PHARMACEUTICAL R&D
What do we get for all that money?

Data indicate that the widely touted "innovation crisis" in pharmaceuticals is a myth. The real innovation crisis, say **Donald Light** and **Joel Lexchin**, stems from current incentives that reward companies for developing large numbers of new drugs with few clinical advantages over existing ones

Since the early 2000s, industry leaders, observers, and policy makers have been declaring that there is an innovation crisis in pharmaceutical research. A 2002 front page investigation by the *Wall Street Journal* reported, "In laboratories around the world, scientists on the hunt for new drugs are coming up dry . . . The $400 billion a year drug industry is suddenly in serious trouble."[1] Four years later, a US Government Accounting Office assessment of new drug development reported that "over the past several years it has become widely recognized throughout the industry that the productivity of its research and development expenditures has been declining."[2] In 2010, Morgan Stanley reported that top executives felt they could not "beat the innovation crisis" and proposed that the best way to deal with "a decade of dismal R&D returns" was for the major companies to stop trying to discover new drugs and buy into discoveries by others.[3] Such reports continue and raise the spectre that the pipeline for new drugs will soon run dry and we will be left to the mercies of whatever ills befall us.[4]

The "innovation crisis" myth

The constant production of reports and articles about the so called innovation crisis rests on the decline in new molecular entities (defined as "an active ingredient that has never been marketed . . . in any form"[5]) since a spike in 1996 that resulted from the clearance of a backlog of applications after large user fees from companies were introduced (fig 1). This decline ended in 2006, when approvals of new molecular entities returned to their long term mean of between 15 and 25 a year (fig 2).[6] Even in 2005, an analysis of the data by a team at Pfizer concluded that the innovation crisis was a myth "which bears no relationship to the true innovation rates of the pharmaceutical industry."[7] So why did the claims and stories not abate?

A subsequent analysis also concluded that the innovation crisis was a myth and added several insights.[8] Based on US Food and Drug Administration records, Munos found that drug companies "have delivered innovation at a constant rate for almost 60 years." The new biologicals have been following the same pattern "in which approvals fluctuate around a constant, low level."[8] These data do not support frequently heard complaints about how hard it is to get any new drug approved. They also mean that neither policies considered to be obstacles to innovation (like the requirement for more extensive clinical testing) nor those regarded as promoting innovation (like faster reviews) have made much difference. Even the biotechnology revolution did not change the rate of approval of new molecular entities, though it changed strategies for drug development.[9] Meanwhile, telling "innovation crisis" stories to politicians and the press serves as a ploy, a strategy to attract a range of government protections from free market, generic competition.[10 11]

The real innovation crisis

More relevant than the absolute number of new drugs brought to the market is the number that represent a therapeutic advance. Although the pharmaceutical industry and its analysts measure innovation in terms of new molecular entities as a stand-in for therapeutically superior new medicines, most have provided only minor clinical advantages over existing treatments.

The preponderance of drugs without significant therapeutic gains dates all the way back to

How have we reached a situation where so much appears to be spent on research and development, yet only about 1 in 10 newly approved medicines substantially benefits patients?

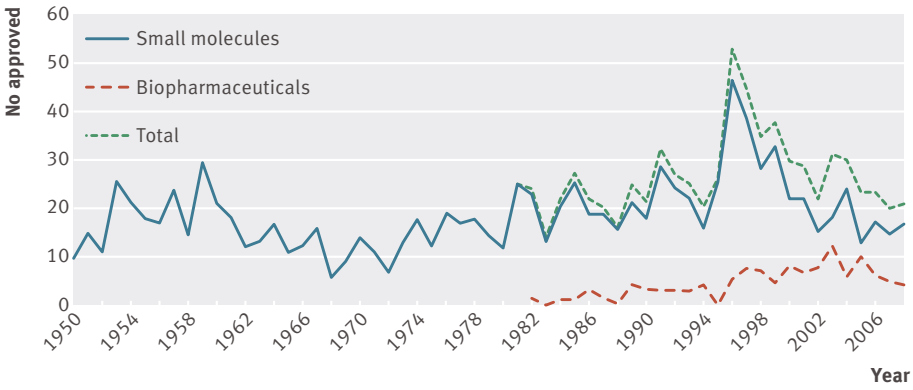

Fig 1 | The innovation crisis starting in 1997 is a return to the long term average range of new approvals from an artificial spike caused by political factors[8]

the "golden age" of innovation. Out of 218 drugs approved by the FDA from 1978 to 1989, only 34 (15.6%) were judged as important therapeutic gains.[12] Covering a roughly similar time period (1974-94), the industry's Barral report on all internationally marketed new drugs concluded that only 11% were therapeutically and pharmacologically innovative.[13] Since the mid-1990s, independent reviews have also concluded that about 85-90% of all new drugs provide few or no clinical advantages for patients.[14-19]

