



# **Evidence-Based Medicine**

## **A State-of-the-Art Report**

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## Abstract

EBM advocates the use of up-to-date best scientific evidence from health care research as the basis for making medical decisions. Each time a physician sees a patient he/she is expected to provide effective and efficient care.

Therefore, physicians have to know the facts about the disease (e.g., frequencies, signs, symptoms) and how all these facts are affected by the patients characteristics (e.g., age, sex, family history, risk factors, and other disease). The number of facts and the connection between these facts that a physician uses for medical decision-making is extraordinary. A book about a medical specialty that summarizes the most important information is typically more than 2,000 pages long [10]. In addition to this books exists a great number of published biomedical journals and articles. On the strength of this information flood physicians have a hard task to deliver the best health care without any additional support. EBM tries to overcome this problem and support the physicians in their daily work providing evidence-based clinical practice guidelines (CPGs) including all information needed for the decision-making process for an individual patient.

In this paper we will discuss the main properties of EBM and the requirements of evidence-based CPGs.

# Chapter 1

## Introduction

Evidence-Based-Medicine (EBM) is defined as "the integration of best research evidence with clinical expertise and patient value" [32]. It means the best medical treatment based on the best available research. EBM uses individual clinical expertise of medical practitioners with the best available external evidence from systematic research [18].

Evidence-based CPGs are developed to provide physicians accurate, relevant and updated decision support to facilitate the clinical management of patients. They are aimed at increasing the effectiveness and quality of clinical practice at the lowest possible cost compatible with available resources [28]. They are developed, edited and validated for different purposes (e.g., treatment, diagnosis). In short, CPGs are widely used in the medical domain to support the medical staff in treatment planning and decision-making.

An important factor in this regard are the recommendations in CPGs. They are based on LoEs and SoRs to provide physicians various treatment options. Several definitions of LoEs and SoRs exist. In our context the following definition seems appropriate [9]:

- Levels of evidence (LoEs): The validity of an individual study is based on an assessment of its study design. According to some methodologies, LoEs can refer not only to individual studies but also to the quality of evidence from multiple studies about a specific question or the quality of evidence supporting a clinical intervention.
- Strengths of Recommendation (SoRs): The SoRs for clinical practice is based on a body of evidence. This approach takes into account:
  - the LoEs of individual studies
  - the type of outcomes measured by these studies
  - the number, consistency, and coherence of the evidence as a whole
  - the relationship between benefits, harms, and costs

Various guideline developing organizations have generated their own grading systems to classify the major recommendations in CPGs. More than 100 different

grading systems are in use by medical publications [9]. The process of grading the evidence information in guidelines and journals are described in several publications (compare e.g., [29, 9, 21]).

Guyatt et al. [21] established seven criteria for an optimal grading system:

1. Separation of grades of recommendations from quality of evidence
2. Simplicity and transparency for clinician consumer
3. Sufficient (but not too many) categories
4. Explicitness of methodology for guideline developers
5. Simplicity for guideline developers
6. Consistent with general trends in grading systems
7. Explicit approach to different levels of evidence for different outcomes

CPGs are usually published as paper-based documents, wherefore, they do not allow physicians to retrieve easily and to apply straightforwardly the knowledge to solve a medical problem. Therefore, many different systems and representation languages (e.g., Asbru, PROforma) have been developed in order to obtain a computer-interpretable representation of CPGs (consider e.g., [39, 36, 30, 15]). But the implementation of CPGs in decision support systems depend on the structure, writing mode, formalisation process from text to formal representation, and last but not least of physicians' attitudes towards CPGs [38].

# Chapter 2

## Evidence-Based Medicine

Knowledge in medicine reduplicates every five to ten years. Annually the number of the publications about the different area of medicine is so high that physicians can hardly observe the important articles in his/her specific field. This kind of information overflow influence the physicians in the sense that they are not quite sure about the state of the art in their field and therefore cannot ensure the best primary care. The Evidence-Based Medicine (EBM) tries to overcome this situation with well defined procedures and methods. This chapter gives an overview about the different definitions of EBM and describes the procedure of EBM. The subsequent section presents the types of studies and discuss the evidence information.

### 2.1 What is Evidence-Based Medicine (EBM)

The term "Evidence-Based Medicine" firstly appeared in the medical literature in 1992 in [20]. The EBM movement and the philosophical origin begin in this time area. After the term appeared in the literature, it was followed by many definitions. Last defines EBM as [25]:

"the process of finding relevant informations in the medical literature to address a specific clinical problem, the application of simple rules of science and common sense to determine the validity of information; the application of the information to the clinical question. In short, patient care based on evidence derived from the best available ("gold standard") studies"

In 1996 Sackett [32] also defines EBM as following:

"Evidence-Based Medicine is the *conscientious, explicit* and *judicious* use of current best evidence in making decisions about the care of individual patients. The practice of Evidence-Based Medicine means integrating individual clinical expertise with the best external evidence from systematic research. By individual clinical expertise we mean the proficiency and judgement that individual clinicians acquire through clinical experience and clinical practice. By best available external

evidence we mean clinically relevant research, often from the basic sciences of medicine, but especially from patient centred clinical research.”

This definition from Sackett is the most used one. Here, EBM uses individual clinical expertise of physicians with the best available external evidence from systematic research.

In the past the physicians’ work relied on clinical experience, so that the physician decided what to do, based on his/her clinical experience. Another way was to ask a local expert or look in medical literature to find the information he/she needs. With the principles of EBM the physician has to know that clinical experience has a limited value and he/she needs knowledge about the use of the evidence found in the literature. The experts opinion should be challenged and controled by the literature. The idea behind EBM is assigning a level of evidence to identify and incorporate such evidence into the patient care recommendations and to help physicians to understand how much research supports the clinical decision processes.

