REVIEW ARTICLE

Drug Saf 2012; 35 (6): 437-446
0114-5916/12/0006-0437/$49.95/0

Web-Based Patient-Reported Outcomes in Drug Safety and Risk Management

Challenges and Opportunities?

Anjan K. Banerjee[1,2,3] and *Simon Ingate*[1]

1 Pope Woodhead & Associates, St Ives, Cambridgeshire, UK
2 Institute of Biotechnology, University of Cambridge, Cambridge, UK
3 Department of Surgery, ULH NHS Trust, Lincoln, UK

Contents

Abstract

Patient-reported outcomes (PROs) from web-based sources are becoming increasingly important, providing opportunities for industry and regulators to understand the benefits and risks of medicines in a real-world context. Although some guidance exists for the use of adverse event (AE) reports from company-sponsored social network sites, this does not cover non-company-sponsored sites. Additionally, there are concerns about the validity of data from social media sources. Techniques for the collection, analysis and reporting of safety data from patients should be defined, and guidelines agreed, to cover PROs and patient-reported adverse drug-related events from more organized sources of patient outcomes.

This review considers drivers for web-based PRO adoption in drug safety, the current regulatory framework and potential methodologies, and concludes that there is an urgent unmet need for guidelines on web-based PRO AEs. Stakeholders for the development of any such guidance should include industry, patients, regulators, academic groups and prescribers.

The US FDA defines a patient-reported outcome (PRO)[1] as any report of the status of a patient's health condition coming directly from a patient without interpretation by clinicians or others, including self-perception symptom severity (absolute or relative to a previous report), and physical performance, but not information derived by others, e.g. physical examinations or performance

assessed by a healthcare professional (HCP). PROs in the post-launch environment have the potential to provide new sources of benefit-risk information augmenting those available through traditional clinical trials and pharmacovigilance. Opportunities include the disclosure of new adverse events (AEs), early signal detection, greater volumes of data, quality of life data, information on patient-centric language and, via proxies, data for elderly, paediatric or infirm patients.[2-5]

This review will consider the use of PROs in the real-world evaluation of the benefits and harms of medicines, with particular focus on AE reporting from non-company-sponsored websites, and post-launch risk assessment. Current FDA guidance only covers the use of PRO in clinical trials 'instruments' to support labelling claims. The FDA defines a PRO instrument (i.e. a questionnaire plus the information and documentation that support its use) as a means to capture PRO data used to measure treatment benefit or risk in medical product clinical trials. However, PROs collected for AEs post-launch are as crucial as clinical trial safety PROs in the ongoing assessment of benefits and harms of a drug through its lifecycle.

We propose that post-launch PRO AEs may be usefully subdivided into AE reports collected from predefined patient groups (i.e. non-interventional post authorization safety studies), as well as non-predefined groups (figure 1). Non-predefined patient groups may enter data into a structured web-based framework (although no consensus criteria for a suitable core dataset for non-predefined PRO AEs currently exist) or as unstructured reports. PRO AEs collected from a pre-specified population post-launch will have many of the same characteristics and dataset requirements as clinical trial PRO AEs; whereas post-launch non-specified population PRO AEs will require distinct datasets, methodologies and