This small, steady increase in clinically superior drugs contrasts with the FDA granting "priority" review status to 44% of all new drugs from 2000 to 2010.[20] The percentage of drugs with a priority designation began to increase in 1992 when companies started funding the FDA's approval process. Other regulatory agencies have classified far fewer of the same medicines as needing accelerated reviews.[21] Post-market evaluations during the same period are much less generous in assigning significant therapeutic advances to medications.[18 21]

This is the real innovation crisis: pharmaceutical research and development turns out mostly minor variations on existing drugs, and most new drugs are not superior on clinical measures. Although a steady stream of significantly superior new drugs enlarges the medicine chest from which millions benefit, medicines have also produced an epidemic of serious adverse reactions that have added to national healthcare costs.[22]

How much does research and development cost?

Although the pharmaceutical industry emphasises how much money it devotes to discovering new drugs, little of that money actually goes into basic research. Data from companies, the United States National Science Foundation, and government reports indicate that companies have been spending only 1.3% of revenues on basic research to discover new molecules, net of taxpayer subsidies.[23] More than four fifths of all funds for basic research to discover new drugs and vaccines come from public sources.[24] Moreover, despite the industry's frequent claims that the cost of new drug discovery is now $1.3bn (£834m; €1bn),[25] this figure, which comes from the industry supported Tufts Center,[26] has been heavily criticised. Half that total comes from estimating how much profit would have been made if the money had been invested in an index fund of pharmaceutical companies that increased in value 11% a year, compounded over 15 years.[26] While used by finance committees to estimate whether a new venture is worth investing in, these presumed profits (far greater than the rise in the value of pharmaceutical stocks) should not be counted as research and development costs on which profits are to be made. Half of the remaining $0.65bn is paid by taxpayers through company deductions and credits, bringing the estimate down to one quarter of $1.3bn or $0.33bn.[27] The Tufts study authors report that their estimate was done on the most costly fifth of new drugs (those developed in-house), which the authors reported were 3.44 times more costly than the average, reducing the estimate to $90m. The median costs were a third less than the average, or $60m. Deconstructing other inflators would lower the estimate of costs even further.

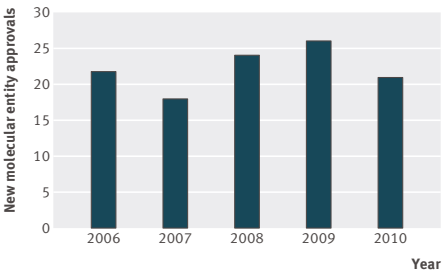

Fig 2 | The rate of approval of new molecular entities returned to the long term average range by 2006

Hidden business model

How have we reached a situation where so much appears to be spent on research and development, yet only about 1 in 10 newly approved medicines substantially benefits patients? The low bars of being better than placebo, using surrogate endpoints instead of hard clinical outcomes, or being non-inferior to a comparator, allow approval of medicines that may even be less effective or less safe than existing ones. Notable examples include rofecoxib (Vioxx), rosiglitazone (Avandia), gatifloxacin (Tequin), and drotrecogin alfa (Xigris).

Although the industry's vast network of public relations departments and trade associations generate a large volume of stories about the so called innovation crisis, the key role of blockbuster drugs, and the crisis created by "the patent cliff,"[28] the hidden business model of pharmaceuticals centres on turning out scores of minor variations, some of which become market blockbusters. In a series of articles Kalman Applbaum describes how companies use "clinical trial administration, research publication, regulatory lobbying, physician and patient education, drug pricing, advertising, and point-of-use promotion" to create distinct marketing profiles and brand loyalty for their therapeutically similar products.[29] Sales from these drugs generate steady profits throughout the ups and downs of blockbusters coming off patents. For example, although Pfizer lost market exclusivity for atorvastatin, venlafaxine, and other major sellers in 2011, revenues remained steady compared with 2010, and net income rose 21%.[30]

Applbaum contends that marketing has become "the enemy of [real] innovation."[31] This perspective explains why companies think it is worthwhile paying not only for testing new drugs but also for thousands of trials of existing drugs in order to gain approval for new indications and expand the market.[32] This corporate strategy works because marketing departments and large networks of sponsored clinical leaders succeed in persuading doctors to prescribe the new products.[33] An analysis of Canada's pharmaceutical expenditures found that 80% of the increase in its drug budget is spent on new medicines

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Donald Light talks about drug research and development in this week's podcast

that offer few new benefits.[16] Major contributors included newer hypertension, gastrointestinal, and cholesterol drugs, including atorvastatin, the fifth statin on the Canadian market.

