Chapter XX

SYNTHESIS OF SCIENTIFIC INFORMATION

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The purpose of clinical research is to improve the quality of care given to patients… including for prevention strategies. Certain fields (therapeutics and in particular drugs) are favored for the development of clinical research studies, if we compare them to the study of prevention, primary care, not to mention so-called “alternative” medicines.

In these privileged fields, the studies are sometimes very numerous. The data are then difficult to access for the practitioner and the care-giver.

Indeed, the number of medical publications is growing but their quality is uneven. It is difficult for a practitioner to know, to evaluate and to assimilate all these new data, and a fortiori to integrate them into his daily practice. Especially since electronic newspapers are multiplying and the quality of the information provided is uneven!

Hence the idea of promoting work allowing the synthesis of information in medicine. Quantitative methods exist - in particular the meta-analysis which is the subject of a chapter of this book. We will rather discuss here the so-called “qualitative” methods, knowing that these, whenever possible, can use and/or benefit from statistical methods of the “meta-analysis” type.

Moreover, the financial constraints in developed countries are such that the so-called "evaluative" approaches justified in the 1980s, particularly in France, the development of these information summaries, with either an individual objective (patient-doctor decision), or collective (political/public health decision).

Finally, the use of EBM (evidence based medicine) to improve medical practice, to disseminate and make accessible scientific information is always a source of questions.

Is it beneficial?...or is it a lost illusion?

The evolution of EBM towards “evidence based management”, even “evidence based decision”…even “managing evidence based knowledge” (1) are questions often debated in Anglo-Saxon newspapers (2) . In concrete terms, the increasing number of good quality published scientific data must be synthesized. All this to better train/inform doctors and better inform patients and healthcare professionals for a decision based on objective data.

The definition of guidelines for clinical practice used in France derives from that proposed by the Institute of Medicine in 1990 in the USA.

Recommendations are “methodically developed proposals to help practitioner and patient seek the most appropriate care in given clinical circumstances”. Care is appropriate when “the clinical benefit it provides outweighs the resulting risks and costs”. This definition implies the ability to quantify beforehand the benefit/risk and cost/effectiveness ratios of a diagnostic and/or therapeutic intervention. The recommendations aim to provide health professionals and patients with an objective summary of the available data in order to help them in their choice of care. They also constitute the preliminary stage in the development of standards or practice guidelines intended for the evaluation, or even the control of professional practice.

Recommendations were developed in the field of health in the 1970s, in North America, then in European countries. An international network, the Guidelines International Network (GIN) was created in 2002 to coordinate efforts in this area.

The development of medical and professional recommendations seeks to respond to the improvement of information for health professionals and that of users of the health system.

The main objective of the recommendations is to set out as clearly as possible which interventions and strategies are appropriate, which are not or are no longer appropriate, and which are insufficiently known. The recommendations can apply to the prevention, diagnosis, treatment or monitoring of a disease. The scope of the recommendations is not limited to medical decision support.

It can also concern the training of health professionals. Information for patients and families must be accessible including its economic, organizational, legal, social or ethical components of medical practice. Recommendations can acquire legal significance when they are incorporated into official texts, circulars, decrees or orders. “Scientific evidence” is incorporated into regulatory objectives. They can help build benchmarks to assess professional. They can guide clinical research by highlighting unexplored or controversial areas of care. This is particularly the case with so-called “alternative” therapies.

The recommendations were initially intended as an aid to decision-making by the patient.

Thus, many recommendations published by national organizations now include a version intended for patients (“paper” version but also sometimes audio or video). It is this principle that is at the origin of the MedlinePlus program, set up by the National Library of Medicine in the USA.

Patients could also be involved in the process of drafting a guideline, but their place remains to be clarified: who should participate? representatives of patient organizations? of consumers? How to assess their representativeness? When should this participation take place? During their development? of their distribution?

I- METHODS FOR DEVELOPING RECOMMENDATIONS

A- Standardized methods

The standardized methods for drawing up recommendations differ according to the importance given to the three possible sources of information: medical scientific literature, expert opinion and investigation (carrying out surveys, in particular concerning practice) and on the means used to collect information and synthesize it. Recommendations must meet quality criteria. A quality grid for recommendations has been validated internationally.

In France, two methods have been proposed to promoters of guidelines: **the consensus conference and the so-called RCP method (recommendations for clinical practice).** Their detailed methodologies are available on the 'Haute Autorité de Santé' (HAS) website. These two methods were initially codified by two American federal organizations, the NIH *(National Institutes of Health)* for the consensus conference, the AHCPR *(Agency for Health Care Policy and Research, now AHRQ, Agency for Health Research and Quality)* for the RCP.

