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Patient-Reported Outcomes, Patient-Reported Information

From Randomized Controlled Trials to the Social Web and Beyond

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Abstract

Internet communication is developing. Social networking sites enable patients to publish and receive communications very easily. Many stakeholders, including patients, are using these media to find new ways to make sense of diseases, to find and discuss treatments, and to give support to patients and their caregivers. We argue for a new definition of patient-reported information (PRI), which differs from the usual patient-reported outcomes (PRO). These new emergent data from the social web have important implications for decision making, at both an individual and a population level. We discuss new emergent technologies that will help aggregate this information and discuss how this will be assessed alongside the use of PROs in randomized controlled trials and how these new emergent data will be one facet of changing the relationship between the various stakeholders in achieving better co-created health.

The role of the patient in the healthcare decision-making process has become more prominent over the last decade. Patients are increasingly regarded as one of the key stakeholder groups that, alongside regulators, payers, and clinicians, influence access to and reimbursement for pharmaceutical products. For example, patient pressure was a key factor driving the decision of the UK National Institute for Health and Clinical Excellence (NICE) to approve Herceptin®, a treatment for early-stage breast cancer, for use by the UK National Health Service.[1] Pharmaceutical companies operate in a highly competitive market and are therefore aware of the need to communicate patient-reported evidence of product benefits, specifically to regulatory and reimbursement authorities. Ensuring product success often warrants companies to generate value propositions that go beyond traditional biomedical safety and clinical efficacy messages. One approach to achieve this is by generating evidence on patients' perspective of treatment via standardized questionnaires known as patient-reported outcomes (PROs). The process has been largely industry led, and the flow of information is unilinear, *viz*., from the patient to industry and on to regulatory, payer, and clinical stakeholders. However, in recent years, a new concept has arisen that brings about a fundamental change in the information-exchange process. Patients are increasingly using the Internet

to retrieve and exchange health-related information. In particular, patients are using web-based social networking sites to share and compare their experiences and satisfaction with pharmaceutical treatments. It is likely that this new information-exchange phenomenon will increasingly influence patients' decisions to seek, comply with, or request changes to their pharmaceutical therapies.

Although the pharmaceutical industry is becoming increasingly aware of the potential for listening to and liaising with patients via the new digital media, the information should not be confused with PROs. Instead, a new term has been recommended to describe the information collected through the social web: patient-reported information (PRI). New technologies and social norms will possibly mean that, in time, gathered data will yield new insights into the pathways of disease, medicines, and the way medicines are delivered. We seek to distinguish PRIs from PROs and discuss some of the challenges that many stakeholders face in closely listening to patients' voices.

1. Patient-Reported Outcomes and Information: Clarifying the Terminology

Patients' views on the effectiveness, or otherwise, of pharmaceutical products are commonly collected in clinical trials or observational trials via PRO measures. PRO is an umbrella term that covers a range of potential measurement endpoints, but is used specifically to refer to outcomes collected directly from the patient, without interpretation by clinicians or others.[2-4] The term PRO was coined to avoid confusion in the regulatory process regarding the different types of outcome data collected as part of clinical trials.[5] PROs may include measures of symptoms, activity limitations, health status, quality of life (QOL) and health-related QOL.[2,6] More recently, PROs have also been used in clinical trials to evaluate patient satisfaction, compliance, and treatment preferences. All of these have potential value, provided the appropriate outcome measure is selected to address the needs of the trial and provided the data are collected using high-quality questionnaire scales that are appropriate for the patient population.[7]

PROs are commonly used in clinical trials to capture patients' voices in a structured manner using validated questionnaires. PROs provide quantitative data, that is, patient responses in terms of a score (or scores) that allows investigators to measure any change in the endpoint(s) assessed following treatment, from a patient's perspective. Thus, they provide a means of quantifying qualitative information. In many conditions, such as irritable bowel syndrome, migraine, and pain, PROs may be used as the primary trial endpoint. However, PROs are more commonly used as secondary endpoints that provide important supportive evidence on treatment effects. As such, they are often viewed as an 'added extra', providing supporting data to supplement traditional biomedical indicators. The use of such outcomes is particularly common among trials on products developed to treat chronic, disabling conditions, wherein the treatment goal is not to cure but to ameliorate symptoms, facilitate functioning, or, ultimately, to improve QOL. In such cases, patient-reported evidence is increasingly viewed as an essential complement to traditional clinical evidence for establishing a product's competitive advantage in the marketplace.[8]

