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REVIEW ARTICLE

A plea for a more epidemiological and patient-oriented pharmacovigilance

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Abstract The present work has the main objective of summarizing the history of pharmacovigilance and the associated methods and legislation and of showing how it could/should be reformulated in terms of a transition from a drug-centered to a patient/population-centered approach. The recurrent emergencies associated with new drug molecules raise many questions about the efficacy and efficiency of methodological tools as well as the role of regulatory systems. Drugs cannot be considered as an independent variable: the evaluation of all their effects must take into account the real contexts in which they are used and which affect not only their efficacy but also their tolerability and safety. Specific emphasis is given to recent and promising developments focused on the participation of patients and populations as key actors in producing knowledge that could technically integrate what has been produced so far and allow the evolution of surveillance from a role of controlling severe adverse reactions attributable to individual molecules to one of promoting a comprehensive assessment of the benefit/risk profile of drugs as they are utilized in society.

Keywords Pharmacovigilance · Patient-centered care · Participation

This review represents part of the work required for the fulfillment of the Doctoral thesis of Veronica Scurti as a PhD student of the Open University, UK.

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Framework and objectives

Over the past 50 years, the scientific and regulatory literature directly or indirectly referring to the area of drug surveillance has been an important protagonist of pharmacology, public health, epidemiology, and clinical debates. Greater attention and more publications have coincided with events related to severe adverse reactions (SAR) of particular relevance and impact, such as the list, far from being exhaustive, in Table 1.

Whatever the terminology with which SARs are defined and documented in clinical trials, in spontaneous reports, or in any kind of register, their operative definition is clear: they are either cases, clusters, groups, or populations in which the expected outcome of a certain pharmacological intervention, registered and marketed on the basis of a favorable or acceptable risk-benefit (R/B) balance, turns into a documented observation of a reversal of the balance, requiring a more or less drastic modification of the drug status with respect to its prescription and/or marketing.

Against the background of major recent reviews [1–4], the aim of this paper is to explore if and to what extent the overall scenario requires some degree of cultural and methodological discontinuity in the intent, and therefore the application, of pharmacovigilance (PV). The intent is not to deny or question its relevance and substantial objectives but to discuss and outline a development that allows its deeper integration into the current reality of medicine and society.

Listening to the history of PV

The essential chronology proposed in Table 2 recalls the key regulatory and institutional steps that have allowed and promoted the development of PV, whose main strategies and methodological tools are represented in Fig. 1. The

Table 1 The history of pharmacovigilance in terms of sentinel events

Drugs	Severe adverse reactions	Year of withdrawal
Thalidomide	Teratogenicity	1961
Practolol	Oculo-mucocutaneous syndrome	1976
Phenacetin	Nephropathy	1980
Benoxaprofen	Jaundice	1982
Tolcapone	Hepatoxicity	1998
Trovafloxacin	Hepatoxicity	1999
Cisapride	Cardiac arrhythmias; QT prolongation	2000
Cerivastatin	Rhabdomyolysis	2001
Rofecoxib and valdecoxib	Myocardial infarction	2004–2005
Rosiglitazone	Myocardial infarction	2010
Sibutramine	Cardiovascular diseases	2010

The Table presents as examples only a few drugs whose withdrawal provoked heated debates in the media (and therefore within public knowledge) and not simply restricted to the medical profession

comments that follow try to summarize what has been learned from this long and complex history.

An overall evaluation of the available literature on PV concerning its methodology, recommendations, and regulatory aspects must point out the substantially repetitive and redundant content about what could or should be done to avoid the recurring events that demonstrate the failure of the current surveillance techniques. These events are discussed each time in terms of the ineffectiveness or inefficiency with which SARs are prevented or identified in a timely way. The methodology of PV could in fact already be considered complete at the end of the 1970s or at the latest in the early 1980s. The periodical recognition of the unsatisfactory status of PV cannot be attributed to the lack of instruments but points to the lack of coherent and effective policies [5–8].

To provide a more concrete description of the distance between what could or should be changed and what actually happens, it may be helpful to compare the development of the PV area with the field of clinical experimentation. In the 1970s and 1980s, the "discovery" of the importance of changing the paradigm (rather than simply adjusting the study design or size) in terms of representativeness of populations led to the era of population trials and of large multicenter and increasingly international networks. This also obviated one of the first reasons for PV, which was to compensate for small, non representative trial populations, which did not allow for sufficient highlighting of safety aspects [9].