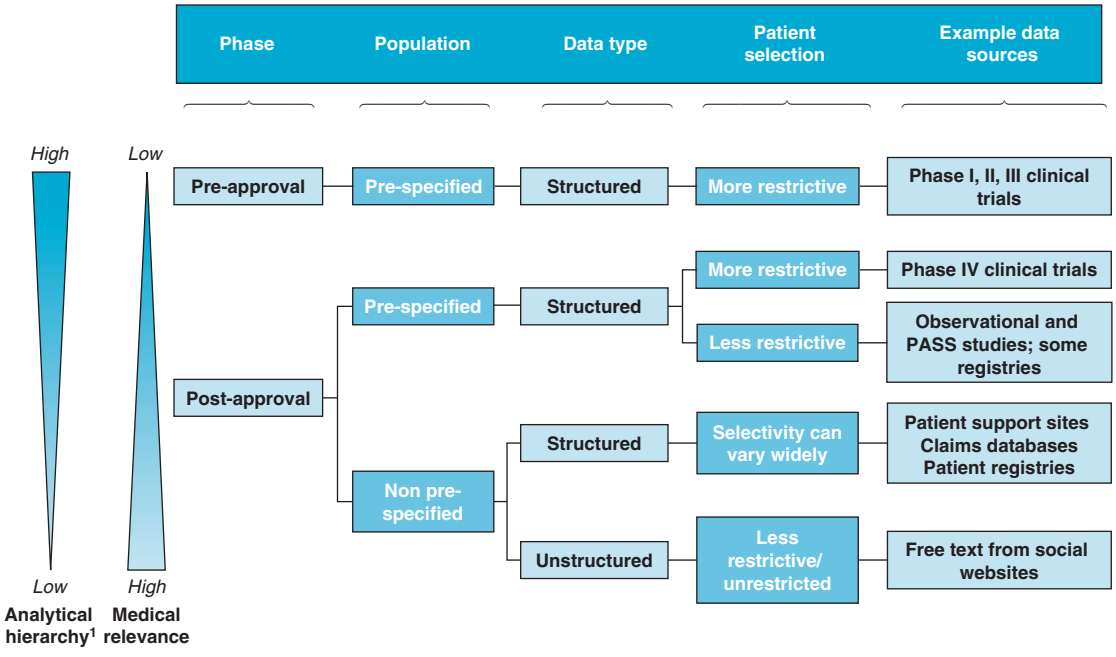


Fig. 1. Different patient-reported outcome adverse event datasets are relevant at varying stages of the product lifecycle. **PASS** = Post-Authorization Safety Study.

analytic approaches in meaningful assessment of safety signals.

With the advent of patient-focussed health social networks and other online and social media[6] such as Facebook[7] or Myspace[8] where patients might discuss outcomes, Physician Q&A sites (MedHelp,[9] Wellsphere,[10] MDJunction,[11] iMedix,[12] WEGO health[13]) where they could discuss their symptoms (including AEs) with medically qualified professionals, or quantified self-tracking sites (CureTogether,[14] MedHelp,[9] PatientsLikeMe,[15] SugarStats[16]) where patients share their medical records and details of their tolerance of treatment with their peers. An organized and/or self-tracking website has enhanced functionality to collect PRO AE data in a structured framework or dataset, and also strengthens valid data collection by reducing the risk of false or duplicate reporting by tracking the email addresses and web signature of participants. It follows that the potential for collecting post-launch PRO AEs both from specified and non-prespecified patient groups has therefore greatly increased, and any current guidance for web-based PROs will need updating.

1. Drivers for Patient-Reported Outcome (PRO) Adoption

Arguments supporting PRO utilization and patient-reported AEs include limitations of current data collection and reporting, discordance between what HCPs and patient believe is important (particularly for those illnesses with subjective symptoms and endpoints) and the ability to obtain richer contextual information from a patient perspective, particularly for aggregated data. Several social and technical changes (patient empowerment and technological improvements) are making PRO commonplace.

1.1 Limitations with Current Data Collection

Post-launch suspected adverse drug reactions (ADRs) are greatly underreported by HCPs,[17] especially if the ADRs are already labelled.[3] This is partly compensated by patient self-reporting in some countries, but haphazard single consumer reports have limited validity.[3,18] However, social media and other sites are generating drug safety information that may go unreported, and it is important to minimize this unreported information especially from the more organized/quantified patient self-tracking sites (e.g. SugarStats[16] or PatientsLikeMe[15]).

1.2 Discordance between Patients and Prescribers

Reliance on outcomes measures reported by HCPs on standard CIOMS and MedWatch forms, which often remain incomplete, even after follow-up from company pharmacovigilance staff, often overlooks the symptomatic patient perspective, concentrating instead on objective clinical outcomes or biomarkers.[19-21] The use of well designed patient questionnaires can provide information to augment medically confirmed reports where underreporting or inaccurate case descriptions are known to be problematic, although such approaches may be resource-intensive and fall within the realms of active surveillance and sentinel site reporting.[20] This is especially relevant where patient-centred outcomes, such as tolerability which is strongly related to treatment adherence and effectiveness, are sought. Differences in focus between patients' and HCPs' perspectives on the benefits and harms of treatments biases the picture of how drugs are tolerated and which adverse outcomes might be of concern to patients.[20-23] This is likely to impact quality of care, patient safety and outcomes. Discordance can be due to a patient's reluctance to discuss certain ADRs with their HCPs,[24] leading to signals being missed. In a study of prostate cancer patients, some expected AEs were identified by physicians, such as erectile dysfunction and urinary incontinence, whereas other symptoms, including fatigue, diarrhoea and rectal urgency, although reported by patients, were overlooked in medically confirmed AE reports.[24]