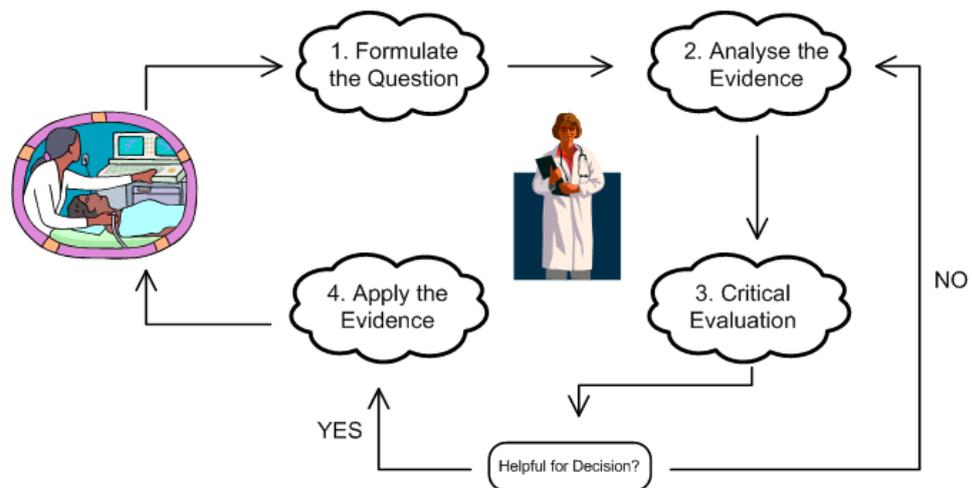
## 2.2 Procedure of Evidence-Based Medicine (EBM)

An explicit approach to EBM in the medicine exists for a short time (e.g., since 20 years). Since the availability of studies, it is possible to explain a way how to use EBM in clinical practice. For a rational EBM we need deliberate accurate measures. Figure 2.1 shows the four important steps in the process of EBM. Raspe describes this process in [31] as following:

1. Formulate the accurate clinical questions
2. Search for the best evidence in the literature
3. Critical evaluation of the found evidence
4. Judging the adaptability of the valid evidence to the current clinical position

An important factor is to formulate the clinical problem in answerable questions, because it is not easy to formulate the correct question in a correct way. A well formed question consists of four elements. In EBM we use the shortcut ”PICO” [31] which stands for ”**P**erson in question, **I**ntervention given, **C**omparison and **O**utcomes considered”. Very important to this points is to be very specific in asking this questions.

- **Person or population in question:** How would I describe a group of patients similar to mine?
- **Intervention given:** Which main intervention am I considering?
- **Comparison** (if appropriate): What is the main alternative to compare with the intervention?



**Figure 2.1:** Procedure of EBM

The four primary points a user of EBM should follow.(Adapted from [41])

- **Outcomes considered:** What can I hope to accomplish?

This methods were developed for helping physicians to solve problems in time and to medicate the patients in the best preferred way. The complexity of a clinical situation may not be a reason for making mistakes because of counterfactual reasoning. The aim of EBM is to give physicians the reliability that they handle correct at the right time.

With formulating the questions using the PICO structure we can see what type of questing we have and what type of answers we need. This brings us to the next step of using EBM in fact searching for the best evidence which provide the best answer. Therefore we have to search for the best source to find the evidence. There are some data collections (e.g. Medline, Embase) which are extensive and not very difficult to use. A very good collection exist also from the Cochrane Collaboration. Four times a year they release a CD-ROM with a database of systematic reviews, a database of abstract of effectiveness, a Cochrane controlled trials register with over 150.000 controlled studies with their abstracts and a Cochrane review methology database [31].

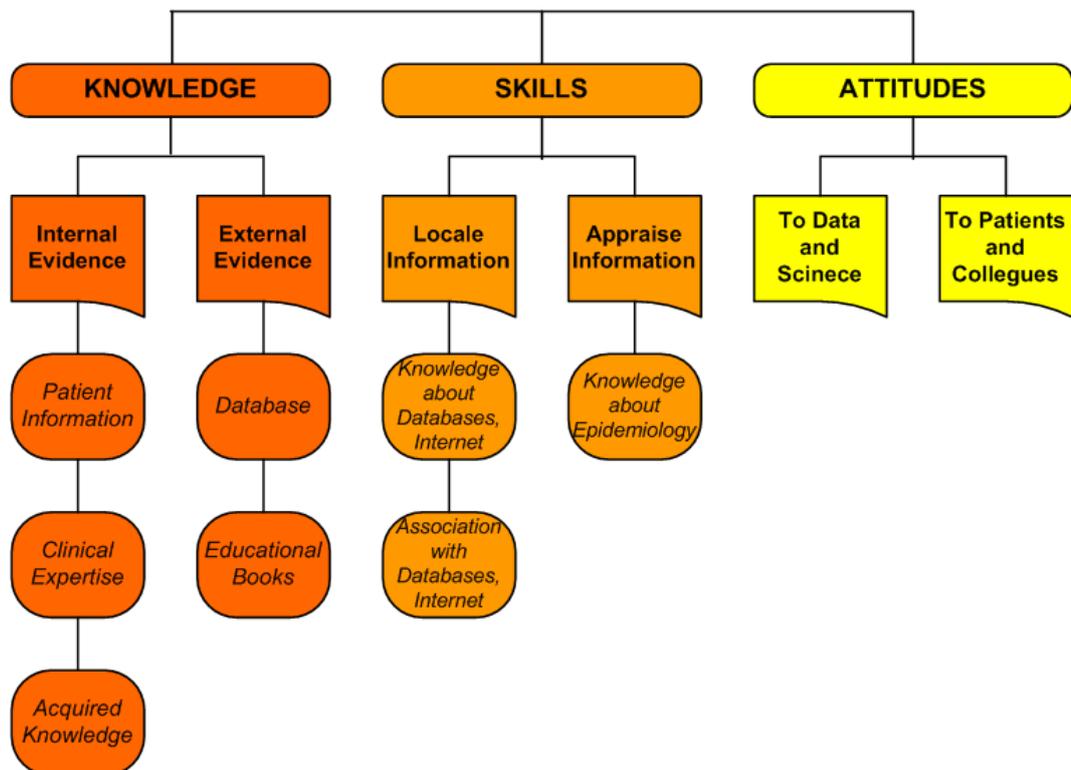
After finding the source it is necessary to locate, appraise, store and retrieve the evidence. The clinicians have to be ensure that the source is updated. Every physician wants to provide the best care for his/her patients. But it is not simple to find the best evidence and to implement it into the clinical practice.

During the critical evaluation of the evidence physicians have to deal accurately. The Oxford Institute of Health Services produced the "Critical Appraisal Skills Programme"(CASP) which helps health personnel to develop skills in appraising evidence about clinical effectiveness. By appraising the articles they have to consider three questions [2]:

1. Are the results of the review valid?
2. What are the results?

## 3. Will the results help locally?

Of great importance of this process is the instruction of the critical appraisal and to include this results with the individual clinical expertise. Of particular importance is to find out if the external evidence can be combined with the individual clinical expertise and if this results can be implemented and used for the respective patient. A way to achieve such evidence is to train physicians who are able to find, appraise, and implement the best external and internal evidence in their practice.