Regulatory authorities commonly expect to see evidence of the patient-reported benefits of new treatments in dossiers submitted for the licensing of new drugs. Indeed, many clinical guidance documents issued by regulatory authorities mandate the inclusion of PRO data for clinical trials.[9] Similarly, reimbursement authorities in Canada, Australia, and many parts of Europe include patient perspectives as part of their evaluation process.[10] For example, NICE in the UK has recommended patient scores on the QoL-AGHDA (a PRO scale for evaluating the QOL in Adult Growth Hormone Deficiency) as one of three criteria for judging patient suitability for treatment with recombinant human growth hormone.[11,12]

Clearly, PROs present a valuable means of communicating patient-perceived benefits of treatment to key stakeholders. However, in order to differentiate their products, pharmaceutical companies are increasingly recognizing the need to supplement this by communicating the patient-reported effects of drug therapies through what

may be described as 'patient-reported information.' Although PRI as a concept is not entirely novel (a Google search on 'patient reported information' between 1 January 2010 and 18 June 2010 yielded 63 results), it has yet to be adequately defined. There are examples where PRO and PRI were used as interchangeable terms on the Internet. However, PRI can be defined as information reported by patients relating to their experience of disease and its treatment. PRO connotes a concise and quantifiable means of measuring clearly defined concepts, whereas PRI constitutes qualitative information relating to illness and treatment that exists outside the clinical trials process. Although PRI may be collected by the pharmaceutical industry via targeted research, more often it is generated directly by patients (or their caregivers), unprompted, via social networking sites on the web. Unlike PRO data, PRI data are not confined to the unilinear model of information exchange. Instead, PRI information is exchanged between many stakeholders. In some cases this information can be amplified and organized in an emergent manner. Thus, the social web has the property of distributed cognition. These stories exist as micronarratives unconstrained by questionnaires and hence are spontaneous. Furthermore, these micronarratives may be accessed in a variety of forms directly, and they also have the property of interacting with each other. Therefore, this system is best described as a complex adaptive system and its further understanding may require an understanding of theories of complex systems.[13]

PRIs represent a quandary for regulatory bodies and other decision makers. On one hand, it provides an opportunity to listen to and enter into dialogue with patients regarding their perception of product benefits. On the other hand, it raises the problem of ensuring that the insights created have a robust and scientific methodology. PRIs can provide valuable information on the key areas of disease impact from a patient perspective. For example, patients with epilepsy reporting on the PatientsLikeMe website[14] list problems with memory, concentration, and fatigue as their key areas of symptom impact. However, even a cursory examination of patient comments on this site highlights the wider impact of the condition on QOL, with patients discussing issues such as embarrassment (due to stigma) and the corresponding impact on closeness and quality of friendships. Such information can, in turn, be used to inform on the most useful concepts for measurement by PRO scales in clinical trials. In the example of epilepsy, a study of PRIs could reinforce the value of assessing both executive function and QOL.[15] Furthermore, such data may substantiate the justification of measuring such constructs in discussion with regulatory and reimbursement authorities. Similarly, in considering existing PROs for clinical trials, an assessment of PRIs can be used to provide further evidence of the content validity of such scales for the target patient group.

2. The Historical Relationship between the Patient and Industry

The value of PRO data to the industry has historically been viewed largely in terms of their potential for securing regulatory claims and in providing supporting arguments for product promotion and reimbursement. In addition, there may be patient-reported data that are included in publications that could indeed enhance and amplify conversations within the social web. However, regulation decrees that manufacturers have no recourse to comment on these, as any commentary could be viewed as 'off-label promotion'. Consequently, the potential added value of the wealth of PRO data currently collected and held by the industry remains largely unrecognized, overlooked and, ultimately, under-utilized. However, the PRO data that are generated by the industry is often reported independently in the social web. These data represent a valuable resource that can be used to communicate patient-perceived benefits of products to all key stakeholders, namely payers, clinicians, patients, and regulators.

3. The Rise of the Empowered Patient

Consumers are increasingly engaging in a dialogue with providers regarding the services they receive. Many seemingly complex products and

services have been rendered comprehensible to the lay consumer as a result of information available across a plethora of websites. Although consumers are interacting in a transparent manner on the social web, health and healthcare systems have properties that are different from other consumer goods, not least because they relate to what are often intensely private issues. Furthermore, the consulting room has historically been neither a democratic nor a transparent forum. Until recently, patients presenting to healthcare professionals have been, by tacit, mutual consent, expected to provide sufficient information regarding their symptoms to inform their doctor's diagnosis, but only at the healthcare professional's request. A consultation may be defined as a dialogue only in the sense that both the parties may have spoken, with the information leading to diagnosis having been elicited reactively, with the doctor questioning and the patient contributing only when asked to do so. However, patients have always spoken about their condition, sometimes as part of their coping strategy. New technologies allow patients to not only find out about their condition but also to interact and discuss their experience with other patients and patient groups.[16]