Other reasons for underreporting safety events include patients not understanding the significance of ADRs they are suffering, or they may be unsure whether it is drug related, and so do not wish to disturb the HCP, or sometimes they might

not want to disappoint their HCP with bad news as it may be perceived that they are complaining about the quality of healthcare provided.[25] Additionally, HCPs might not discuss ADRs or concerns about medication with their patients,[26,27] or underestimate a patient's desire to be informed about ADRs.[28] Poor communication between patients and HCPs can limit the reporting of important safety issues[23,25] and may lead to patients continuing sub-optimal treatment after suffering safety issues.[25]

The provision of risk minimization communications and company-sponsored or independent websites have increased patient awareness of drug safety issues. Nevertheless, patients may be more willing to discuss quality of life and drug safety issues with their peers on social media sites.[29] For example, reports of insomnia (hydrocortisone), bruising (Azilect®) and anxiety (St John's Wort) have been discussed on the PatientsLikeMe website.[29] Publicizing safety issues of interest in the media has been shown to lead to peaks in HCP and consumer ADR reporting,[3,30] and social media sites either sponsored by companies or set-up by health interest groups are likely to also encourage similar behaviours.

1.3 Better Patient Context

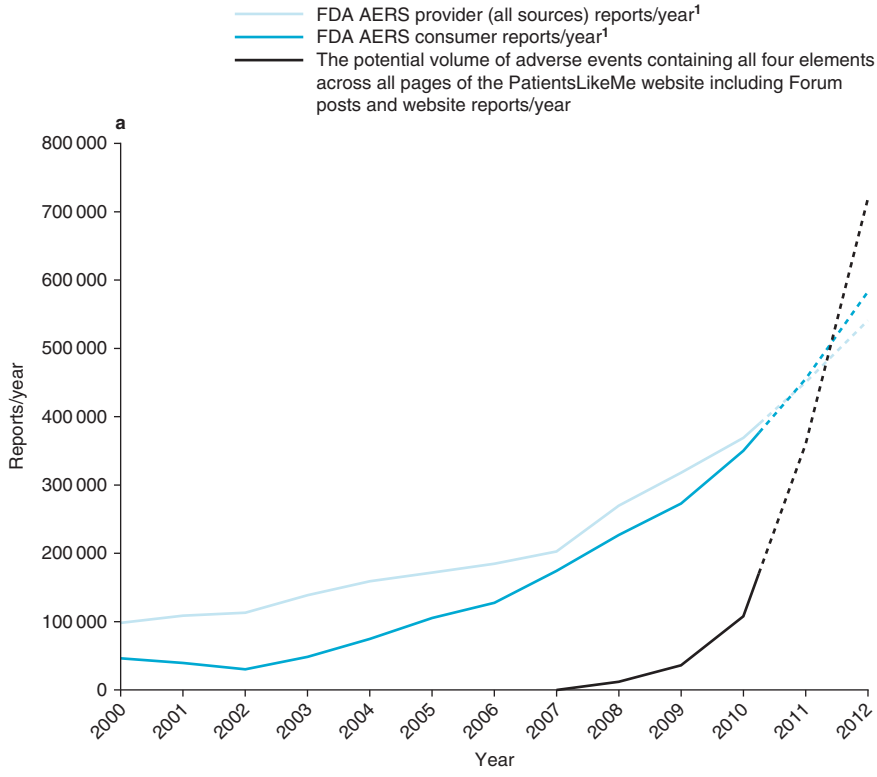
PROs therefore provide a number of advantages, including higher volume and richer context, leading to a better understanding of AE prevalence data; the availability of online AE reporting mechanisms improves patient satisfaction and ultimately drug safety. Blenkinsopp et al.[18] reviewed the potential benefits and drawbacks of patient reporting of AEs and found that patient and HCP AE reports may be of similar quality, and patients often reported new AEs and symptoms more quickly than HCPs. However, processing patient reports is marginally more time consuming than reports supplied by HCPs, and current levels of patient reporting remain low, both in absolute terms and as a proportion of all reports.

Today, with the advent of web-based PROs, consumer AE reports are increasing and there is now evidence that the number of AEs generated on patient self-reporting PRO sites may outstrip those reported by other means (figure 2).