Myth of unsustainable research and development

Complementing the stream of articles about the innovation crisis are those about the costs of research and development being "unsustainable" for the small number of new drugs approved. Both claims serve to justify greater government support and protections from generic competition, such as longer data exclusivity and more taxpayer subsidies. However, although reported research and development costs rose substantially between 1995 and 2010, by $34.2bn, revenues increased six times faster, by $200.4bn.[25] Companies exaggerate costs of development by focusing on their self reported increase in costs and by not mentioning this extraordinary revenue return. Net profits after taxes consistently remain substantially higher than profits for all other Fortune 500 companies.[34]

This hidden business model for pharmaceutical research, sales, and profits has long depended less on the breakthrough research that executives emphasise than on rational actors exploiting ever broader and longer patents and other government protections against normal free market competition. Companies are delighted when research breakthroughs occur, but they do not depend on them, declarations to the contrary notwithstanding. The 1.3% of revenues devoted to discovering new molecules [23] compares with the 25% that an independent analysis estimates is spent on promotion,[35] and gives a ratio of basic research to marketing of 1:19.

Towards more cost effective, safer medicines

What can be done to change the business model of the pharmaceutical industry to focus on more cost effective, safer medicines? The first step should be to stop approving so many new drugs of little therapeutic value. The European Medicines Agency (EMA) does Europe a disservice by approving 74% of all new applications based on trials designed by the companies, while keeping data about efficacy and safety secret.[36 37] Twenty nine per cent of new biologicals approved by the EMA received safety warnings within the first 10 years on the market,[38] and therapeutically similar drugs by definition have no advantages to offset their unknown risk of increased harm. We need to revive the Norwegian "medical need" clause that limited approval of new drugs to those that offered a therapeutic advantage over existing products.[39] This approach led to Norway having seven non-steroidal anti-inflammatory drugs on the market compared with 22 in the Netherlands.[40] Norway's medical need clause was eliminated in 1996 when it harmonised its drug approval process with that in the EU. EU countries are paying billions more than necessary for drugs that provide little health gain because prices are not being set to reward new drugs in proportion to their added clinical value.

We should also fully fund the EMA and other regulatory agencies with public funds, rather than relying on industry generated user fees, to end industry's capture of its regulator. Finally, we should consider new ways of rewarding innovation directly, such as through the large cash prizes envisioned in US Senate Bill 1137, rather than through the high prices generated by patent protection.[41] The bill proposes the collection of several billion dollars a year from all federal and non-federal health reimbursement and insurance programmes, and a committee would award prizes in proportion to how well new drugs fulfilled unmet clinical needs and constituted real therapeutic gains. Without patents new drugs are immediately open to generic competition, lowering prices, while at the same time innovators are rewarded quickly to innovate again. This approach would save countries billions in healthcare costs and produce real gains in people's health.

The true crisis in pharmaceutical research

The number of new drugs licensed remains at the long term average range of 15-25 a year
However, 85-90% of new products over the past 50 years have provided few benefits and considerable harms
The pharmaceutical industry devotes most research funds to developing scores of minor variations that produce a steady stream of profits
Heavy promotion of these drugs contributes to overuse and accounts for as much as 80% of a nation's increase in drug expenditure
Overinflated estimates of the average cost of research and development are used to lobby for more protection from free market competition

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HEALTH SYSTEMS PERSPECTIVES

Raising the bar for market authorisation of new drugs

Huseyin Naci and colleagues find that requiring comparative evidence for market entry of new drugs could have numerous benefits, including providing incentives for development of drugs for conditions that have few treatment options

Calls are increasing for manufacturers to provide evidence of comparative efficacy of new drugs at the time of regulatory approval.[1] However, drug manufacturers maintain that doing so would create unrealistically high barriers for market entry and deter innovation. At a time of a perceived productivity crisis in the drug industry, many claim that stricter market authorisation regulation will be detrimental to the development of new drugs.[2] We review the historical effect of regulating market authorisation and examine the benefits and risks of raising evidence standards by requiring evidence of non-inferiority for market entry.

What's the hype?