**Figure 2.2:** The three properties a medical practitioner has to own. Knowledge about internal and external evidence means enough information about patients and the use of databases and literature. Skills are helpful in finding and evaluating information with modern electronic media. Critical attitude to data and science, to patients and to the opinion of colleagues are also needed [41]

This procedure of EBM comes to the conclusion that EBM is based on three properties (see Figure 2.2), which a medical practitioner should own. The crucial factor is the **knowledge** about the internal and the external evidence. This means to have sufficient information about the patient and individual clinical expertise. Knowledge about external evidence helps to precisely handle with data bases and the existing literature. Therefore, correctly using and applying the EBM in to the clinical practice demands for certain knowledge. In addition to specific knowledge, certain **skills** are important for finding and evaluating the information particularly with regard to modern electronic media. In addition to specific knowledge, skills are defined from Guyatt et al. For providing an evidence based solution to a clinical question consists defining the problem, constructing and conducting an efficient

search to locate the best evidence, critically appraising the evidence, and considering that evidence, and its implications, in the context of patients' circumstances and values. In order to attain these skills physicians have to pass through an intensive study. High quality health care implies practice that is consistent with the best evidence [22]. Therefore, critical **attitudes** to data and science and also to the opinion of colleagues brings physicians nearer to the definition of EBM from Sackett.

## 2.3 Types of Study

In any single area of medicine exists a great number of published studies. This section presents a brief description of these types of studies, which are an important factor to grade the levels of evidence (LoEs) and strengths of recommendations (SoRs).

### 2.3.1 Systematic Reviews

Reviews have always been a part of the medical literature. Most of these reviews were about assessing the effectiveness of therapeutic interventions. This traditional narrative reviews are explicit about how studies are selected, assessed, and integrated. Such narrative reviews were and are widespread and influential.

Problems with these reviews appear until 1980s with the unadequacies of the process and the consequent bias in recommendations. Small but important effects were missed, different reviewers were reaching different conclusions from the same research base and the findings reported often had less to do with the underlying evidence [7]. The cognition was that extracting the knowledge from combining existing research with traditional methods were not effective. After this insights the decision arrived that systematic reviews are needed to obtain relevant and precise information. A systematic search for research is one of the major differences between a traditional literature review and a systematic review. The aim is to identify as many studies on the topic of interest as is reasonably possible [12].

Systematic reviews are superseding narrative reviews as a way of summarising research evidence. The Joanna Briggs Institute in South Australia and David Evans [12] describe systematic reviews as "summaries of all past research on a topic of interest. Unlike the traditional approach to reviewing literature, they utilise the same principles and rigor that is expected of primary research. As the name suggests, they are systematic in their approach and use methods that are pre-planned and documented in a systematic review protocol." Therefore, the critical appraisal and summarisation of all possible information to a specific issue is called "Systematic Review". In this case "systematic" means the systematic identification of all possible information about a specific issue. It also refers to systematic critical appraisal of the quality of selected studies. Accurate accomplished systematic reviews provide the securest and precise information to a specific issue. They appear at the top of the "Hierarchy of the Level of Evidence" (see Table 2.1). But this does not mean that systematic reviews are automatically of good quality. Problems can arise, if they are done badly. Therefore, they should be appraised critically.

<b>Grade</b>	<b>Description</b>
<b>Level I</b>	Evidence obtained from a Systematic Review of all relevant randomised controlled trials.
<b>Level II</b>	Evidence obtained from at least one properly designed randomised control trials.
<b>Level III.1</b>	Evidence obtained from well designed controlled trials without randomisation.
<b>Level III.2</b>	Evidence obtained from well designed cohort or case control analytic studies preferably from more than one centre or research group
<b>Level III.3</b>	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments.
<b>Level IV</b>	Opinion of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

**Table 2.1:** Hierarchy of the Level of Evidence [12]

### The Need of Systematic Reviews

A physician has to deal with a great number of patients with different problems and he/she has to make many decisions. The factors that affect these decisions and their outcomes are complex and depend on several attributes. Every physician has unique knowledge, values, and experiences. Each patient expects from his/her physician to provide him/her the best medical care. Therefore, if there is one treatment that has shown to be better than another, the physician has to know it, so that he/she can recommend this treatment to his/her patients. To be up to date with this new informations is not trivial. In this case systematic reviews support physicians to keep them up-to-date.

Physicians need wide ranging and good information on the effectiveness of a large number of therapeutic interventions. But the explosion in biomedical publishing in the latter half of the 20th century, with more than 30.000 journals and more than 2 millions articles a year, makes it not easier. In any single area of medicine exists a great number of published studies. This makes it difficult to know which studies should be used as the basis for clinical practice. The result of these studies are often unclear, confusing, or contradictory [12].

High-quality systematic reviews take great care to find all relevant studies published and unpublished. The reviewers assess each study, synthesise the findings from individual studies in an unbiased way, and present a balanced and impartial summary of the findings with due consideration of any flaws in the evidence [7]. With systematic reviews the reviewers attempt to get a clear and consistent picture with sorting the important information from each published and non-published study.

### Process of Systematic Reviews

The development of systematic reviews needs several steps to obtain good and quality results (compare Figure 2.3). In the following these steps are described as [7]:

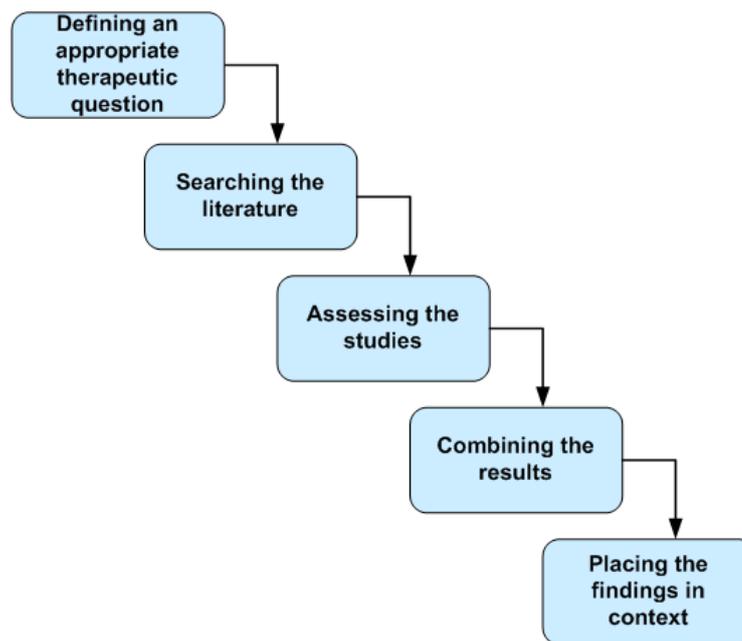
1. **Defining an appropriate therapeutic question:** This requires a clear statement of the intervention of interest, relevant patient groups, as well as appropriate outcomes. These details are used to select studies for inclusion in the review.
2. **Searching the literature:** The published and unpublished literature are carefully searched for all reports of controlled trials of this intervention. For an unbiased assessment, this search must cover all the literature, including non-English sources, conference proceedings, and company reports. The use of only published studies may overestimate the effect of the intervention.
3. **Assessing the studies:** Once all possible study reports have been identified, each study needs to be assessed for appropriate inclusion, study quality and reported findings. The best way to get ideal results is to involve two independent reviewers.
4. **Combining the results:** To obtain an overall evaluation of the effectiveness of an intervention or a treatment, the results of the different studies are combined. Depending on the type of data and the quality of studies, this is achieved by meta-analysis (see Section 2.3.2).
5. **Placing the findings in context:** The findings from this aggregation of an unbiased selection of studies then need to be discussed to put them in context. This will address such issues as the quality and heterogeneity of the included studies, the likely impact of bias and chance, and the applicability of the findings. Thus, judgement is not obviated by the rigour of Systematic Reviews, they are just reduced in impact and made more explicit.