Online reporting of chemotherapy toxicity monitoring has been shown to be feasible even with patients with advanced cancers,[31] although patient reminders to provide data was important, suggesting a stimulated element to successful PRO safety reporting may be needed. Electronic PROs were reported to be accurate and efficient, and promoted better patient-doctor communication as alerts of any PRO were sent to HCPs.[32] These systems help in the early identification of AEs, and improve patient outcomes, research data quality and patient satisfaction.[31-33] Where patients cannot report themselves (elderly, children or the infirm) proxies (parents, carers) can be used. This means most patient types could be accessed when collecting PROs. However, the reliability of proxy/patient concordance needs to be considered when developing data collection techniques.[4,34] Patients and carers can also give better context than HCPs on the effects of treatment on patient's functioning and quality of life, especially with transient symptoms which HCPs may not have the opportunity to observe.[22]

There are a number of sociological and technical drivers that have increased the demand for PROs, including the increased prevalence of chronic diseases, patient empowerment, advances in information technology (prevalence of the Internet, wider access to broadband),[35] the use of the Internet for information seeking[1] and social networking by patients and pharmaceutical companies[6,33,36,37] and the observation that peer-to-peer information sharing, especially via social media, encourages reporting.[29,33] A consequence of this is that patients are more informed about diseases and treatments and are willing to discuss treatment-related outcomes with their peers. However, not all health-related social media sites are set-up to identify and report AEs. Since their primary purpose is to connect people with similar diseases or

1 Pew Research Centre estimates that 73% of US adults have Internet access and, of these, 83% use the Internet for health-related information.



1 See data table below.

b

Year	Healthcare provider: physician	Healthcare provider: pharmacist	Other healthcare provider	Total healthcare provider	Consumer
2000	59 090	18 794	20 191	98 075	46 249
2001	66 001	19 050	23 685	108 736	39 517
2002	67 967	17 184	27 944	113 095	30 282
2003	79 793	19 410	39 392	138 595	48 352
2004	92 737	20 329	46 056	159 122	74 644
2005	106 362	21 540	43 820	171 722	105 308
2006	113 444	21 512	49 827	184 783	127 475
2007	121 000	21 343	60 343	202 686	174 216
2008	154 044	27 070	88 651	269 765	226 647
2009	177 861	29 208	110 815	317 884	272 989
2010 (Q1)	49 680	7 734	34 825	92 239	70 033

Fig. 2. (**a**) The ever-increasing burden of consumer reporting and follow-up could overload the system (adapted from PatientsLikeMe,[15] previously unpublished data). Dashed lines refer to extrapolated data. (**b**) Number of reports in the US FDA Adverse Event Reporting System by report (2000–Q1 2010).

who are using the same medicines, AE discussions arise as a consequence of their existence. Some non-company-sponsored sites can identify and analyse AEs but, to date, these reports are not passed onto either regulators or drug manufacturers and no regulations cover them.[1,38,39] Scurti et al.[40] recently called for a reformulation of pharmacovigilance methods and legislation away from the current drug-centric paradigm to a real-world patient/population-centred focus. In this model, the qualitative and narrative accounts of patients become an important and routine component of research studies. Pharmacovigilance becomes more than establishing benefit-risk profiles covering safety, acceptability and satisfaction of overall care.

2. A Regulatory Perspective

FDA guidance on the use of PROs to support labelling claims focuses on their use in organized clinical trials and how the FDA reviews and evaluates clinical trial PRO instruments[1] (as defined in the introductory section) and provides guidance on the choice and development of PRO instruments and how they fit within the traditional clinical trial framework. However, it does not cover PROs that are used for other purposes such as patient or disease communities, nor those that are not company-sponsored. In Europe, several pieces of legislation and guidance are relevant to web-based PRO use, and are summarized in table I.

A recent Association of the British Pharmaceutical Industry (ABPI) white paper on pharmacovigilance on the Internet[39] recognizes that current legislation is restricted predominantly to company-sponsored sites, but with new ways in which patients access information about medicines, record and share their experiences and as a consequence generate either intentional or inadvertent PROs including AEs, there is a gap in legislation and guidance. The white paper suggests that vigilance needs to be proportional to public health benefit and recognizes that non-company-sponsored sites may produce relevant, although different and non-traditional, pharmacovigilance data, and suggests that companies should:

Table I. Current legislation and guidance relevant to patient-reported outcomes

Legislation or guidance	Description	Comments
Regulation 726/2004[41] Directive 2001/83/EC[42]	Key legislation underpinning pharmacovigilance in Europe	General principles, non-specific for PROs
Volume 9A, Part I, Section 4.3.3, 2008[43]	Deals with regular screening of company-sponsored websites for potential reports on AEs. If companies become aware of AEs on other websites, they should examine the case and determine if it needs to be expedited. Company-sponsored websites should facilitate AE reporting	• Interventional vs non-interventional studies well defined • Medically confirmed vs consumer reports differentiated • PRO safety may have to be added in future editions
Volume 9A, Part I, Section 4.2[43]	Individual Case Safety Reports requiring expedited reporting should be transmitted within 15 days of the date they become aware of the event	Timelines likely also to apply to PROs (company sponsored)
CIOMS Working Group 5 Report, Section IId[44]	''The working group does not believe it is necessary for regulators or companies to 'surf' the internet beyond their own sites for individual spontaneous reports''	Gives non-binding guidance on active solicitation of consumer reports
ABPI Code of Practice for the Pharmaceutical Industry (UK)[45]	Covers promotional materials about prescription medicines direct to a UK audience via the Internet	Relevant for promotional aspects
ABPI Guidance Notes on the Management of Adverse Events and Product Complaints on Company-Sponsored websites[38]	Provides detailed guidance about company-sponsored sites	Relevant for promotional aspects

ABPI = Association of the British Pharmaceutical Industry; **AE(s)** = adverse event(s); **PRO(s)** = patient-reported outcome(s).

1. not be obliged to collect and follow-up individual cases;
2. treat data as an adjunct to conventional sources;
3. work with regulators on aggregate analysis to generate or confirm signals appropriate to the drug and the data, not mandated by legislation;
4. record the intention to examine non-company-sponsored data in appropriate regulatory documentation (e.g. in risk management plans or pharmacovigilance plans).

This pragmatic approach is suitable for the majority of simple health-related social network sites (e.g. Facebook and Twitter, which are unlikely to yield useful data) but may be inappropriate for either Physician Q&A (where systems similar to the Medicines and Healthcare products Regulatory Agency [MHRA] Yellow Card Scheme may be useful for individual case reports) or self-tracking sites (where aggregate data can be generated or direct report forms could be provided). Hence, the latter types of PRO sites need serious consideration in playing a key role in future post-launch pharmacovigilance, and therefore require corresponding legislation and guidance.

3. Methodological Considerations for Web-Based PRO Sites

PROs provide valuable information for the holistic assessment of the benefits, risks and outcomes of real-world medicine utilization. They could be used to supplement current pharmacovigilance and postmarketing studies such as post-authorization safety studies, disease and patient registries, and may be employed in the evaluation of the effectiveness of risk management approaches, including risk minimization tools. For PROs, especially AEs from web-based PRO sources, to be considered acceptable by industry and regulators the following areas need consideration:

- how should data be collected?
- how should safety signals be managed?
- does the concept of medically confirmed fit within the PRO paradigm when patients or carers are reporters?

Additionally, there are some potential drawbacks specific to web-based health communities and their hosts which should be tackled.

PRO data are traditionally collected using formal questionnaires or patient diaries, depending on the type of data sought. Health-related quality of life assessments[4,23,34,46,47] use such instruments as the EORTC QLQ-C30,[2] SF-36,[3] EuroQoL[4] and QL-index,[5] and AE reporting in oncology is well served by the CTCAE[6] questionnaire;[22,32,33] simple forms for more general AE report collecting are also available.[30,48]

Modern IT technologies used on self-reporting PRO sites such as PatientsLikeMe[15] are capable of identifying symptoms and potential safety signals that appear in the natural language data input by users.[49] This is achieved through creating user generated taxonomies (containing scientific and lay terms) from patient data to produce semi-structured lists of terms. These are reviewed periodically and relevant items become core terms. These are used for analysing the database to identify symptoms and signals that can be matched against recognized medical data references. This data is complimented by detailed patient demographic information, including treatment start and stop dates, dose, frequency and the purpose for which the medication was taken, for all medicines used by the patients.[50] Limitations of the approach include dealing with items that do not match recognized clinical terms due to the use of fragments of phrases, spelling mistakes, vague reports, slang, using two concepts in a single expression or other less easily computer–classifiable terms; however, manual review can be used to match them to standard medical terms. PRO AEs

2 EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (30 questions).

3 SF-36: Short Form (QoL questionnaire) – 36 questions.

4 EuroQoL: EQ5D – standardized health outcome instrument.

5 QL-index: Spitzer Quality of Life Index.

6 CTCAE: National Cancer Institutes' Common Terminology for Adverse Events.

have now been shown to have greater validity and reliability in assessing safety signals compared with data from traditional medically reported AEs from clinical trials, particularly for disease conditions with fluctuating underlying symptoms, with subjective endpoints.[50]