Within the context of what now may perhaps be considered 'mainstream' social media sites, rich patient-reported narratives are encountered not only as textual status updates on microblogging platforms such as Twitter or social networks such as Facebook, but also as videos on YouTube, as well as via patient blogs, patient forums, and patient communities. Due to its ubiquity, fluidity, and sheer volume, the notion that a 'complete' set of PRI may be captured in some way is a chimerical one. Yet observers must take pleasure from, rather than find frustration in, the fact that patients will comment where they wish, when they wish, and in the manner of their choosing.

Again, since many of the face-to-face discussions of patient groups in the past are now codified on the social web (written down, achievable, and searchable), individual data about experiences hold greater value, especially when aggregated and even clustered to provide new insights. Unsurprisingly, the increasing use of the Internet to expedite access to data on all health-related subjects by patients and healthcare professionals is ''redefining the roles of patient and physician.''[17] This reorientation has led an increasing number of patients to expect that the consulting room will be democratized: the monologue will become dialogue, the patient will be empowered to participate proactively, and the opinion of each party will be listened to and respected by the other. Patients have found their own solutions to this asymmetry of information, driving out complexity through their commitment to transparency. Patient advocacy groups, patient communities, and individual patient bloggers who self-identify as 'e-patients' (where the 'e' stands for 'empowered' rather than 'electronic') consider themselves to be 'equipped, enabled, empowered, and engaged in their health and healthcare decisions', as well as 'educated about the evidence'.[18,19] They deport themselves online and in person with confidence on the basis that, at least for them, this egalitarian ideal is already a reality within the online environments within which they connect, converse, and collaborate.

4. The Future Potential of Industry-Patient Communications

The challenge for the pharmaceutical industry is to identify the most effective means of communicating patients' perceptions of treatment benefits to the different stakeholders in a changing technological climate. This challenge comes in the wake of two key revolutions: first, how companies market their products and second, how information is exchanged and co-created in the age of the social web.

It is no longer accurate to use the future tense when referring to the potential of the social web for those seeking and sharing health information, advice, and support as this potential has already been realized for many patients. Therefore, the pertinent questions are whether healthcare professionals, regulators, and the pharmaceutical industry are able to keep pace with this transition and whether they are able to make the corresponding reorientation of their perception to view patients as partners rather than as subjects or as part of a target audience.

Patients may now have unprecedented access to health information, but it is not certain that the

information they may encounter will be relevant, reliable, readily accessible, or intelligible to them. It may prove a source of valuable facts if the patient is able to interpret its data, corroborate its findings, and verify its authority, but in isolation such data could just as easily prove to be a source of misinformation, anxiety, or even danger. Patients also have the unprecedented ability to publish information unfettered and alongside a social context that positively encourages sharing.

5. The New Terrain

This leads to a new terrain for the health conversation: one that is essentially flat, equitable, and that strives to be democratic. While patients clearly require information that is readily accessible, comprehensible, and from a trustworthy source, they must also be afforded the opportunity to add knowledge to the process. One approach to achieve this is using the clinical trial process. It is conceivable that information on drug effectiveness could be pooled to the mutual benefit of all parties, not only by combining evidence gathered as PRO data from relevant clinical trials, but also through channeling the rich narratives that are constructed within multiple fora as PRI. These may be bold aspirations, assuming, as they do, that the companies in question are aiming to align the future growth of their enterprise with a commitment to the social good in a substantive rather than a rhetorical manner. The question for the whole health community is how to undertake the curation of this discussion, that is, the collection and preservation of PRI data (which, due to its nature, is often transient), in an emergent scientific way in order to make robust evidence-based decisions.

However, in order to expedite open, productive engagement with the patient, with the intention of registering, collating, and curating PRI, the pharmaceutical industry faces at least two major barriers. The first may be broadly described as intercessionary, the second, contextual.

6. Challenges to the Industry

Externally, the pharmaceutical industry faces an intercessionary barrier in the form of its reception by the very patients with whom it wishes to engage. While social media is trust-enabling, it is also enabled by trust in the first instance. The industry's equivocal reputation in the eyes of the public at large and its patient community in particular means that any correlation that may be inferred between participation, visibility, and transparency on the industry's part in relation to the amelioration of its reputation does not need to be borne out in fact as a trust-generative benefit.