### Critically Appraising of Systematic Reviews

To understand the methods and results of research and to assess the quality of the research we need critical appraisal. Critical appraisal is helpful for deciding if a research is good enough to be used in decision making. It provides a systematic way of assessing the validity, results, and usefulness of published research papers.

Systematic reviews should be critically appraised by users so they can decide whether their methods are valid, assess what the results are saying, and decide whether these results can be applied locally [23]. The most common questions addressed during the critical appraising of systematic reviews are shown in table 2.2 and described below [6].

**Review Questions.** Systematic reviews have to deal with clearly defined questions. This review questions address the population of interest and condition, the intervention, a comparison or control, and finally the outcome measure that



**Figure 2.3:** Process of Systematic Reviews

is to be used to determine effectiveness. These components of the question determine what type of studies will be required to provide the appropriate answer.

**Literature Searching.** The rigorous part of systematic reviews is the location of research addressing the topic of interest. The primary objective of the search is to locate as much of the completed research on the topic as possible. Like all steps in the review process, the search strategy should be documented in sufficient detail to allow others to critique its quality. Usually, systematic review searches include electronic databases but in addition to this, other specialised databases may also be searched depending on the topic of interest. The bibliographies and reference lists of all retrieved articles are searched to increase the likelihood of identifying all relevant studies. Another important factor is to contact experts and professional organisations for identifying missed papers, unpublished or in-progress research.

**Study Selection.** Of particular importance is to decide which studies should be included in the review and which ones should not. Selection of studies for reviews is based on the population, intervention, outcomes, and research method, rather than on the results of the studies. While the question defines the area of interest, it is the study selection that explicitly documents the focus, nature, and limits of the review. This criteria is used to determine if the population, intervention, and outcome measures of a study are consistent with the focus of the systematic review.

**Critical Appraisal of Studies.** The appraisal of the validity of all identified studies is one of the important parts of the systematic review process. The expectation

Focus	Specific Questions
Question	Is the specific purpose of the review stated? Is the review question clearly and explicitly stated?
Literature Search	Were comprehensive search methods used to locate studies? Was a thorough search done of appropriate database and were other potentially important sources explored?
Study Selection	How were studies selected? Are the inclusion criteria reported?
Critical Appraisal	Was the validity of included studies assessed? Was the validity of studies assessed appropriately? Are the validity criteria reported?
Similarity of Groups and Treatments	Are treatments similar enough to combine? Were reasons for any differences between individual studies explored?
Data Synthesis	Were findings from individual studies combined appropriately? Are the methods used to combine the studies reported?
Methods Documented	Are review methods clearly reported?
Summary of Findings	Is a summary of findings provided? Are specific directives for new research proposed? Were the conclusion supported by the reported data?

**Table 2.2:** Checklist for Appraising Systematic Reviews [6]

here is that by excluding lesser quality studies the risk of error and bias in the findings of the review will be reduced.

**Similarity of Groups and Treatments.** If studies are different in terms of their population, intervention or how outcomes are measured, it makes no sense to use meta-analysis. Usually, if treatments evaluated in the individual studies are different, combining these results to obtain an average of the treatment effect will be meaningless. The result is that findings of individual studies, which differ significantly, should not be combined in meta-analysis.

**Data Synthesis.** The objective of a systematic review is to summarise the results from different studies to obtain an overall evaluation of the effectiveness of an intervention or treatment. In this case, meta-analysis is used to provide a framework for a systematic review, where similar measures from comparable studies are listed systematically and the measures of the effect of an intervention are combined. Meta-analyses are useful, if many studies address the same issue and if studies are too small and so lack the power to detect treatment effects, as combining studies increases the sample size and therefore the power.

**Reporting and Recommendations.** The methods used during the review should be reported in sufficient detail to allow replication of the review and critical appraisal of the processes employed.

### 2.3.2 Meta-Analysis

Meta-analysis is a technique to appraise the results of more than one study. Clinical studies are more often too small to get significant information about their results and effects of treatments. Meta-analysis is a statistical evaluation of study-collections on a given subject and it is used to get general results from these different studies [1]. More generally, meta-analysis combines the results of several independent clinical trials to improve the potential for uncovering and studying any differences in available scientific material and to provide a basis for explanations of them [34].

#### Benefits

The relevant advantage of meta-analysis is the possibility to obtain a complete picture about the treatment effects. Davies describes four points to facilitate dealing with practical difficulties and to make sense of effectiveness research [8].

