Clinical guidelines at stake

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> The knowledge imposes a pattern, and falsifies, for the pattern is new in every moment and every moment is a new and shocking valuation of all that we have been.
> —*East Coker*, T.S. Eliot

Medicine is not a science: it is a cultural product. As such, the way it is practiced and conceived is much affected by cultural contexts, academic traditions, politics, personal interests, the health industry, experts' and medical bodies' opinions, journalists and medical publishing companies. Obviously, science and research have played and will continue to play a key role in the development and progress of medical knowledge. Science, however, proceeds slowly, requires the test of time and relies on strict methodological principles and in personal integrity; briefly, good science is at stake in a world dominated by technolatry[1]: a self-imposed commitment for continuous innovation within an industrial culture dominated by planned obsolescence and profit increase for the myriad companies that live on the global health market.

Evidence-based medicine was launched to encourage a scientific and proof-based approach to medical practice.[2] As an ideological movement, it has had a significant impact on how doctors read the medical literature, how clinical research should be planned and how new concepts and therapies are scrutinised before being implemented. However, because medicine, in opposition to science, requires bedside decision making, it cannot rely only on hard data. First, because in many domains, such hard, class A data are not available in many instances. Second, the robustness of the data may be challenged by new findings. Third, because the clinical setting is much more complex than the scenario created by clinical trials that, in order to obtain meaningful conclusions, oversimplify the decision-making process through strict inclusion and exclusion criteria. Fourth, because the acquisition and implementation of new knowledge is a difficult multilevel process, involving researchers, sponsors, publications and expert criticism. Fifth, because scientific advance is fragmentary, whereas clinical practice is an integrative endeavour. In short, medical practice takes place in an environment of relative uncertainty where doctors are supposed to perform according to 'the best evidence available', a sentence that refers to the use of the evidence that is judged to be scientifically sound according to consensus appreciation by different experts, in different clinical, economical and intellectual scenarios.

Clinical guidelines were developed to build a two-way bridge between the demand for a radical scientific approach to medical practice and the inherent difficulties to adopt it at bedside. Their main objective would be to support doctors' decisions by identifying the most scientifically based medical practices, thus reducing the heterogeneity of clinical care for the benefit of patients. Although the history of guidelines dates back to the late 1960s,[3] in their modern version, they grew up in parallel to evidence-based medicine that introduced new concepts on how guidelines should be written and appraised.[4] Clinical guidelines would compile and rank the available peer-reviewed information on the pathophysiology, diagnosis and therapeutic approaches to specific diseases in order to facilitate and improve the decision-making process by making the most appropriate recommendations.

In the process of drafting and implementing clinical guidelines, however, some unforeseen problems arise. First, it is not always clear how panellists are selected leaving open the possibility that bias is introduced from the start if like-minded experts are chosen. Despite evidence-based medicine places expert's opinion in the lowest rank, paradoxically, guidelines are usually written by people who have worked and carried out some meaningful research in the field. Unfortunately, this creates intellectual conflicts of interest and we can never be sure about equal weight given to people from other disciplines with experience in methodology. Second, disease definition has been a matter of debate in cases in which numerical thresholds are considered (ie, hyperlipidemias, osteoporosis, hypertension). Lower and lower thresholds for diagnosis and treatment are being proposed without considering the potential harms of overdiagnosis and increasing the target population for pharmacological or surgical treatment. Moynihan *et al*[5] reported the majority of panels propose definitions that increase the number of individuals considered to have disease. Most of these 'widening the spectrum of disease guidelines' were written by panellists disclosing financial ties to pharmaceutical companies. For example, lowering diagnostic thresholds had been proposed for hypercholesterolaemia, depression and arterial hypertension. The corresponding proportion of panellists with ties with the industry for these three conditions were 88, 67 and 82%, respectively. Third, in these days no one probably works for free ('for love to art', we say in Spain) and most current guidelines have been sponsored by companies with financial interests in the diagnosis and treatment of the condition under study. In a recent survey of 16 influential guidelines on 14 common conditions, the average proportion of panellists with ties to companies was 75%. An even greater proportion of panels were chaired by people with ties.[5] Fourth, there has not been a truly global international effort to build up consensus guidelines, and different national scientific societies have proposed their own guidelines. These amount to at least 10 in the case of differentiated thyroid cancer (box 1). Finally, different subspecialties may play complementary roles in the treatment of a single condition and this may also pose also conflicts of interest. For example, German nuclear medicine doctors[6] do not agree on the relatively restricted indications for the use of radioactive iodine (post-thyroidectomy ablation

Box 1 Currently available clinical guidelines for the management of differentiated thyroid cancer*

American Thyroid Association
American Association of Clinical Endocrinologists
British Thyroid Association
European Society for Medical Oncology
German Association of Endocrine Surgeons
British Association of Thyroid and Endocrine Surgeons (BAETS)
European Thyroid Association
Latin America Thyroid Society
Croatian Thyroid Society
French Society of Endocrinology
*No mention is made to subguidelines concerning lymph-node management, invasive cancer or specific therapies (ie, radioidine, thyroxine)

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and body scans) in the management of differentiated thyroid cancer proposed by the American Thyroid Association guidelines,[7] nor do experienced surgeons who rely much more on thorough specialised surgical treatment.[8–10]

Health medicalisation may lead to increases in drug and treatment side effects and even deaths. The enthusiastic acceptance and dissemination of the European Society of Cardiology guidelines on the perioperative administration of β-blockers in non-cardiac surgery for individuals at risk of postoperative cardiac events may have resulted in many deaths. The story has been well covered for over 2 years by cardiology news journalist Larry Husten. According to his recent publication in *FORBES*,[11] treatment recommendations by the European panel of experts were biased because not all the trials were included in the initial meta-analysis and because fraudulent databases were used in the study. The overworked and 'overpapered' chair of this research on β-blockers has been charged of creating fictitious data and breaching academic integrity. When independent UK investigators looked at the evidence, including in their analysis only the secure trials, they found that β-blockade was associated with a statistically significant 27% increase in 30-day all-cause mortality.[12] Their conclusion is iron clad: "Guideline bodies should retract their recommendations based on fictitious data without further delay".