Surveys of side effects allow patients to report specific effects of treatments and rate the severity on a scale of none-mild-moderate-severe. Patients' data include prompted data which are selected from a list and unprompted data which are entered using free text. Information is unfiltered and reported by the patient non-conditionally and can be computed and connected,[50] allowing long-term aggregated data generation, which are of far greater value than single case reports.[23] The generic name, rather than the brand name, of drugs is used, partly to increase objectivity of reporting from patients, i.e. to disassociate the manufacturer from the side effect, but also to avoid distortion of aggregate reporting with brand names. A few pharmaceutical companies currently use this technology for drug safety monitoring for specific products within selected disease conditions. These companies receive serious AE reports consistent with expedited reporting obligations and non-serious events in a CIOMS-like line listing report.

Should early signals of PRO websites be suspected or sites wish to identify specific measures, there is no reason why more formal questionnaires cannot be implemented irrespective of industry ownership. For some of the physician Q&A social media sites, links to patient-specific AE reporting tools (i.e. Yellow Cards) might be more appropriate.[51]

The current paradigm of 'medically confirmed' in AE reporting may need to be adjusted in the light of evolving technology and data gathering. Consumer reports from most PRO sites are probably best treated as aggregate signal detection information of a special type because the data come from patients (who may or may not be the reporter) or proxies (carers). Analysis of data for medical relevance will be done by the scientists managing the sites, but for practical or ethical or legal (data protection) reasons they may not be able to contact the patient to follow-up individual cases.

Other potential issues with PRO AE reporting, and the use of PROs in risk assessment, also include the following:

1. In the real world, patients take multiple medicines, prescriptions and over-the-counter (OTC) medications so attribution of an event to a single drug may be difficult.
2. The Internet might bias reports from certain age populations although proxy reporting by parents or carers of the elderly reduces this.
3. Careful validation is required to satisfy regulators that data are robust.
4. There is a risk of malicious or false reports perhaps from patients reporting a single event multiple times, although data mining algorithms for fraud detection may help.
5. There is no legal obligation for reporting.
6. Perhaps most importantly, if the large numbers of AEs available on these sites were to be reported today, industry and regulators might not be able to cope with the volume of data.

4. Conclusions

There are few, if any, limitations in the quality of drug safety information that can be provided by patients or their proxies via the use of specific data collection instruments. Appropriate validated analysis approaches need agreement to allow signal detection and benefit versus harm assessment to be performed. In any case, this is an unstoppable reality that the industry and regulators need to urgently deal with. Patients, prescribers, industry, academia and regulators should therefore collaborate to develop validated guidance on patient-provided data and the PRO methodology used to generate and validate it, with a particular focus on harms and benefits of medicines.

Acknowledgements

The authors would like to thank Sally Okun from PatientsLikeMe for supplying figure 2 and the accompanying Adverse Event Reporting System data.

No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest that are directly relevant to the content of this review, but are currently chairing and convening a not-for-profit Patient Reported Outcomes in Safety Event Reporting (PROSPER) consortium between industry, regulators, prescribers, aca-

demics and patients to develop tangible guidelines in this area. Interested parties are requested to contact Dr Banerjee directly at the correspondence address to obtain further details of the PROSPER consortium.