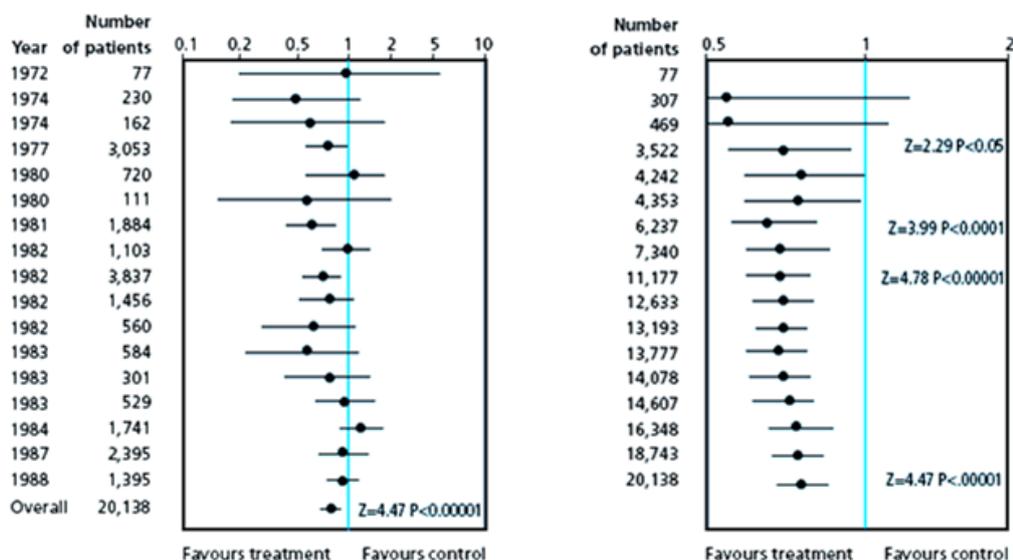
1. **A clearer picture:** Individual clinical trials may mean little, especially when they are small-sized. Small studies tend to be inconclusive and they may show no statistical difference between the treated and controlled groups. But also they may be unable to exclude the possibility of there being a sizeable effect. Aggregating studies in a systematic and unbiased way may allow a clearer picture to emerge. The question to ask is if a particular treatment confers significant benefits when used for specific patient groups. Meta-analysis allows this aggregate picture to emerge.
2. **Overcoming bias:** The danger of unsystematic reviews is that there is plenty of scope for bias. Certain reports are preferred over those without benefit. Meta-analysis carried out on a rigorous systematic review can overcome this danger with offering an unbiased synthesis of the empirical data.
3. **Precision:** The precision with which the size of any effect can be estimated depends on the number of patients studied. Meta-analyses that draw on patients studied in many trials thus have more power to detect small but clinically significant effects, and can give more precise estimates of the size of any effects uncovered. This is especially important when a reviewer is looking for beneficial effects in specific subgroups. Individual studies contain mostly too few patients in the subgroup of interest to show anything. To obtain a clearer picture the systematic aggregation of data from many individual studies are needed.
4. **Transparency:** The advantage of meta-analyses lie in the openness with which good meta-analyses reveal all the decisions that have been taken throughout the process of achieving the final aggregate effect sizes. Good meta-analyses should allow readers to determine for themselves the reasonableness of the decisions taken and their likely impact on the final estimate of effect size.

### Representations of Meta-Analysis

Meta-analysis can be graphically represented in two ways: blobbograms and odds ratio. In the following, we will describe these two techniques [8].

**Blobbograms:** The blobbograms display the findings from each individual study as a blob or square with a horizontal line, which usually is the 95% confidence interval, around the main findings. The size of the blob and the small vertical line vary to reflect the amount of information in that individual study. The length of the horizontal line represents the uncertainty of the estimate of the treatment effect for that study. The aggregate effect size for certain sub-groupings and the overall effect size are also usually displayed in the same figure. (see Figure 2.4).

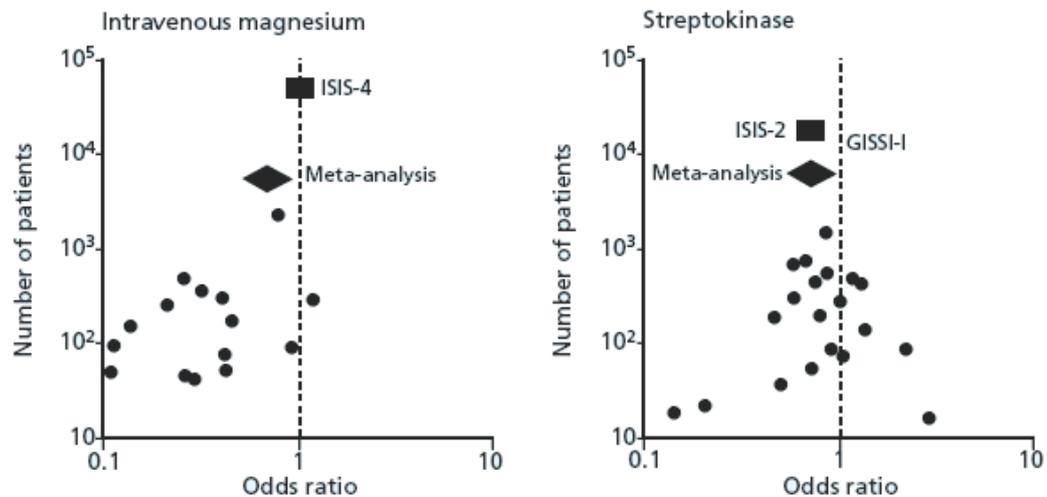
**Odds ratio:** The main measure of effect used in meta-analysis is the odds ratio. It offers some technical advantages when combining data from different studies (see Figure 2.5). For most practical purposes, the odds ratio can be interpreted as though it is a relative risk. For example, an odds ratio of 2 implies that the defined outcome happens about twice as often in the intervention group as in the control group. An odds ratio of 0.5 implies around a 50% reduction in the defined event in the treated group compared with the control group.



**Figure 2.4:** The blobbograms display the findings from each individual study as a blob or square with a horizontal line, which usually is the 95% confidence interval, around the main findings [8].

The basic idea of meta-analysis is to construct a "big study" from many small studies. Each study has a certain measure of information to obtain an objective combination of the data, which come from different and independent randomized studies. The difficulty lies in deciding which sets of studies are combinable [8]. After

the relevant studies have been identified, decisions must be taken about which studies are sufficiently well conducted to be worth including [8]. Good meta-analysis will use explicit and objective criteria for inclusion or rejection of studies on quality ground [8]. A way to assess the probable presence of selection bias is to examine a funnel plot (see Figure ??). If the plot is asymmetrical this shows that the meta-analysis has missed some trials. These are mostly smaller studies which have no effect.



**Figure 2.5:** Points illustrate odds ratio from small and medium sized trials, diamonds illustrate combined odds ratios with 95% confidence intervals from Meta-Analysis of these trials, and squares illustrate odds ratio with 95% confidence intervals from mega trials [8].

The description of unequal data from different kinds is called heterogeneity related to meta-analysis. The main question is to find out the real cause of the heterogeneity. Heterogeneity can be described with the differences of studied populations, by unequal interventions, or by inconsistent study results. Data from smaller studies provide more heterogeneity than large studies [33].

Meta-analyses offer a systematic and quantitative approach to reviewing important therapeutic questions. The reviewer of meta-analyses searches for relevant studies on the basis of predefined criteria to aim for completeness. Found data is evaluated critically and bias, which can exist in the found data, should be considered. Data are represented graphically and are combined quantitative if possible. Healthcare managers and clinicians are now able to appraise meta-analyses for validity and therefore to decide if they are implementable in their daily work [33].