The establishment of systematic reviews in the most critical areas of therapy further emphasizes how little technological innovation has affected PV: in the classic

Table 2 Main regulatory steps in the history of pharmacovigilance

Year	Description
1937	Food and Drug Administration starts to register adverse drug reactions following a few sudden deaths due to poisoning by an elixir of sulphanilamide (with diethylene glycol as vehicle).
1961	The tragedy of thalidomide malformations represents a turning point in the perception of safety problems and of the risk of insufficiently controlled market approval [5].
1961–65	Following the thalidomide disaster, national centers monitoring adverse drug reactions (ADR) develop in Europe.
1963	Following the thalidomide disaster, the Committee on the Safety of Medicines (CSM) designed to monitor new drugs was set up in Great Britain; for 40 years CSM reported to the UK Licensing Authority on drug quality, efficacy, and safety. In 2005 it was replaced by the Commission on Human Medicine.
1963	The World Health Assembly adopted a resolution (WHA 16.36) reaffirming the need to give more attention and surveillance to ADR.
1968	WHO launches the Pilot Research Project for International Drug Monitoring, which was subsequently developed as the WHO Programme for International Drug Monitoring, currently coordinated by the Uppsala Monitoring Centre in Sweden.
1971	A WHO Consultation Meeting formalizes the need for national centers for drug monitoring and for reference centers in charge of further studies on drug-related problems.
1980	The Council for International Organizations of Medical Sciences (CIOMS) launches a program for drug development and use that includes recommendations (to policy makers, drug industries, governments, academics) to improve the exchange of safety information between drug industries and regulatory agencies.
2001	EudraVigilance is an international network set up by EMA that includes all reports of ADR to the drugs authorized in the European Union, forwarded by regulatory agencies and by drug industries in the EU.
2005	The Risk Management Plan is introduced by EMA.

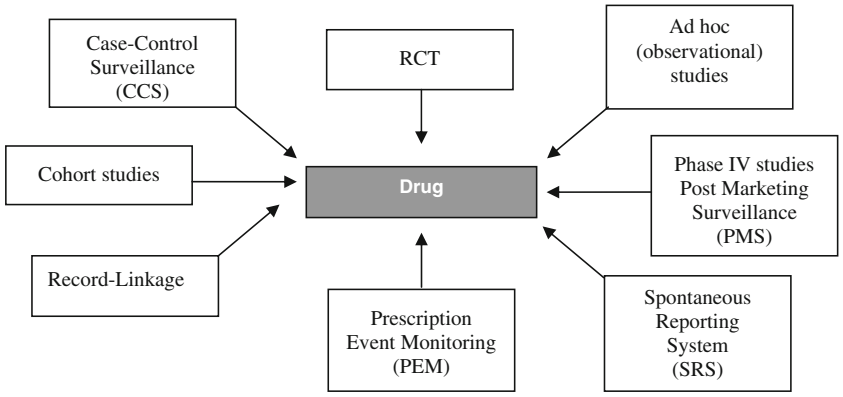

Fig. 1 Synopsis of pharmacovigilance strategies and methodologies

benefit/risk (B/R) ratio, the B variable dominates the picture. Interestingly, however, the R component has never become an object of regular interest even in the field of systematic reviews (nor is this for methodological reasons) [10].

While a partial explanation of the unsatisfactory efficiency of PV might be that professionals have little motivation for documenting "adverse events," in the early days of PV, key players in the field had already underlined broader and more widespread structural and cultural problems [11, 12].

The "Seven Pillars of Foolishness" [13] represents the most clear diagnosis of the interplay of (most often nonmedical) factors that may allow PV to be transformed from a separate discipline of vigilance into an activity capable of taking responsibility for the safety aspects of drugs or—better still—for the B/R profile attributable to real populations.

An important (forgotten? planned?) indicator of the secondary importance attributed to the monitoring of R is the size of the economic resources allocated, which are orders of magnitude lower than those available for clinical trials. Even the recent proposal of risk management strategies by the EMA to monitor the post-registration life of molecules for which insufficient documentation is available epitomizes this discrepancy [14]. This is all the more suspicious in light of the well known fact that pressures and conflicts of interest are increasingly present in the market context and that they are even more widespread and effective than those emerging in the controlled experimentation phases; one of the most recent cases is a model of this [15].