References

1. FDA Guidance for Industry. Patient-reported outcomes measures: use in medical product development to support labeling claims. December 2009 [online]. Available from URL: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf [Accessed 2012 Mar 26]
2. Ahmed AM, Izham IM, Subish P. The importance of the consumer pharmacovigilance system in developing countries: a case of Malaysia. J Clin Diag Res 2010 Aug; 4: 2929-53
3. van Hunsel F, Passier A, van Grootheest K. Comparing patients' and healthcare professionals' ADR reports after media attention: the broadcast of a Dutch television programme about the benefits and risks of statins as an example. Br J Clin Pharmacol 2009 May; 67 (5): 558-64
4. Sneeuw KCA, Aaronson NK, Sprangers MAG, et al. Comparison of patient and proxy EORTC QLQ-C30 ratings in assessing the quality of life of cancer patients. J Clin Epidemiol 1998 Jul; 51 (7): 617-31
5. Wade AG, Crawford GM, Pumford N, et al. Baseline characteristics and patient reported outcome data of patients prescribed etanercept: web-based and telephone evaluation. BMC Med Res Methodol 2011 Jun 14; 11: 91
6. Swann M. Emerging patient-driven health care models: an examination of health social networks, consumer personalised medicine and quantified self-tracking. J Environ Res Public Health 2009 Feb; 6 (2): 492-525
7. Facebook [online]. Available from URL: www.facebook.com [Accessed 2012 Feb 22]
8. Myspace [online]. Available from URL: http://www.myspace.com/ [Accessed 2012 Feb 22]
9. MedHelp [online]. Available from URL: http://www.medhelp.org/ [Accessed 2012 Feb 22]
10. Wellsphere [online]. Available from URL: http://www.wellsphere.com/ [Accessed 2012 Feb 22]
11. MDJunction [online]. Available from URL: http://www.mdjunction.com/ [Accessed 2012 Feb 22]
12. iMedix [online]. Available from URL: http://www.imedix.com/ [Accessed 2012 Feb 22]
13. WEGO health [online]. Available from URL: http://www.wegohealth.com/ [Accessed 2012 Feb 22]
14. CureTogether [online]. Available from URL: http://curetogether.com/ [Accessed 2012 Feb 22]
15. PatientsLikeMe [online]. Available from URL: http://www.patientslikeme.com/ [Accessed 2012 Feb 22]
16. SugarStats [online]. Available from URL: https://sugarstats.com [Accessed 2012 Feb 22]
17. Lopez-Gozalez E, Herdeiro MT, Figueiras A. Determinants of under-reporting of adverse drug reactions: a systematic review. Drug Saf 2009; 32 (1): 19-31
18. Blenkinsopp A, Wilkie P, Wang M, et al. Patient reporting of suspected adverse drug reactions: a review of published literature and international experience. Br J Clin Pharmacol 2006 Sep; 63 (2): 148-56
19. Basche E. The missing patient voice in drug-safety reporting. N Engl J Med 2010 Mar 11; 362 (10): 865-9
20. Skinner KM, Miller DR, Lincoln E, et al. Concordance between respondent self-reports and medical records for chronic conditions: experience from the veteran's health study. J Ambul Care Manage 2005 Apr-Jun; 28 (2): 102-10
21. Pakhomov SV, Jacobsen SJ, Chute CG, et al. Agreement between patient-reported symptoms and their documentation in the medical record. Am J Manag Care 2008 Aug; 14 (8): 530-9
22. Cerillo M, Venturini M, Ciccarelli L, et al. Clinician versus nurse symptom reporting using the National Cancer Institute common terminology criteria for adverse events during chemotherapy: results of a comparison based on patients' self-reported questionnaire. Ann Oncol 2009 Jul; 20 (12): 1929-2935
23. Fromme EK, Eilers KM, Mori M, et al. How accurate is clinician reporting of chemotherapy adverse events? A comparison with patient-reported symptoms from the quality of life questionnaire C30. J Clin Oncol 2004 Sep; 22 (17): 2485-90
24. Litwin MS, Lubeck DP, Henning JM, et al. Differences in urologist and patient assessments of health related quality of life in men with prostate cancer: results of the CaPSURE database. J Urol 1998 Jun; 159 (6): 1988-92
25. Weingart SN, Tejal K, Gandhi K, et al. Patient-reported medical symptoms in primary care. Arch Intern Med 2005 Jan; 165: 234-49
26. Sleath B, Roter D, Chowning B, et al. Asking questions about medication: analysis of physician-patient interactions and physician perceptions. Med Care 1999 Nov; 37 (11): 1169-73
27. Marvel MK, Epstein RM, Flowers K, et al. Soliciting the patient's agenda: have we improved? JAMA 1999 Jan 20; 281 (3): 283-7
28. Zeigler DK, Mosier MC, Beunaver M, et al. How much information about adverse events of medications to patients want from physicians? Arch Intern Med 2001 Mar 12; 161 (5): 706-13
29. Brownstein CA, Brownstein JS, Williams DS, et al. The power of social networking in medicine. Nature Biotech 2009 Oct; 27 (10): 888-90
30. Aagaard L, Hansen EH. Consumers' reports of suspected adverse drug reactions volunteerd to a consumer magazine. Br J Clin Pharmacol 2010 Aug; 69 (3): 317-8
31. Basch E, Artz D, Iasonos A, et al. Evaluation of an online platform for cancer patient self-reporting of chemotherapy toxicities. J Am Med Inform Assoc. 2007 May-Jun; 14 (3): 264-8
32. Basch E, Iasonos A, Barz A, et al. Long-term toxicity monitoring via electronic patient-reported outcomes in patients receiving chemotherapy. J Clin Oncol 2007 Dec 1; 25 (34): 5374-80
33. Basch E. Patient-reported outcomes in drug safety evaluation. Ann Oncol 2009 Dec; 20 (12): 1905-6
34. Sneeuw KC, Sprangers MA, Aaronson NK. The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease. J Clin Epidemiol 2002 Nov; 55 (11): 1130-43
35. Acquadro C, Berzon D, Dubois D, et al. Incorporating the patient's perspective into drug development and commu-

nication: an ad hoc task force report of the Patient-Reported Outcomes (PRO) Harmonization Group meeting at the Food and Drug Administration, February 16, 2001. Value Health 2003 Sep-Oct; 6 (5): 522-31