Furthermore, some in the health community can be seen to have a mistrust of the social web as 'social chit chat' and a low grade of evidence. Many healthcare sites do not feature tools allowing the sort of one-click content redistribution via status updating platforms such as Twitter, social networks such as Facebook, or lifestreaming content consolidators such as Posterous that encourage patients to report and share outcomes. These sites are neither truly social web-enabled nor likely to attract the enduring interest from patient communities that will produce rich PRI data. Furthermore, they are not always adequately equipped or prepared to record and share data with the community that creates it.

A further possible future contextual barrier may coalesce around the overuse of a small number of patient community sites on the basis that they are perceived to be safe havens for patient-facing initiatives. Vanguard enterprises such as the open online community for organ transplant patients established between PatientsLikeMe and Novartis will perhaps encourage other companies to partner with one of the many successful patient communities or patient-healthcare professional alliance sites rather than to seek to augment the same platform with further resources of their own suggestion.[20]

The final and perhaps the most problematic contextual barrier for the industry is that patient communities that appear to be the current leaders in successfully collating PRI are also independent of visible pharmaceutical industry involvement. This does little to advance the case for the industry having a role in supporting communities wherein PRI are recorded, measured, and assessed against or even factored into PRO data. An example of this is the open-source health research resource CureTogether, which presents

statistical information on symptoms, treatments, causes, and related conditions by disease state as an open informational resource. CureTogether also affords registered members the opportunity to submit their own experiences to each existing survey category in addition to adding unlisted criteria. For example, under the CureTogether entry for chronic obstructive pulmonary disease, the most frequently reported symptoms were shortness of breath, tiring on simple tasks, wheezing, and sleeplessness. Bronchodilators, quitting smoking, albuterol, and corticosteroids were the treatments deemed most effective by members. Second-hand smoke, pollution, and smoking were considered to be the causes of the condition by members.[21]

A signpost to the future of social web-facilitated, appropriately weighted PRI collection and analysis was erected with the publication on the CureTogether blog of the post *6 Surprisingly Effective Treatments for Depression*.[22] A CureTogether community survey (n = 944) indicated that members considered exercise, cognitive behavioral therapy, and meditation as effective as well known treatments for depression. The author chose to interpret the data in order to foreground the fact that it was less well known that some respondents considered light therapy and massage therapy to be more effective individually than a named therapeutic in the treatment of depression. CureTogether members were left with the message that they may wish to consider incorporating such practices into their treatment pathways. Such PRIs can be hypothesis generating and can provide useful information in designing clinical studies.

It should be recognized that symptoms are often self-evident to patients who exhibit and subsequently live with them. Accordingly, patients are more interested in learning about the impact of their disease, the treatment pathways available to them, and the associated evidence, as well as the outcomes they may expect. The information they elect to share with their peers within the patient communities of the social web is rarely available on product labels, which calls into question the importance of PRO labels. Within this context PRO labels may actually be deemed too extrinsic and abstract to be of universal value. While these PRI data may indeed be interesting, they would fail at the first hurdle of many regulators in their decision-making framework in recommending that a product has such attributes. Further change would be necessary for regulators to evaluate and recommend the optimal path an individual patient should take.

7. Conclusions

This article posits a new definition for 'patient-reported information.' The exploration of PRI can lead to new insights for patients into their disease and medicines. However, there are many hurdles to overcome before such data can be successfully used by the pharmaceutical industry, including the following.

- Social aspect: patients will continually need and discuss information about their condition and will also volunteer information in the interest of the collective good.
- Technology aspect: it is likely that novel technologies will continually emerge to uncover new insights from this collective wisdom.
- Regulation aspect: as the importance of PRI is more widely recognized, agreements will be needed to determine how these can be used alongside and in a complementary fashion to PROs and label claims. This involves both promotional material from pharmaceutical professionals to (and now from) healthcare professionals, an aspect discussed extensively at a recent US FDA meeting, and in a wider consideration between how acting in a socially responsible way could yield new emerging insights about treatment and disease. The concern is that these approaches could be viewed as off-label promotion by some stakeholders.
- Economic aspect: the value to patients of distributed knowledge, which will be made up of the investment to collect and interpret these data. New business models of collaboration may result in the declining costs of being able to perform these actions on the social web.

These challenges may ultimately culminate in a cultural change whereby the pharmaceutical industry will adopt a genuine service culture, where a business and legal model enables it to engage responsibly in the health conversation, as

a trusted partner able to present patients with clear and robust information to allow them to make sense of, and make decisions regarding, their healthcare. However, to do this, the industry will need to engage in open, transparent conversations with patient communities within the social web. The challenge is ongoing and needs new leadership from all stakeholders.