In the perspective of this paper, a last (but not least) difference between what "should be" and actual reality should also be stressed. While the medical and pharmacological literature (and culture) recommends the promotion of patients' participation because of the value of their subjective viewpoint in the specific evaluation of quality of care and life, the same does not happen so often in the area of PV literature. Quite interesting and original exceptions to this rule are represented by a few "narrative" texts concerning the particularly controversial (at least thus far) sector of psychoactive drugs [16–20].

The narrative of the history of patient populations emphasizes the importance and the feasibility of broadening the domain of PV competencies and techniques beyond strictly clinical-pharmacological and regulatory actors and objectives. Transferring this innovative paradigm of research and language into current practice, however, is far from easy. Qualitative methodology, applied with formal controlled techniques (see the whole spectrum of interviews and questionnaires), is undoubtedly interesting but definitely reductive in terms of wide applicability. An overall evaluation of its role in the generation of innovative and representative knowledge documents its limits and explains why it can hardly be recommended as an essential element at the regulatory level [21–24].

Why a broader scenario for PV?

The implications of what has been said so far can be summarized in a statement that can be assumed to be widely shared, at least conceptually, but that is easily disregarded in clinical pharmacology and drug epidemiology [25, 26] and even more in PV: drugs (and their use) cannot be considered primarily "objects" to be studied per se, but rather as "tracers" of health needs and policies, prescribing attitudes, and market exigencies, i.e., of the way medicine and public health goals are perceived and pursued in society.

Research needs flexibility to produce relevant knowledge

Any evaluation technique or strategy strictly centered on drugs is doomed to provide not only partial but also misleading information, insofar as it will tend to view the context of use either as a secondary variable that is only marginally relevant for the production of knowledge and decision-making, or, worse, as a powerful confounder. The challenge of accepting this new framework is undoubtedly a difficult one, but it cannot be avoided when addressing the problem of the transferability of the "registered" B/R profile of a drug to the patients and populations and problems that are the real world.

Let's flashback again to the 1980s, which saw the change in paradigm for the methodology focused on the B side of drugs (see above). This development generated the now well established (with some rigidity and all its limits) culture of evidence-based medicine (EBM). The large population trials run by intra- and intercountry-wide networks radically changed the scenario of experimental evaluation, with a substantial transformation of the "benefit" component of the B/R ratio, both because efficacy measures could increasingly be represented by hard endpoints with clear relevance in terms of public health and because events more directly classifiable as safety evaluations could already begin to be available in phase III (traditionally and normatively defined as reserved for clinical efficacy evaluation). The case of the comparative evaluation of the safety profile of thrombolytics obtained in clinical trials on the basis of systemic and/or cardiovascular hemorrhagic complications may be taken as a model of this [27–31].

The same decade may be further characterized as one of the periods with less normative activity and more independent scientific productivity, with an impact on most major pathologies. It should be stressed however that it is precisely the strictly medical objectivity of the results obtained that fails to encourage attention to the participatory (or community-oriented) aspects of the management-evaluation of therapeutic choices.

However, by the end of the 1980s—for very different, almost opposite reasons—society and individuals acquired a protagonist role in two crucial areas that closely linked the evolution of knowledge and of roles within medicine to some deeper value reference categories within society. For one, it was the participation of women in determining the focus and priorities of research in areas of direct concern in their lives, particularly in the fields of breast cancer, prenatal diagnosis, and hormone replacement treatments [32–34]. For another, it was the role assumed by the gay communities claiming their right to be "subjects-promoters" of experimental appraisals of therapies for AIDS, the disease that produced a profound crisis in the credibility and confidence of medicine [35, 36]. This is clearly not the place for a detailed history of these complex areas. It should however be emphasized that methodology and norms are forced to be flexible to the point of changing radically when society begins to perceive the values under discussion and actively participates, even in the early phases of the decision process, which are normally reserved to technical and institutional actors.

The "global" contexts of PV

The experimentation with autonomy and independence in clinical and epidemiological research that took place during the 1980s would soon come into conflict during the strongly controversial and contradictory period of the 1990s. During this time, the health sector came to reflect the deep evolution that has taken place in economics (an obvious mandatory point of view for a discussion on drugs) and that adopted as a catch phrase the rigorously nonscientific but strongly suggestive term "globalization" (Table 3) [37–42].