36. Pew Research Centre. Trend data survey: what internet users do online (survey completed 2010) [online]. Available from URL: http://www.pewinternet.org/Trend-Data/Online-Activites-Total.aspx [Accessed 2011 Nov 10]
37. Brownstein CA, Wicks P. The potential research impact of patient reported outcomes on osteogenesis imperfecta. Clin Orthop Relat Res 2010 Oct; 468 (10): 2581-5
38. ABPI. Guidance notes on the management of adverse events and product complaints from pharmaceutical company sponsored websites, 13th June 2011 [online]. Available from URL: http://www.abpi.org.uk/our-work/library/guidelines/Pages/safety-data-websites.aspx [Accessed 2011 Nov 10]
39. ABPI. Pharmacovigilance and the internet: a call for change. A white paper from the ABPI pharmacovigilance expert network, 13th June 2011 [online]. Available from URL: http://www.abpi.org.uk/our-work/library/industry/Pages/pharmacovigilance-the-internet.aspx [Accessed 2011 Nov 10]
40. Scurti V, Romero M, Tognoni G. A plea for more epidemiological and patient-oriented pharmacovigilance. Eur J Clin Pharmacol 2012; 68 (1): 11-9
41. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency [online]. Available from URL: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2004_726_cons/reg_2004_726_cons_en.pdf [Accessed 2012 Mar 26]
42. European Commission/European Medicines Agency (EC/EMA). Directive 2001/83/EC of the European Parliament and the council of 6th November 2001 on the community code relating to medicinal products for human use (as amended 2002, 2004) [online]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004481.pdf [Accessed 2011 Nov 5]
43. European Commission/European Medicines Agency (EC/EMA). Volume 9a of the rules governing medicinal products in the European Union: guidelines on pharmacovigilance for medicinal products for human use. London, September 2008 [online]. Available from URL: http://ec.europa.eu/health/ files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf [Accessed 2011 Oct 7]
44. World Health Organization. Current challenges in pharmacovigilance: pragmatic approaches (report of CIOMS Working Group V). Geneva: World Health Organization, 2001
45. ABPI. Code of practice for the pharmaceutical industry, 2011 edition, together with the prescription medicines code of practice authority: constitution and procedure [online]. Available from URL: http://www.pmcpa.org.uk/files/sitecontent/ABPI_Code_2011.pdf
46. Wiklund I. Assessment of patient-reported outcomes in clinical trials: the example of health-related quality of life. Fundam Clin Pharmacol 2004 Jun; 18 (3): 351-63
47. Perry S, Kowalski TL, Chih-Hung C. Quality of life assessment in women with breast cancer: benefits, acceptability and utilization. Health Qual Life Outcomes 2007 May; 5: 24
48. Hohl CM, Abu-Laban RB, Zed PJ, et al. Patient-reported adverse drug-related events from emergency department discharge prescriptions. CJEM 2010 Jul; 12 (4): 331-8
49. Arnott-Smith C, Wicks PJ. PatientsLikeMe: consumer health vocabulary as a folksonomy. AMIA Annu Symp Proc 2008; 682-6 [online]. Available from URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2656083/ [Accessed 2012 Apr 12]
50. Wicks P, Vaughan TE, Massagli MP, et al. Accelerated clinical discovery using self-reported patient data collected online and a patient-matching algorithm. Nat Biotechnol 2011 May; 29 (5): 411-4
51. Van Hunsel F, Harmark L, Pal S, et al. Experiences with adverse drug reaction reporting by patients: an 11 country survey. Drug Saf 2012; 35 (1): 45-60

Correspondence: Dr *Anjan Kumar Banerjee*, Deputy Managing Director, Pope Woodhead & Associates, The Old Grammar School, 1 Ramsay Road, St Ives, Cambridgeshire PE27 5BZ, UK.
E-mail: swapu.banerjee@popewoodhead.com