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References

1. Berg S. Herceptin: was patient power key? BBC News 2006 Jun 9 [online]. Available from URL: http://news.bbc.co.uk/1/hi/health/5063352.stm [Accessed 2010 Oct 29]
2. Acquadro C, Berzon R, Dubois D, et al. Incorporating the patient's perspective into drug development and communication: an ad hoc task force report on the Patient-Reported Outcomes (PRO) Harmonization Group Meeting at the Food and Drug Administration, February 16, 2001. Value Health 2003; 5: 522-31
3. Burke LB, Kennedy DL, Miskala PH, et al. The use of patient-reported outcome measures in the evaluation of medical products for regulatory approval. Clin Pharmacol Ther 2008 Aug; 84 (2): 281-3
4. European Medicines Agency. Committee for Medicinal Products for Human use (CMHP). Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products. London: EMA, 2005 Jul 27. Doc. ref. EMEA/CHMP/EWP/139391/2004
5. Burke L. Acceptable evidence for pharmaceutical advertising and labeling. Drug Information Association workshop on Pharmacoeconomics and Quality of Life Labeling and Marketing Claims; 2000 Oct 3; New Orleans (LA). Horsham (PA): Drug Information Association, 2000
6. Doward LC, McKenna SP. Defining patient-reported outcomes. Value Health 2004; 7 Suppl. 1: S4-8
7. Doward LC, Meads DM, Thorsen H. Requirements for quality of life instruments in clinical research. Value Health 2004; 7 Suppl. 1: S13-6
8. Doward LC, Gnanasakthy A, Baker MG. Patient reported outcomes: looking beyond the label claim. Health Qual Life Outcomes 2010 Aug 20; 8: 89
9. Mordin M, Lewis S, Gnanasakthy A, et al. Patient-reported outcomes in product development guidance [abstract no. PMC21]. Value Health 2010; 13 (3): A17-8
10. Draborg E, Gyrd-Hansen D, Poulsen PB, et al. International comparison of the definition and the practical application of health technology assessment. Int J Technol Assess Health Care 2005; 21 (1): 89-95
11. Holmes SJ, McKenna SP, Doward LC, et al. Development of a questionnaire to assess the quality of life of adults with growth hormone deficiency. Endocrinol Metab 1995; 2: 63-9
12. National Institute for Health and Clinical Excellence. Human growth hormone (somatropin) in adults with growth hormone deficiency. Technology appraisal 64. London: NICE, 2003 Aug [online]. Available from URL: http://www.nice.org.uk/nicemedia/pdf/TA64_HGHadults_fullguidance.pdf [Accessed 2009 Nov 12]
13. Snowden DJ, Boone ME. A leader's framework for decision making. Harv Bus Rev 2007 Nov; 85 (11): 68-76, 149
14. PatientsLikeMe epilepsy community. What are patients sharing? [online]. Available from URL: http://www.patientslikeme.com/epilepsy/community [Accessed 2010 Oct 18]
15. PatientsLikeMe. Manage your epilepsy like a PRO [online]. Available from URL: http://blog.patientslikeme.com/2010/02/11/manage-your-epilepsy-like-a-pro/ [Accessed 2010 Oct 18]
16. Hartzband P, Groopman J. Untangling the web: patients, doctors and the internet. N Engl J Med 2010 Mar; 362 (12): 1063-6
17. E-patients.net. About us [online]. Available from URL: http://e-patients.net/about-e-patientsnet [Accessed 2010 Jul 23]
18. deBronkart D. EPatientDave [online]. Available from URL: http://twitter.com/ePatientDave/status/12703809401 [Accessed 2010 Jul 23]
19. Spong A. Patient community (curated list of sites) [online]. Available from URL: http://bit.ly/cNR5ho [Accessed 2010 Jul 23]
20. PatientsLikeMe collaborates with Novartis to create an open online community for organ transplant recipients: two new programs unveiled to help patients 'give back' [press release]. 2010 Mar 9 [online]. Available from URL: http://bit.ly/eJhB4w [Accessed 2010 Dec 10]
21. CureTogether. Chronic obstructive pulmonary disease (statistics and survey) [online]. Available from URL: http://www.curetogether.com/chronic-obstructive-pulmonary-disease/symptoms [Accessed 2010 Apr 16]
22. Carmichael A. 6 surprisingly effective treatments for depression [online]. Available from URL: http://curetogether.com/blog/2010/04/22/6-surprising-depression-treatments/ [Accessed 2010 Nov 2]

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