The formulation of a common normative framework is overdue, particularly because it involves goods that directly influence people's lives and health. Efficacy is ensured more effectively by following rules that promote, protect, and control data reliability and accountability. However, the ambivalence of a legislation (GCP-ICH) focusing entirely on the "products" to be registered is obvious: the research objects are the drugs, rather than the problems to be solved through a variety of means including drugs. Parallel to this legislation, a more general framework of investments reducing public contribution has developed, hence reducing the autonomy of research groups that are not dependent on "commercial" investments, i.e., those whose primary objective is obviously the creation and fruition of market areas, rather than research on unmet public health needs.

Evidence-based medicine constituted a substantial step forward towards structuring a widespread culture of responsibility by favoring interventions whose efficacy is systematically and cumulatively assessed, beyond the results of individual studies. Nonetheless, the risk of dependence of this comprehensive knowledge on the availability of individual results derived from clinical trials that are mainly promoted and carried out for drug registration is immediately apparent. Furthermore, although the evidence is based on "experimental" efficacy, the claim is that it will be able to be transformed into guidelines for long-term practice in very heterogeneous contexts of care and in populations only very partially represented in clinical trials. In the ensuing B/R ratio, the R component has inevitably and concretely taken second place (particularly if R is considered to go beyond drug-related SAR).

It is well known that while procedural rules were being enforced, conflicts of interest (CI) started increasing. Notwithstanding the reports, the scandals, and all the initiatives undertaken to check for CI through authors' "declarations," the situation does not appear to have improved over the years. Some of the most dramatic episodes of SAR belong to the epoch of perfect procedural control over clinical trials. What happened for coxib [43, 44], antidepressants [45], and antipsychotics [46–48] (to quote some of the most widely known cases) shows in fact that CI have involved regulatory agencies quite heavily, in the more or less direct role of concealing information on the B/R profile of drugs intended for wide use with important epidemiological and public health implications [49–54].

Table 3 The context of dates, facts, concepts, and institutions that changed the operative-cultural context of drug development and therefore of pharmacovigilance

Year	Description
1990–92	The normative structure of registering drugs in the three major market areas (USA, Europe, and Japan) is defined through the Good Clinical Practice (GCP) and the International Conference on Harmonization (ICH).
1993	Twenty years after A. Cochrane's *Effectiveness and Efficiency* [37], the Cochrane Collaboration resumes and formalizes the need to substantiate the choices of medical interventions available on the world market on the basis of scientific evidence derived from methodologically sound experimentations and periodically and systematically reviewed through meta-analyses (EBM).
1994	As a mandatory framework for the circulation of market goods, the World Trade Organization (WTO) is established and is given responsibility over medical products, i.e., mainly drugs but generally all things within the health services that have the characteristics of a "product."
1996	The report on the Global Burden of Disease [38], prepared by the World Bank and accepted and signed by the WHO, is proposed as the reference to set priorities for investments, research, and planning world-wide, regardless of the degree of health care development and of the political-economical autonomy of the countries [39, 40].
End of the 1990s to the early 2000s	The macro-political framework (from wars to forced political and economical migrations to "terrorism") progressively substitutes the policies of *universal rights promotion* (including access to health resources such as drugs) with policies of *protection-security defense* (including the protection of the interests of those producing or possessing economic goods, of which patents and competitiveness in the drug area are both expression and symbol) [41, 42].

It is highly significant that an independent organization such as the International Society of Drug Bulletins (ISDB), established in the mid-1980s to provide an independent bridge between knowledge and information on prescriptions [55], had to focus first on the problem of apparent (vs. real) therapeutic advances—which must be considered severe adverse events, as they profoundly damage research and rational prescribing [56, 57]—and second on the need for a more diversified PV involving both prescribers and patients in an innovative way [58, 59] and mandatorily based on transparency and accountability, which was fiercely opposed by the key players in the definition of the B/R profiles (industry and regulators).