Harm to patients may also come from not taking into account the side effects of new diagnostic or therapeutic tools when applied massively as a result of expert recommendations. This appears to be the case for prostate cancer screening with PSA, screening mammography or the implementation of the new expensive anticoagulants. These are currently being marketed aggressively through different national scientific societies sponsored by drug companies despite over 500 deaths having already been reported to be associated with dabigatran administration and hundreds of lawsuits been filed with trials expected to start early this year.[13] Needless to say, the 'cholesterol issue' is burning again after North American bodies recently published guidelines asking for lowering once more the threshold for statin administration almost doubling the target population.[14] The majority of panellists including the chair declared industrial ties.

Potential harm to patients from guidelines does not only ensue from bias due to financial ties of panellists, fraudulent research or overtreatment, they also derive from intellectual conflicts of interest and investigators bias going from good faith-biased interpretation of the results to conscious attempts to mislead.[15] Established opinion leaders often ignore or disregard emerging innovative concepts developing far from their environment. In 1984, after two failed previous attempts to publish our findings in respected internal medicine journals due to what we believed was biased peer reviews, our team reported for the first time that intravascular catheters could get contaminated from bacteria reaching the catheter hub at the time of its manipulation and then migrating down the catheter lumen to cause bacteraemia.[16] These observations challenged the widespread belief held by global experts, that intravenous catheters did get contaminated from microorganisms present at the skin entry site and migrating downstream over the external catheter surface (extraluminal route). It took 9 years to see the first US publication on the endoluminal contamination route,[17] and it was not until 2001 that the US guidelines included prevention recommendations regarding hub contamination.[18] This is a first-hand experience of intellectual conflicts of interest that undoubtedly played a major role in delaying the adoption of appropriate preventive measures against catheter-related sepsis, thus harming thousands of patients.

To improve the quality and thoroughness of clinical guidelines, the Institute of Medicine has published a 300-page document (!) containing sound proposals to reduce financial and professional conflicts.[19] Unfortunately, these admonitions have not met great success. Moynihan *et al*[5] reported that there was no difference in the proportion of panellists with conflicts in guidelines written before or after the Institute of Medicine recommendations. They found similar proportions of members disclosing industry ties (76% was the average across 2012 panels; 74% was the average across pre-2012 panels) and similar proportions of panel publications widening definitions (4 of 6 of 2012 publications; 6 of 10 of pre-2012 publications). Professional conflicts of interest are also reflected in 'panel stacking', meaning that only members belonging to the same school of thought are recruited. A notable example is the industry-sponsored current guideline of the American Thyroid Association for the management of differentiated thyroid cancer,[7] which is a source of permanent controversy.[10] Thus, the issue is far from solved and continues to attract much interest as shown by recent reports, coming from professional organisations, dealing with integrity in guideline drafting.[19 20] Meanwhile, as Greenland has put it: *openness of journals to unpopular research and strenuous debate remains the primary line of defence against information abuse and distortion.*[15]

The executive committee of the American College of Chest Physicians has developed a triple strategy for improving the quality and reliability of clinical guidelines: first, place equal emphasis on intellectual and financial conflicts; second, a methodologist without important conflicts of interest should have primary responsibility for each chapter; and third, only panel members without important conflicts can be involved in developing the recommendation for a specific question.[21]

The *BMJ* has taken a well-founded critical approach to the way guidelines are currently drafted and is backing an international 'Guideline Panel Review' working group. In a recent article, Lenzer *et al*[22] have taken a firm position against conflicts of interest and have presented evidence to support the need for in-depth review of the way panels are constituted in order to place patient's needs foremost. Proposals made by this group include a drastic reduction in the proportion of panellists with conflicts of interest, incorporating methodologists, including other stakeholders (patients, representatives, public health groups) and including explicit comments on areas of uncertainty and comments made by dissenting minorities within the panels. From a methodological point of view, Vandvik PO *et al*[23] have publicised an online tool for drafting and updating clinical guidelines that may be of interest to those planning creating clinical guidelines in the future.

Guidelines are and will continue to be an important scientific instrument to help physicians taking the best decisions according to the current state of science in many fields of medicine. There are not meant, however, to be absolute rules with legal implications because they are the result of a complex drafting process involving schools of thought, conflicts of interest, industrial lobbying and dealing with areas of uncertainty and rapidly evolving concepts from research. Professional societies and medical bodies embarking in publishing guidelines should be aware of the potential harms that can be inflicted on patients by widening target populations or making arguable recommendations. Accordingly, they should proceed only after considering the ethical issues involved and critical comments of various independent experts to ensure their integrity and value. They should place the patient's needs foremost.

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