting a sufficient number of participants, to generate the evidence for medical decision-making.

In many randomized trials recruitment is usually slower and more complex than expected. In a cohort of 114 multicenter trials funded by the UK Medical Research Council and the UK Health Technology Assessment Program between 1994 and 2002, less than one-third recruited their original target within the time originally planned, and around one third had extensions.\(^6\)

If the targeted sample size is not achieved, the clinical trial will have less statistical power to convincingly estimate the effectiveness of the medical intervention under study with sufficient precision, which could lead to erroneous healthcare decisions, or suboptimal dissemination of study findings. Reasons for slow recruitment can be found at different levels: a patient may decide not to participate, a clinician can refrain from inviting an eligible patient, and a department or hospital board could decide not to participate. Multiple reviews on barriers and motivators for participation in clinical trials have been published,\(^7\)\(^-\)\(^13\) but it remains uncertain to what extent these results can be generalized to other trials and patient populations. Selection cannot be excluded, with an overrepresentation of either very successful or very unsuccessful recruiting trials in published evaluations of recruitment, as these trials can especially invoke a study of determinants of recruitment.
In Chapter 2 we present the design of the IMPACT study - Improving Participation in Clinical Trials, in which we tried to capture characteristics associated with successful patient recruitment at three levels: the level of the trial organization (Chapter 3), the level of the doctor or hospital (Chapter 4) and the level of the patient (Chapter 5).

In the project reported in Chapter 3 we studied recruitment at the trial level. A questionnaire regarding achieved recruitment and factors potentially influencing recruitment was sent to principal investigators of a cohort of trials registered in the Netherlands Trial Register. We looked at whether recruitment had been successful (at least 80% of the patients was recruited within the timeframe) and at characteristics associated with recruitment success.

In the study presented in Chapter 4 we looked at recruitment at the level of the center. We sent a questionnaire to local coordinators of 17 trials running within the Dutch Consortium for Women’s health and Reproductivity studies, to look at factors influencing recruitment in their center. We looked at factors motivating centre decisions about participation in new trials, the research orientation of the department, and the (perceived) logistic support by research personnel.

Chapter 5 presents an analysis of recruitment at the level of the patient. We performed semi-structured interviews with 21 women invited to participate in a trial in obstetrics. We invited in a 1:1 ratio patients who had participated and patients who had declined the invitation to be enrolled in one of eight trials in obstetrics: the Allo, Apostel I, Apostel II, Chips, WOMB, Ppromexil, Hypitat II and the ProTwin trial.

In Chapter 6 we look at whether recruitment for clinical trials improves dissemination and timely implementation of the trial results. We sent a questionnaire to gynaecologists, residents, nurses and midwives in all centres in Obstetrics and Gynaecology in the Netherlands. For nine trials we asked whether they were aware of the trial results, were convinced by the results, and what percentage of their patients were treated according to the results of these trials. We compared the answers to these questions between respondents who worked in a hospital that had recruited for a trial and respondents who worked in a hospital that had not recruited for a trial.
CHAPTER 1 | GENERAL INTRODUCTION

PART 2: IMPROVING THE TEACHING AND EVALUATION OF EVIDENCE-BASED CLINICAL PRACTICE

A famous quote of Dr. Sackett is: ‘Half of what you’ll learn in medical school will be shown to be either dead wrong or out of date within five years of your graduation; the trouble is that nobody can tell you which half – so the most important thing to learn is how to learn on your own.’\textsuperscript{14,15} Given this fast expansion of medical knowledge, varying in quality and applicability on a patient, an explicit and systematic way to search for answers in daily clinical practice is needed: evidence-based medicine (EBM). Generally, the process of EBM is divided in 5 steps:\textsuperscript{5}

1. Define a clinically relevant question
2. Search for the best evidence
3. Critically appraise the evidence
4. Apply the evidence
5. Evaluate the performance of EBM

Although EBM is nowadays mostly considered an integral part of medical training, integration of (teaching) various steps in busy clinical practice remains a challenge. EBM teaching is an essential element for bringing EBM in clinical practice. In the study reported in Chapter 7 we identified the availability and contents of Teach the Teacher EBM courses in various European countries. As a limited number of Teach the Teacher EBM courses was available, we describe the development and evaluation of a Teach the Teacher EBM e-learning course in Chapter 8. The e-learning course demonstrates in different clinical settings the application of EBM and aims to encourage integration of EBM teaching in daily clinical practice.

In Chapter 9 we look at barriers that refrain clinical teachers from teaching EBM in clinical practice in various European countries. We compared the level of the barriers between countries. As there is currently no standard for evaluating how evidence-based individual health professionals or departments work, Chapter 10 presents a review of the literature for tools to assess the level of evidence-based practice performance of health professionals.
REFERENCES

7. Rendell JM, Merrit RK, Geddes J. Incentives and disincentives to participation in randomized controlled trials *Cochrane Database of Systematic Reviews* 2007. MR000021.