### 2.3.3 Randomised Controlled Trials (RCTs)

For evaluating the effectiveness of studied intervention the best way is to use Randomised Controlled Trials (RCTs). They are experiments in which the efficiency of medicines and medical procedures are tested. In this case treatments, interventions, or enrollment into different study groups are assigned by random allocation rather than by conscious decisions of clinicians or patients. If the sample size is large

enough, this study design avoids problems of bias and confounding variables by assuming that both known and unknown determinants of outcome are evenly distributed between treatment and control groups [42]. RCTs are considered the "gold standard" for determining effectiveness of health care interventions, and they generally held to be the most powerful research design available to assess the effects of mental health care [5]. RCTs are the best way to get effective results but they are very time and labor intensive. It must be pointed out that with RCTs it is possible to obtain unbiased distribution and that they facilitate statistical analysis, but such trials are expensive and sometimes ethically problematic. Like any other research, the results of RCTs should be handled critical [4].

### **2.3.4 Cohort Study**

With cohort studies a group of people are studied, who potentially share one or more characteristics such as common experiences or conditions [11]. The study groups are observed over a time period to describe differences between a condition during an earlier period to a condition at a later period. Prospective cohort studies normally begin to measure relevant indicators of variables prior to an exposure or incidence of diseases. Retrospective cohort studies identify the cohort, their exposure, and outcomes afterward, as a follow-up study [26]. In practice, researchers identify two groups, where one group has a particular condition or receives a particular treatment and the other group does not have such a condition or treatment. For a period of time they are observed by the researchers. At the end the outcomes between the two groups are then compared in the analysis.

### **2.3.5 Case-Control Study**

In case-control studies persons who have a specific adverse effect or disease ("case") are compared with a group of persons without the specific adverse effect or disease ("controls") [26]. In practice, case-control studies are used to establish possible causes for a condition. An existing present condition is analyzed by looking back at the past events to identify causative factors for disease.

### **2.3.6 Cross-Sectional Survey**

Cross-sectional survey is a study in which disease and exposure status are measured simultaneously in a given population. Patients are interviewed, examined, and studied to gain answers about the prevalence of acute or chronic conditions in a population. The data of this study is collected at a single time but they refer to experiences in the past. In a cross-sectional survey a particular population will be observed at one point in time. The researchers collect information from one particular population and compare this data on specific subgroups. The exposure and the outcome are determined simultaneously. It is useful for looking disease prevalence but it is unable to establish a temporal relationship between a presumed cause and an effect [16].

The advantages of cross sectional surveys are that they are cheap, simple, and ethically safe. Another important advantage is also that the results of such studies are relatively quickly available, because information is collected during a finite time period.

### **2.3.7 Cross-over Design**

Cross-over design is a clinical trial design in which patients receive each treatment after a specified or random order. In this design, every patient serves as their own control. This type of design is useful for studying the differences between individual treatments or sequences of treatments [35].

The advantages of cross-over design are that all subjects serve as own controls and error variance is reduced. They also receive treatment and statistical tests assuming randomization can be used.

### **2.3.8 Case Report and Case Series**

A case report describes the medical history of only one patient in a form of an anecdote. A collection of case reports are needed to form case series. Case series are medical histories of more than one patient with defined conditions and treatment, which are reported [16].

Depending on the primary hypothesis or the topic of research the type of the study changes. RCTs are mostly used for treatment whereas cohort or case-control studies are recommended to establish causation. Cross-sectional survey is preferred to establish diagnosis or screening to determine the test values.

# Chapter 3

## Clinical Practice Guidelines

Clinical practice guidelines (CPGs) are "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances." [13]

Evidence-based CPGs for health care follow a rigorous development process and are based on the best available evidence. They exist in various formats, such as text, tables, flowcharts, graphs, maps, and lists. Therefore, the structure of the CPGs is complex and not easy to interpret. A difficult task of the physicians is to correctly interpret the information in this CPGs and to combine this with their own knowledge to derive medical decisions and treatment plans. CPGs extent recommendations for physicians and support them during the decision-making process, wherefore they become a part of clinical practice. Despite these difficulties, CPGs are increasingly used to prescribe how a physician should behave in certain circumstances during the medical treatment [3].

This section describes the guideline development process (Section 3.1) and discusses guideline properties (Section 3.2), which are necessary to develop qualitative CPGs.

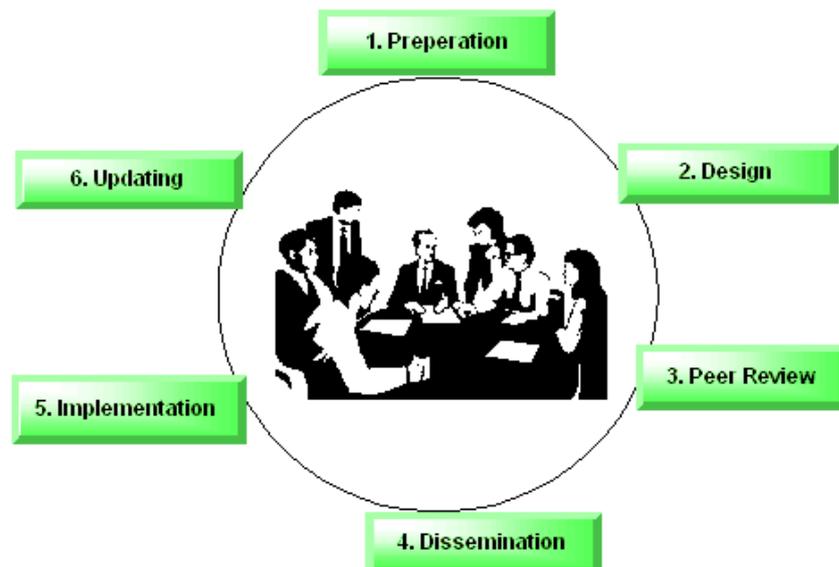


Figure 3.1: Development Process

## 3.1 Guideline Development Process

In order to develop qualitative guidelines the development methods have to be transparent to guideline users, because they can see with confidence that the potential biases of guideline development have been addressed adequately and the recommendations are internally and externally valid. In the following we present an overview of this development process and describe the main factors as shown in Figure 3.1. The information and facts in this section base mostly on [29, 14].

### 1. Preparation

**Topic Selection.** The guideline development process begins with the selection of the appropriate topic to define the main areas the guideline should address. The following criteria have to take into account in selecting topics for guideline development [29]:

- Wide variations in practice and outcome
- High burden of disease
- High health care costs
- High prevalence of morbidity and mortality
- Potential to improve outcomes

**Guideline Development Group.** One of the most important steps on developing CPGs is to convene a guideline development group. This group need to be multidisciplinary, including professionals, patients, and other health care providers. A multidisciplinary group is important to provide expertise from all stages in the patient's journey of care, to locate and critically evaluate all relevant scientific evidence, and to solve practical problems with using the guideline [29]. Membership of the guideline development group are responsible for the formulation of specific clinical questions, grading levels of evidence, and developing the recommendations [14]. The most important skills of a development group are [29]:

- clinical expertise
- specialist expertise (e.g., health economics, social services)
- practical understanding of problems faced in the delivery of care
- communication and team working skills
- critical appraisal skills

**Patient Involvement.** Patients have a specific role in the development group. The presence of patients is important to ensure that the CPGs reflect their needs and address issues that are significant to patients and carers. Physicians and other experts have a different perspective on health care priorities, processes and outcomes from those of patients. Therefore patients can support the group on developing CPGs that reflect their perspectives [29, 14].