In the consensus conference, the recommendations are drawn up by a group of health professionals, in principle non-experts in the subject, during a public session. For two days, they heard from experts responsible for answering specific predefined questions. This method uses three different models: the judicial model where witnesses (experts) are heard by an "impartial" jury; the scientific meeting during which experts present and discuss their work; democratic debate where each person can express their point of view. The recommendations are written by the jury "in camera" within twenty-four or forty-eight hours of the public session and then presented to the public. This often nocturnal and urgent writing (which also limits the influence of lobbies) is a negative point of this method. The second major criticism is the way in which the scientific literature is taken into account. What means do we have to control what experts say? This is why, as early as 1990, the ANDEM (National Agency for the Development of Medical Evaluation) had requested that, for a consensus conference to be valid, a systematic review of the literature be carried out by people independent of the experts, so that the jury is better informed and prepared. Under these conditions, the methodology of the consensus conference is similar to the RCP.

In the RCP, the key stage is the review of the literature carried out according to predefined and standardized methods (precise definition of the subject, criteria for researching scientific information, selection and analysis of articles, finally criteria for summarizing information), independently of the experts in order to guarantee its quality. The method involves: a promoter (who takes the initiative to draw up recommendations and provides funding), an organizing committee (which specifies the theme and the questions to be resolved, decides on the general organization of the work, chooses the participants in the working group and ensures the logistics of the whole process), a working group (which carries out the analysis and synthesis of the available data, synthesizes the opinions of experts and drafts the recommendations), and finally a reading group which gives its opinion on the substance, form and applicability of the recommendations and provides additional information and expert opinions to the working group. This method is long (at least a year) which is the main disadvantage. It results in documents that are generally of high quality but lengthy. More than documents for wide distribution, the text of these recommendations should be taken as a working document intended to draft simple practice guidelines that can constitute directly applicable quality improvement tools.

B- Specific methodological aspects

Two key aspects in the development of recommendations, the consideration of scientific evidence and that of expert opinion, are the subject of research work.

- Consideration of scientific evidence

It is important to know the strength of a recommendation and the quality of the evidence on which it is based. The concept of level of evidence was proposed at the end of the 1970s by the Canadian Task Force on Periodic Health Examination and then by the US Preventive Task Force to develop recommendations concerning the medical examinations to be carried out regularly in the field of preventive medicine. [3-4].

The level of proof of a study can be defined as a standardized gradation of the scientific validity of the study, according to the quality of its methodology and its realization, the analysis of its results and the relevance of its conclusions. By using a pre-established scale of level of evidence, it is possible to systematically classify the medical literature according to the quality of each study. In this context, randomized controlled trials are superior to cohort studies. They are even superior to case-control studies and any other type of study.

Despite a gain in objectivity and reproducibility brought by the standardized quantification of scientific evidence, there remains a subjective part linked to the judgment of experts. For example, what is the value of several cohort studies with converging results compared to the results of a randomized controlled trial? What value should be given to the results of a meta-analysis of small trials compared to those of a large multicenter trial? How to take into account the opinion of experts when there is no study with a high level of scientific evidence available?

- Quantification of expert opinion

The RAND Corporation has proposed a “nominal group” type method derived from the Delphi method, which aims to define all the possible indications for an intervention in a given pathology: a review of the scientific literature is first carried out on the subject treated, from which an exhaustive list of possible medical indications for the intervention studied is established. This review and this list are then sent to nine experts, general practitioners and hospital-university and liberal specialists in the geographical region for which the recommendations are intended. Each expert assigns a score from 1 to 9 to each indication in the list depending on whether they consider the intervention to be “appropriate” (score = 9) or “not appropriate” (score = 1) in this indication. The assigned scores are then compiled, and the result of this first rating of the list is presented and discussed during a plenary meeting of the nine experts. At the end of this discussion, each expert performs a second rating of the list. The compilation of all the scores assigned during this second rating makes it possible to establish the definitive list of indications in which the intervention is considered “appropriate”, “not appropriate” or “doubtful”. This method results in a repertoire of indications, which can be used as recommendations, or which can be used to build a decision tree [5].

This method, used in Europe [6], has the disadvantage of leading to conclusions that risk being influenced by the choice of experts [7], and in which the respective place of scientific evidence and expert opinion is difficult to place. However, it can be used during the development of a RCP in order to formalize the expert opinion.