Various components of drug development, including experimentation, evidence generation, and marketing are already subject to regulation. However, there is interest in expanding the remit of regulatory agencies in Europe and the United States in order to make drug manufacturers more accountable and market authorisation more stringent.[3] Recent proposals include making the raw data collected in pivotal randomised controlled trials of new drugs publicly available and developing a framework for independent appraisal of evidence.

One particularly important aspect is the standards of evidence for marketing authorisation.[4] Currently, each new product is evaluated on its own merit, without being assessed against other available treatments. As a result, many drugs are approved on the basis of placebo controlled trials without showing their equivalence, non-inferiority, or superiority to existing alternatives. There are proposals in the United States and Europe to require evidence on comparative efficacy at the time of licensing.[1 5] This is because the current regulatory environment crowds the marketplace with products that offer marginal, if any,

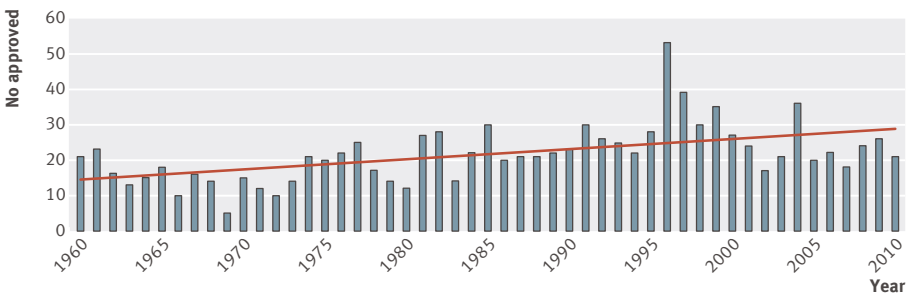

Fig 1 | Number of new molecular entities approved in the United States, 1960-2010

With an ever increasing number of seemingly similar drugs for a given condition, prescribers do not have adequate evidence on the comparative clinical effect and safety to determine the best drug option

improvements in therapeutic value over existing options.[6 7] With an ever increasing number of seemingly similar drugs for a given condition, prescribers do not have adequate evidence on the comparative clinical effect and safety to determine the best drug option.[8]

Yet manufacturers have expressed concerns about being required to provide comparative evidence at the time of marketing authorisation. Some argue that existing experimental designs—such as active-comparator trials—are expensive and take a long time to complete.[9] Delays in launching new products are also said to be costly, as companies lose exclusivity periods and receive potentially lower returns to research and development; this lowered profit expectation, in turn, discourages future investment.[10] Manufacturers maintain that regulation requiring them to show that their products provide added value would also discourage investment and hinder the development of new drugs.[11] In a recent survey, 64% of respondents from these sectors stated that demonstrating that their products have added value, whether clinical or economic, is a major challenge.[12]

Regulatory environment

The market for pharmaceutical products is highly regulated compared with that of other sectors, with regulators given the power to restrict products from entering the market. Manufacturers are prohibited from marketing new drugs before they are licensed by the Food and Drug Administration (FDA) in the United States or the European Medicines Agency (EMA) in Europe.

The defining piece of legislation that has had a lasting effect on the evidence standards for pharmaceutical market access in the United States is the Kefauver-Harris Drug Amendments of 1962, which mandated that manufacturers establish proof of efficacy and safety through recognised "well-controlled studies."[13] These amendments formally required manufacturers to establish rules of consent, good manufacturing practices, processes for reporting adverse events, and accurate labelling of new products. The amendments were partly a response to the thalidomide controversy—when a drug marketed in Europe to treat the symptoms of morning sickness caused birth defects in thousands of babies. Since Kefauver-Harris, there have been very few legislative developments in the United States.[14]

In Europe, there has also been no formal expansion of regulatory legislation on evidence standards since the EMA's inception in 1996. European regulatory standards, and in particular evidence requirements for marketing approvals, largely parallel those of the United States. Although there is no legal requirement to provide comparative evidence, the EMA is increasingly encouraging its submission. The EMA's Committee for Medicinal Products for Human Use recently stated it was in favour of three arm non-inferiority trials including the experimental drug, placebo, and active control when the use of placebo is deemed ethical and one or more established medicines are available.[15] EMA also rewards manufacturers with an extended (11 year) marketing protection period if they can demonstrate that their product offers improved efficacy or safety over existing treatments.

In both the United States and Europe, while submission of comparative evidence is encouraged, regulatory agencies have been reluctant to set comparative assessments as the default evidence standard for market approval, although there have been renewed calls to impose stricter regulation on latecomer products that have questionable therapeutic value.