**Formulation Specific Clinical Questions.** The clinical questions should be formulated as soon as the development group is convened. The questions have to "clearly identify the population concerned, the intervention under investigation, the type of control used, and the outcome measures used to measure the effectiveness of the interventions" [29]. They are also decisive for the systematic literature search and the development of recommendations by the development group. Questions about interventions can be developed with the patient intervention comparison and outcome (PICO) framework (see 3.2). Questions about diagnosis have to identify key issues specifically relevant to diagnosis test for their accuracy, reliability, safety and acceptability to the patient. Like mentioned above the selection of the key questions is the responsibility of the development group. Therefore they must involve their knowledge and experience to formulate questions addressing the key issues in the area to be covered by the guideline [14].

## 2. Design

This stage of the development process begins with literature searching to identify the evidence for translating the evidence into recommendations.

**Literature Search.** Evidence-based guidelines are based on systematic reviews, (see 3.3.1) therefore the literature search base on an explicit search strategy. There exist several databases (Cochrane Library, Medline, Embase, Guideline International Network, National Guideline Clearinghouse) which are recommended for literature search from several guideline development organizations. To this literature search follows the critical appraisal of the literature. The literature has to be selected with defined including and excluding criteria to cover all relevant aspects of the clinical questions [29, 14].

**Identifying the Evidence.** There are several steps needed to identify the most appropriate data for answering the clinical questions. The identification of the evidence begins with selecting relevant studies (see 3.), assessing their quality, synthesising the results and finally grading the evidence [14]. A key stage in the guideline development process is the assessment of the quality of studies, because the results will affect the level of evidence, which will again influence the strength of recommendations. In this stage of the development process evidence tables play a significant role. They help to identify the similarities and the differences between studies and give information about the characteristics of the study population and interventions or outcome measures [14]. Evidence tables summarise all the validated studies recognised from the literature review relating to each clinical question. These tables are important to facilitate comparing results across studies and ensure that the basis of the recommendations is transparent [29]. On the basis of studies levels of evidence help the guideline developers and guideline users to understand the type of the evidence on which the recommendations have

been based [14]. Forming clear and unambiguous recommendations for any given clinical question is a challenging task. SIGN has described in [29] a concept of considered judgement to facilitate this development process:

- Quantity, quality, and consistency of evidence
- Generalisability of study findings
- Directness of application to the target population for the guideline
- Clinical impact
- Implementability

By means of this concept the development group can summarise their view of the evidence and assign a level of evidence, before forming and grading recommendations.

**Forming Recommendations.** Guideline recommendations are based on the best available evidence, because they are graded to differentiate between recommendations based on strong evidence and those based on weak evidence. This assessment is made on the basis of critical appraisal of the design and quality of each study. Recommendations should be clear, unambiguous and easy to translate into clinical practice. Many users have not enough time to read the whole guideline or they are only interested in recommendations, because they are important for the decision making process in clinical practice. Therefore, they should be clear and transparent. Like mentioned above, translating the evidence into recommendations is a challenging task. The National Institute for Health and Clinical Excellence (NHS) shows in [14] problems that mostly occur during the formulation of recommendations:

- Literature search founded no evidence that answers the clinical question
- Quality of the evidence is poor
- Available clinical evidence is conflicting and of similar level
- The evidence is not directly applicable to the population covered by the guideline (e.g., different age group)
- No published estimate of cost-effectiveness that is applicable to the relevant population

The most disagreements between the group members occur in this part of the development process. Therefore, it should be clearly defined how this disagreements have been handled by the development group.

### 3. Peer Review

All guidelines should be reviewed by independent expert referees prior to publication. The best time for reviewing is during the development process where the draft recommendations of each guidelines can be discussed with health care professionals, patient representatives and others interested in the guideline topic [29]. The aim in this part of the development process is to

ensure that each information has been addressed adequately and that any risk of bias in the development process has been minimised. The main issue of this development phase is to increase the likelihood of a successful implementation of CPGs into clinical practice for the benefit of patients [29].

#### 4. Dissemination

Dissemination means to bring the guideline to the attention of the guideline users. The guidelines should be published in different forms to reach the target group and all relevant organisations. They can be published and presented in medical journals or by means of the world wide web. A deliberate dissemination of guidelines is necessary to be used.

5. **Implementation** The guideline implementation part is also a challenging task. There are several steps needed to convince the user of the advantages of CPGs in clinical practice. There exist no "cookbook" how to present and implement the guidelines, because each implementation strategy is effective under certain circumstances. However, SIGN presents six steps towards guideline implementation to provide a direction, how to overcome these problem [29]:

- (a) Decide who will lead and co-ordinate the team and identify stakeholder representatives for the implementation group. It is often helpful to have a key facilitator for this process. The team should be multiprofessional in composition.
- (b) Determine where you are now. First, you have to know how you are doing and identify where changes need to be made. It is helpful to audit current clinical practice. It is also important to review the local environment considering people, systems, structures and internal and external influences. Through this process it is possible to identify potential barriers and facilitators to implementation.
- (c) Prepare the people and the environment for guideline implementation. It is important to ensure that the professionals are receptive with a positive attitude to the initiative and have the skills and knowledge to carry out the procedures. This requires time, enthusiasm and commitment with good communication and offers of tangible help. It is important also to involve patient groups in planning the initiative so they are involved from the outset and can influence the way that the guideline is implemented into local services.
- (d) Decide which implementation techniques to use to promote the use of the clinical guidelines in practice. This should take into account the potential barriers already identified and use the research evidence on effective strategies.
- (e) Pulling it all together. This requires an action plan for the improvement process. It requires everyone to agree the aims with a named person responsible for the action plan, a time scale identified with contingency plans to deal with any problems along the way.

- (f) Evaluate progress through regular audit and review with feedback to the team. Rewarding achievements is important. Plans may be required to be modified in the light of difficulties or surprises found during the implementation process. It is always important though to celebrate successes and aim for small achievable steps along the way to improve the quality of patient care.
6. **Updating CPGs** Updating CPGs is an important task to provide guideline users the updated and state-of-the-art knowledge. The medical progress causes changes in evidence, benefits and harms, outcomes, available interventions, improvement in current performance, and resources available for health care. Therefore, updated levels of evidence and strengths of recommendations are major quality criteria for the validity of CPGs. The most important changes during the time are described in [37] as below:

**Changes in benefits and harms of interventions.** The actual strength of the benefits and harms can make the existing information in CPGs irrelevant.