The global context chronologically described in Table 3 adequately defines the current situation with respect to a PV policy that is very different. A drug-centered PV that insists on procedural formality (until the last proposal by the EMA) seems bound to remain marginal with respect to real prevention and protection from unsafe strategies. Obviously PV must also be concerned with individual molecules, but it cannot choose not to consider the much more relevant questions simultaneously posed to drug policies and public health. The model scenarios in Table 4 (to which many more could be added, from the drugs for the family of dementias, to those for schizophrenia, to the need of including, mainly for the "Low Income Countries" among the SAR the non availability of basic drugs) provide a concrete idea of the questions that will arise with a vigilance centered on patients and populations and their epidemiology, which focus the attention on the respect of patients' rights and their violations.

Table 4 Three model scenarios that require downplaying strict pharmacovigilance (PV) definitions and focusing on the epidemiology of problems and populations

- What is the B/R profile of antidepressant drugs, whose registered indications include a spectrum of heterogeneous diagnoses that coincide with even less well-defined populations and that are based on surrogate end-points that do not reflect the real lives of people? Are we measuring placebo B/R profiles or are we producing a "disease mongering" effect with the process (i.e., a culturally iatrogenic, epidemiologically relevant side-effect)?
- The release of the coxibs with their promise of lower gastrotoxicity was a great market event. It soon became, however, on the one hand, a model case of "global" misconduct and failure by the main actors of PV (producers and regulatory bodies) leading to the drugs' withdrawal, and on the other hand a success story of problem-oriented epidemiology. Nobody, however, apparently considered the SAR of the absence of their "benefit." What is the epidemiology of the unmet needs of the huge populations of chronic sufferers, e.g., of osteoarthritis?
- The new generation oncological drugs are most often approved and used on the basis of minimal or doubtful benefit, despite exorbitant costs and "standard" biological and quality of life–related toxicity. What could/should be the object of a pertinent PV? The trade-off between hope (the B) and disillusion (the R)? What is the impact of the (cultural, methodological, economic) R of concentrating research and care resources and expectations on pharmacological effects and less on the overall epidemiology of care of oncological patients?

Proposal and perspectives

The best synthesis of the general suggestions that have guided this review and the more appropriate framework to introduce the specific proposal formulated as a perspective for a renewed culture and practice of PV can be found in the old text authored by Archie Cochrane [37]. It anticipated the present awareness of trials and epidemiology, efficacy and effectiveness, risk management and rights of patients and populations, as a continuum of complementary tools, strategies, and actors to make institutions and health care systems accountable to and in dialogue with society. At a time when trials were still developing as a specific technique to measure the efficacy of interventions, the focus of the essay was not on the interventions per se but on the shared responsibility of medicine and society to look for appropriate answers to unmet needs. Experts were requested to declare their uncertainty by choosing the random allocation of the available choices instead of their decision, so that informed patients could be conscious and indispensable participants in the production of an innovative knowledge, which is relevant only if and when it becomes a component of the culture and of the behaviors of a society.

The scenario proposed in Fig. 2 (not a substitute, but on top of and as the framework for Fig. 1) summarizes the practical implications for PV of that seminal intuition [60].

As "tracers" of the quality of the interplay between medicine and society, drugs are not simply the "object" of a discipline, PV, which is directed to monitor their post-registration life as products: they are indicators of the *goals* of the various approaches and tools that aim to monitor and assess the overall—good and bad—role of drugs in the life of society and patients. The products of this approach are not limited to the data that define the safety profile of one or the other molecule but are part of a more comprehensive production of knowledge, where citizens and patients are active subjects and partners and do not simply correspond to percentages and rates of "SAR".

Permanent/periodical monitoring of administrative databases (not to measure generic exposure to drugs in terms, e.g., of DDDs) to give visibility to the clinical history of well-defined populations, is a powerful, easily accessible, highly flexible method to produce transverse and longitudinal epidemiological denominators at very low cost, which allow all events to be explored and qualified both in terms of effectiveness and SAR and to relate them both to market variables and to the cultural attitudes of easily identifiable settings [61–65].

Excess, undue, or insufficient treatments are critical determinants of avoidable events. Outcome research and the epidemiological surveillance of appropriateness and/or non-accessibility become an integral component of strategies and policies that transform the evaluation of the impact of general recommendations or guidelines into a dialogue among stakeholders, a dialogue that can be targeted to the problems and adequately tailored to the information needs of specific populations [66–69]. The language of a knowledge that is not swinging from peaks of alarms to even greater peaks of promotion becomes in this sense a shared communication of the uncertainties and limits of medicine (and of drugs) and includes close interaction with public opinion [70–72].