II. USE OF RECOMMENDATIONS

The RCP widely distributed in France are accepted by health professionals. A database of French-language recommendations has been under development since 2005, based on the model of what exists in the USA. Apart from the HAS, many learned societies of medical specialties as well as the National Federation of Centers for the Fight Against Cancer have established their own recommendation programs (SOR program). The development of recommendations by such thematic structures raises the question of the difficulty of mastering divergent interests, sometimes institutional and scientific...

The recommendations have also until now mainly concerned the practice of doctors, less often that of other health professionals, often due to a lack of valid scientific information. Without credible and valid clinical research, how can we have objective information to describe the processes of care and their economic or sociological impacts?

The RCPs were seen in France as a means of regulating medical practices, as was the case in the United States in the 1970s. This has sometimes led to confusion between the concept of prescription assistance and that of monitoring practices. Two different logics were taken into account, one for hospital practice, the other for private practice.

In hospitals, the 1996 ordinances established the accreditation of public and private hospitals, according to the Anglo-Saxon model, in which the evaluation of medical practices had, in its initial version, a limited place. This place should be strengthened in the future.

In liberal medicine, the orientation towards the medicalized control of health expenditure was clearly affirmed with the introduction in 1993 of opposable medical references (RMO).

Then, the concept of evaluation of professional practices (combining peer review, Anglo-Saxon peer review, and audit of practices) was proposed. It was a non-punitive professional device for continuous quality improvement.

The law "Hospital, patients, health and territories" adopted in 2009, enshrines the concept of fusion between continuing medical education and the evolution of personal practices to lead to continuous professional development.

Overall the production of RPC is quite considerable to date, in France but also in all European countries.

The study of Internet sites (www.g-i-n.net and www.guidelines.gov) confirms this movement of international production: on these sites, it appears that certain subjects are covered many times in several countries (for example, the asthma in children, treatment of low back pain or heart failure) and others that are largely unaddressed (e.g. first aid care, all

treatments carried out by paramedics and strategies diagnostics). Finally, on Anglo-Saxon sites, recommendations in French are the exception (2 out of 212 recommendations on the "guideline.gov" site in 2007.

CONCLUSION

Medical and professional recommendations aim to respond to demand from doctors, patients and healthcare and funding organizations. This demand grows as the mass of scientific publications increases, health expenditure increases, but also the legitimate desire of the community to obtain optimal quality of care at the best cost. In order for the responses provided by the development of recommendations to be followed by a positive effect, which is still limited today [8] [9], it is necessary they be developed according to a rigorous methodology, even if it must be expensive, cumbersome and restrictive. One of the first studies published more than twenty years ago in the USA, studying the impact of consensus conferences on the knowledge of American doctors of their results [8], shows an impact similar to that of a recent European study relating to the treatment of coronary artery disease [9]: one doctor in five knows the results.

This is why producing good quality recommendations must be done by carefully selecting the clinical theme.

Significant efforts must be devoted to the dissemination of the recommendations, to their transformation into benchmarks of practice, and finally to their implementation. The development of recommendations is essentially a national process, while their implementation is a local process. There is no single solution to improve medical practices. The impact will be greater by combining different intervention methods and taking into account the context of practice (for example, home visits when one is interested in outpatient prescription, opinion leaders in hospital settings).

It should be emphasized that the intervention methods described in the literature are very variable and it is therefore difficult to draw "universal" conclusions. The works published by French teams with methodologies considered valid have had results identical to those of the Anglo-Saxon works. This clearly shows that the recommendations have an impact on practices regardless of the health system within which they are developed. The recommendations also have an educational value through the collective work of health professionals, "decision-makers", representatives of the public. Their effectiveness largely depends on the means that we give ourselves to develop them, update them [10] and implement them [11].

__Annex 1:__ quality criteria for guidelines for clinical practice

Recommendations should be:

1- developed by or in collaboration with groups of practitioners, according to a multidisciplinary process from which none of the parties concerned by the theme must be excluded, so that all points of view are considered;

2- valid, because they are based on all available information: scientific evidence published in the literature, expert opinions, possibly additional investigations (surveys);

3- documented according to an explicit methodology. Recommendations must be reasoned and verifiable. Uncertainties (insufficient scientific data, impossibility of reaching a professional agreement) must be explained. All the means used to draw up the recommendations must be described: documentary research strategy, method of selection and analysis of the literature, grading of the level of proof of the studies retained, grading of the recommendations, names and qualifications of the experts consulted and of the persons having carried out the work, funding;

4- detailed with regard to the clinical situations and the care contexts in which they apply (ambulatory medicine, hospital, operating theatre, emergency services, etc.), the types of patients concerned, the necessary personnel resources qualified, in equipment and structures;