**Changes in outcomes.** Since the development of a CPG new outcomes may be identified, which were uncared and not recognized earlier.

**Changes in available interventions.** New preventive, diagnostic, or treatment interventions may have emerged to replace or complete the existing ones.

**Changes in evidence that current practice is optimal.** Guidelines should provide an ideal clinical practice. Therefore, the gap between the ideal and the current clinical practice has to be narrowed using CPGs. There can be changes over time where a guideline is no longer needed.

**Changes in values placed on outcomes.** The values of different outcomes are placed from situation to situation. Currently, in most guidelines costs play not an important role. In future, costs will be considered explicitly in CPGs.

**Changes in resources available for health care.** The increases of the level of available resources over time have to be included in the CPGs.

Guidelines should be updated when new information becomes available. Currently, CPGs are updated every two to five years. This is a problem domain in developing CPGs, because mostly, knowledge in guidelines ages rapidly over time. A new concept to update CPGs is to develop "living guideline", which are updated annually [40].

## 3.2 Quality of CPGs

The positive effect of CPGs in clinical practice was demonstrated by several studies [27, 17]. Therefore, the number of guidelines available to physicians grows rapidly.

This causes that guideline developers have an increasing responsibility to develop guidelines with a set of requirements. They include validity, reliability, applicability, flexibility, clarity, multidisciplinary, updateability, and usability that have been defined in [13] as following:

**Validity.** CPGs are valid if they lead to the health and cost outcomes planned for them. The most important factors for the validity of CPGs are:

- Relationship between the evidence and the recommendations
- Quality of the scientific and clinical evidence
- Means used to evaluate the evidence
- Outcomes and costs of alternative courses of action

**Reliability.** One of the assessment of the reliability of CPGS is that with given the same evidence and methods for the guideline development, two different expert panels produce essentially the same statements. An important factor for the reliability is also that the information in the guidelines are interpreted and applied consistently by different physicians under same circumstances.

**Clinical Applicability.** CPGs should include information about the target population.

**Clinical Flexibility.** Identification of the specifically known or generally expected exceptions to recommendations in CPGs are very important.

**Clarity.** CPGs should be clear, transparent, and easy to understand. Use of unambiguous language, precisely terms, and transparent modes of the presentation are crucial factors. The major recommendations have to be distinguishable, significant on their own and explicitly interpretable.

**Multidisciplinary Process.** The guideline development process should include all representatives (e.g., patients, experts...) of key affect.

**Scheduled Review.** CPGs should include information when a guideline should be updated.

**Documentation.** Usability of CPGs increases if the guidelines are well structured and include information about the involved participants, levels of evidence, strength of recommendation, development methods, and study design.

### 3.3 Evidence Information in CPGs

When discussing the properties of the evidence information in CPGs, we must first look to the methods used to convey information to physicians regarding the levels of evidence (LoEs) that support the major recommendations and the strengths assigned to the recommendations by the guideline developing organizations. Guideline users need to know how much confidence they can place in evidence and recommendations [19]. This section gives an overview about the LoEs and SoRs, which are of particular importance to classify the recommendations.

### 3.3.1 Levels of Evidence (LoEs)

The LoEs identify the similarities and the differences between studies and give information about the characteristics of the study population and interventions or outcome measures [14]. They help physicians to understand the type of the evidence on which the recommendations are based. The tables of LoEs are important to facilitate comparing results across studies and ensure that the basis of the recommendations is transparent [29]. Thus, decision about the LoEs require assessments of the validity of the results of individual studies for important outcomes. Four key elements are of particular importance in grading the LoEs [19]:

**Study design.** Study design refers to the basic study design that can be broadly classified in systematic reviews, meta-analysis, RCTs and observational studies 2.3.

**Study quality.** The quality of individual studies refer to the detailed study methods and execution. Guideline developers should use appropriate criteria to assess the study quality for each important outcome.

**Consistency.** Consistency refers to the similarity of estimates of effects across studies. If there is important unexplained inconsistency in the results, the confidence in the appraisal of effect for that outcome decreases.

**Directness.** Directness refers to the extent to which the people, interventions, and outcome measures are similar to those of interest. For example, uncertainty about the directness of the evidence can occur if the people of interest are older, sicker, or have more comorbidity than the people in the studies.

The above description of the four elements have to be considered in grading the LoEs. For practical purpose, judgement should be made in the context of systematic reviews, but judgement about the overall quality of the evidence and recommendations typically require information beyond the results of a review [19].

### 3.3.2 Strengths of Recommendations (SoRs)

In CPGs recommendations are of particular importance, because they are intended to influence physicians behaviour. Guideline recommendations should convey clear, informative, and helpful information to physicians during the decision-making process. Therefore, they should be distinguishable, significant on their own and explicitly interpretable. The classification of the recommendations are based on the assessment of the study design (see Section 2.3) and the quality of each study. The consistency, clinical relevance, and the external validity of the whole body of evidence is of particular importance in order to assign an appropriate strength to the major recommendations in CPGs [29]. Therefore, guideline developing organizations have to consider a number of factors in grading recommendations as defined in [21]:

- Methodological quality of the evidence supporting estimates of likely benefit, and likely risk, inconvenience, and costs

- Importance of the outcome that treatment prevents
- Magnitude of treatment effect
- Precision of estimate of treatment effect
- Risks associated with therapy
- Burdens of therapy
- Risk of target event
- Costs
- Varying values

The major recommendations in CPGs are graded to differentiate between recommendations based on strong evidence and those based on weak evidence. Evidence-based recommendations are mostly classified in particular grading schemes to provide an unique format at least for guidelines of the developing organization.

# Chapter 4

## Conclusion

The idea behind EBM is to assign a level of evidence to identify and incorporate such evidence into the patient care recommendations. But it is not simple to find the best evidence and to implement it into the clinical practice.

CPGs are increasingly used to specify how a physician should behave in certain circumstances during the medical treatment and decision-making process [3]. But making diagnostic or therapeutic decisions requires a sensitive interpretation of patient data of multiple types and the evidence information. Therefore, CPGs represent the best judgement of experienced clinicians and methodologists addressing the scientific evidence for a particular clinical topic [24].

The evidence information in CPGs cover important factors for the decision-making process. Because, grading the LoEs and the SoRs enhances the practicability and usefulness of CPGs. Therefore, professional societies and other guideline developing organizations developed different grading systems to classify the major recommendations in CPGs. For practical purposes, precise definitions of recommendations improve the use of CPGs in clinical practice [18].

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