Groups of patients and their families are perfectly able and motivated to produce pertinent information on how treatments (beyond this or that molecule) affect the autonomy of their lives with greater reliability and more direct implications for timely adjustments of prescribing behaviors (as well as of criteria of compliance) [73–78].

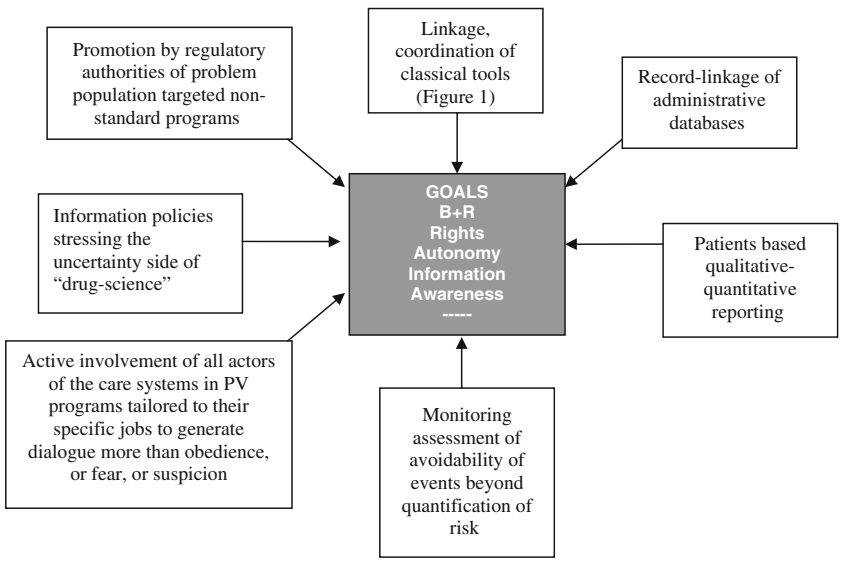

Fig. 2 Realistic goals, tools, strategies of pharmacovigilance

The "fragile" populations should not be the objects of worries and caveats coming from experts but rather the partners with whom the B/R profile—or even better the documentation of the safety, acceptability, and satisfaction of the overall care they receive—can be monitored, assessed, modified. The PV should not be so much for drug-drug interactions (which are certainly a potential, although more rarely a real, epidemiological problem), but for the flexible capacity to adjust (pharmacological) interventions within the contexts of care and the life of citizen-patients (which are the main determinants of fragility) [79–81].

It is obvious that, in this perspective, the standard reporting forms for SAR recommended by international agencies, focused on molecules, are a rather marginal element whose limits must be well recognized and advertised also in teaching, in permanent education forums, in regulatory rulings, to avoid the idea that doctors, nurses, and pharmacists are requested simply to be occasional, more or less compliant, "security" (rather than safety and acceptability) agents.

The qualitative and narrative accounts of patients must become less an object of ad hoc studies and more a routine component of an effort aimed to develop and shape languages (the plural is critical) that give patients and citizens confidence about their right and duty to speak out: not to protest and claim only, but more to be part of the production of a knowledge that can and must also be incorporated in the teaching and normative material and not remain a sophisticated exercise that is scarcely transferred on a wide scale in real life [82–90].

Last, but certainly not least, a word on the economy of PV. The proposals that have been made (all of which refer to concrete experiences) do not advocate major supplementary financial incentives or investments for PV per se. More public and independent investment is definitely needed to counteract the trend of delegating health care to public-private partnerships, where, by definition, the dominant interests are under the control of those who put forward the resources. While recognizing that all economic supports are needed and welcome, the plea of this review necessitates the very concrete challenge that the even more critical investment belongs to all those (the many and diverse professional actors of care, public opinion, patient representatives, media,…) who think that the future of PV has to do with the growth of the concept and practice of health as a human right.

Along this line, drugs are a challenging scenario of research and action, not only for PV but to field test the capacity and the willingness of medicine to be(come) what should be an indicator of practiced, not declared, democracy. The "goals" set for PV shown in Fig. 2 are good proxy measures for the achievement of these objectives.

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