Health of pharmaceutical innovation

Many have suggested that the pharmaceutical industry as a whole is suffering from a productivity crisis.[17] Defining innovation in the pharmaceutical sector remains controversial. One commonly used metric by which to measure innovation is the number of new molecular entities entering the marketplace.[13] The figure shows that by this definition of innovation, the rate of pharmaceutical innovation is not declining. In fact, since the 1962 regulatory requirement in the United States for manufacturers to establish evidence of safety and effectiveness, there has been an increase in the number of new products reaching the market. Furthermore, an analysis by Munos shows that the rate of drug approvals has been constant over the past 60 years with an upward trend from 1980-95 (culminating in 53 approvals in 1996).[16] The argument that regulation has reduced pharmaceutical innovation is therefore unsubstantiated.

Although the number of new products reaching the market has not decreased with existing regulation, manufacturers argue that stricter market authorisation will lead to fewer new drug approvals at increasingly higher cost.[17] The cost of developing new drugs has reportedly increased, as have total research and development expenditures,[18] while the number of new drugs introduced to the market has increased moderately.[19] However, there are disagreements regarding the research and development costs of a new drug,[20] with some research finding oft stated figures to be grossly overestimated.[21] Total research and development expenditures may include promotional spending that is not directly tied to developing new products.[22] Inflation adjustment often does not properly account for changes in the price of investment, and reported research and development figures sometimes do not account for changes in prices.

Effects of requiring comparative evidence

Without historical evidence to suggest that regulation leads to declines in innovation, what are the other potential outcomes of introducing higher evidence standards? Requiring comparative evidence at the time of market approval could have a number of advantages. In the current regulatory environment, relative benefits and harms of a new drug often emerge only after market entry, which may be too late to adequately meet the information needs of decision makers in clinical practice.

Milestones in US legislation on market authorisation[14]

1906: Food and Drugs Act—prohibits interstate commerce in misbranded and adulterated drugs

1927: Regulatory functions pertaining to drugs are located under the Food, Drug, and Insecticide Administration (named Food and Drug Administration in 1930)

1938: The Federal Food, Drug, and Cosmetic (FDC) Act requires new drugs to be shown to be safe before marketing

1962: Kefauver-Harris Drug Amendments—requires drug manufacturers to provide FDA with evidence of safety as well as effectiveness of their products before marketing them

1966: Fair Packaging and Labeling Act—requires all consumer products in interstate commerce to be honestly and informatively labelled, with FDA enforcing provisions on drugs and medical devices

1970: FDA requires the first patient package insert, mandating manufacturers to provide patients with information about specific risks and benefits of drugs and devices

1976: Medical Device Amendments—requires manufacturers to register with FDA and follow quality control procedures to ensure safety and effectiveness of medical devices and diagnostic products

1983: Orphan Drug Act—enables FDA to promote research and marketing of drugs needed for treating rare diseases

1988: Prescription Drug Marketing Act—bans the diversion of prescription drugs from legitimate commercial channels

1992: Prescription Drug User Fee Act—requires manufacturers to pay fees for product applications and other services

1997: Food and Drug Administration Modernization Act—reauthorises the Prescription Drug User Fee Act of 1992. Provisions include measures to accelerate review of devices, regulate advertising of unapproved uses of approved drugs and devices, and regulate health claims for foods

In addition, unlike regulatory agencies, payers need manufacturers to provide comparative evidence to support decisions for coverage and reimbursement. In some cases, this discrepancy in evidence requirements results in conflicting decisions by regulatory agencies and healthcare funders. For example, health technology assessment agencies such as the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom, which makes decisions on value for money on behalf of the National Health Service, require comparative evidence to inform decisions on coverage and reimbursement. A lack of relevant head to head trial data was one of the reasons NICE cited for recommending against reimbursement of bevacizumab, cetuximab, and panitumumab, which were approved by the EMA for metastatic colorectal cancer. There is a need to align the evidence needs of regulatory bodies, country level payers, and health technology assessment agencies.[23]

Requirements for comparative evidence at the time of market approval could also encourage manufacturers to focus on therapeutic areas with limited treatment options or where comparators have poor efficacy or serious side effects, because drugs in those areas would face fewer obstacles to authorisation. There are indications that this is already happening—manufacturers are increasingly evaluating their portfolios to identify the products likely to face the greatest scrutiny.[24] These include product classes with numerous, similar alternative therapies such as biological treatments for rheumatoid arthritis and oral treatments for diabetes. Given that investment in active-comparator trials varies tremendously across therapeutic areas, standardising evidence requirements and making comparative evidence the default option could shift drug development towards areas where innovation has historically been lacking.[25]

Nonetheless, there are legitimate concerns regarding changes in evidence standards. Critically, judgments of efficacy are often based on surrogate outcome measures, not clinical endpoints, which can complicate the assessment of benefits and harms at the time of market entry. Even if comparative evidence for market approvals becomes the norm, the full effects of new treatments approved on evidence from surrogate endpoints may remain unknown until after marketing, as in the case for rosiglitazone and pioglitazone in type 2 diabetes.