5- specific to a precise clinical situation. Exceptional situations, known or expected, must be identified, thus allowing a certain freedom of action in the application of the recommendations, which defines their flexibility;

6- clear in their wording and in their presentation: they must be easy to use in daily practice and be interpreted in the same way by all the target persons. The terminology used must be adapted to the intended target;

7- applicable in practice: they must be adapted to the means available and specify the human, material and organizational needs (training, planning) that they require;

8- disseminated widely to all professionals (and patients) concerned;

9- regularly revised so as not to become obsolete even though they must constitute a lasting reference. A quality grid containing these different characteristics has been validated internationally and in French. Only specific, national and independent organizations are able to develop recommendations that meet all of these criteria. It was suggested that most recommendations be reviewed every 3 years. Any structure setting up a program of recommendations must determine, a priori, the criteria for choosing the themes of recommendations, the methods of development and dissemination and finally the methods and timetable for revising these recommendations.

Internet Site: http://www.agree.com

Annex 2: *Classification of recommendations according to the American College of Chest Physicians and taken over by ANAES then by HAS (www.has-sante.fr/)*

The degree (grade 1 or 2) of the recommendation is an estimate of the relationship between the benefits resulting from the implementation of the recommendation and its risks and costs. Level A, B or C takes into account the scientific proof provided by the analysis of the literature.
In this classification, level 1C+ appears stronger than level 1B. C+ versus C means that the authors believe that the results of a trial can be safely extrapolated from one population to another, or that the data from observational studies are convincing. Level C, however, means that the evidence is not directly provided by the results of a randomized controlled trial.
In the event of trials with small samples, or contradictory results, or if the studies are of poor quality, the grade always goes from level A to level B. When the event rate is low, or the results are not statistically significant, or the addition of a small number of adverse effects to the treated arm would render the result insignificant, or the importance of the effect is weak, the grade is systematically downgraded from level 1 to level 2.

Annex 3: *Grading of recommendations used by ANAES*

Recommendation A-grade	Recommendation based on scientific evidence established by studies with a high level of evidence (for example: randomized comparative trials with high power and without major bias, meta-analysis of randomized comparative trials, decision analysis based on studies carried out)
Recommendation B-grade	Recommendation based on a scientific presumption established by studies with an intermediate level of evidence (for example: low-powered randomized controlled trials, well-conducted non-randomized controlled studies, cohort studies)
Recommendation C-grade	Recommendation based on studies with a lower level of evidence (for example: case-control studies, case series)

References

1. Strauss S, Haynes RB. Managing evidence-based knowledge: the need for reliable, relevant and readable resources. CMAJ, 2009,180(9)

2. Young C, Godlee F. The BMJ Evidence Centre: a novative approach to healthcare information. BMJ, 2008,337:a2438 doi:10.1136/bmj.a2438

3. Canadian Task Force on the Periodic Health Examination. The periodic health examination. Can Med Assoc J,1979,121:1193-233.

4. Battista RN, Fletcher SW. Making recommendations on preventive practices: methodological issues. Am J Prev Med,1988,4:53-67.

5. Brook RH, Chassin MR, Fink A, et al,. A method for the detailed assessment of the appropriateness of medical technologies. Int J Technol Assess Health Care,1986,2:53-63.

6. Nicollier-Fahrni A, Vader JP, Froehlich F, et al. Development of appropriateness criteria for colonoscopy: comparison between a standardized expert panel and an evidence-based medicine approach. Int J Qual Health Care,2003,15:15-22.

7. Fraser GM, Pilpel D, Kosecoff J, et al. Effect of panel composition on appropriateness ratings. Int J Qual Health Care, 1994, 6 : 251-5.

8. Jacoby I, Rose M. Transfer of information and its impact on medical practice: the US experience. Int. J. Technol Assess Health Care,1986,2:107-15

9. Hobbs R. Erhardt L. - Acceptance of guideline recommendations and perceived implementation of coronary heart disease/ disease prevention among primary care physicians in five European countries : the Reassessing European Attitudes about Cardiovascular Treatment (REACT) - Family practice 2002;19:596-604

10. Shekelle P, Eccles M, Grimshaw JM, et al. When should clinical guidelines be updated? BMJ, 2001,323:155-7

11. Durieux P. Comment élaborer l'état des connaissances pour contribuer à améliorer les pratiques cliniques ? In Matillon Y, Maisonneuve H. L'évaluation en santé: de la pratique aux résultats. 3ème édition. Paris: Médecine Sciences Flammarion;2007