Requiring manufacturers to generate comparative evidence could also lead to more costly and lengthy clinical trials, particularly if superiority claims are sought and multiple comparators are needed. To alleviate manufacturers' concerns, our proposal is to require evidence of similarity (equivalence or non-inferiority at a minimum) for all conditions for which an alternative treatment option exists. Given that only about 10% of new medicines that reach the market are deemed superior to existing alternatives,[26] requiring evidence of superiority could limit the number of therapeutically viable alternatives for a given condition and make it more difficult for clinicians to individualise treatment options. Nevertheless, others have proposed that for conditions with an existing generic treatment, manufacturers

should demonstrate the superiority of the new drug over the next best option in terms of either greater efficacy or improved safety.[27]

Conclusions

A stricter regulatory environment for market access is likely to be opposed by manufacturers, who will claim that patients will suffer from fewer medicines reaching the market. However, there is no evidence that increased regulation limits the number of new drug approvals. Requiring comparative evidence at the time of market entry would ensure that patients, clinicians, and other healthcare decision makers such as payers and health technology assessment bodies are adequately informed about the relative merits of new treatments. Furthermore, changing the nature of regulation and raising the evidence standards at the time of licensing decisions could encourage manufacturers to concentrate on the development of new drugs in therapeutic areas with few or no alternatives. While formal regulation can take years to develop, supplementing regulation with scientific advice and guidance can steer manufacturers' interest and efforts into key research priorities and important technical issues. Overall, the risks associated with making market entry stricter seem to be relatively modest, particularly when compared with the potential benefits.

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Contributors and sources: HN, JC, and SV have written several articles on pharmaceutical policy and regulation in the European Union and the United States. HN, JC, SV, and AS have experience in pharmaceutical regulation at the market entry and pricing levels. KP has experience in health technology assessment through his role at the National Institute for Health and Clinical Excellence. The views expressed here do not necessarily reflect those of NICE. JC has extensive experience of European health systems through his involvement with the European Observatory on Health Systems and Policies. HN, JC, SV, AS, and KP devised the article. All authors developed the first draft and also contributed to subsequent drafts. All have read and agreed to the final version. HN is the guarantor.

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BMJ BLOG **Pritpal S Tamber**

To inform we need to enable


LIFE IN VIEW/SPL

Last week I was in the "patient participation group" of my local practice. We were reviewing the text proposed for the new practice leaflet and one of the patients—a journalist—was slamming almost every word of it for being medical-speak.

It was too delicious to simply observe so I joined in. "What," I asked the other patients, "is a DRCOG?" One guessed, the others looked blank (I wasn't sure myself). "What," I continued, "is an HCA?" No one knew. "And who," and this was my favourite, "was Harmoni?"

It turned out that Harmoni was the local out-of-hours service, the organisation patients should call when the practice is closed. The GPs were so used to it that they used it throughout the proposed text for the leaflet but to patients like me it's just jargon.

It also turned out that practices have to list the qualifications of their general practitioners, hence the listing of a DRCOG (Diploma of the Royal College of Obstetricians and Gynaecologists), but the journalist and I agreed that there was little point in listing the acronym if it meant nothing to the average patient.

Getting a practice leaflet right is about understanding what patients need and want to know, and then delivering it in a format that communicates.

There is a chasm between political rhetoric and the daily reality of how the NHS uses, or could use, information.

I can't help worrying that it's because it's easier to reflect on the "power of information" than it is to truly understand how new information can or should influence behaviour.

For a start, frontline clinicians and managers need help to get the basics right, such as practice leaflets. It's only when we master the basics will we ever want tools that show us that our problems are bigger than we thought.

It's only if we enable can we truly inform.

Pritpal S Tamber is the director of Optimising Clinical Knowledge Ltd, a consultancy that helps organisations improve how they use established clinical knowledge.

Read this blog in full and other blogs at bmj.com.