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Improving Patient Involvement in Medicines Research and Development: A Practical Roadmap

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Abstract

The value of patient involvement (PI) in medicines research and development (R&D) is increasingly recognized by all health stakeholders. Despite numerous ongoing PI initiatives, PI so far lacks structure and consistency in approach. Limited formal documentation of PI activities further hampers the sharing of experience and learnings, preventing timely and systematic implementation. This article summarizes the outcomes of several multistakeholder discussions during 2013-2016 in a practical roadmap for PI in medicines R&D. The roadmap highlights specific opportunities for PI along the 4 key stages of the medicines R&D life cycle and is illustrated with concrete examples. This roadmap's aim is to provide a tool to facilitate PI during medicines research and development and is being shared to encourage implementation and further refinement.

Keywords

patient involvement roadmap, patient input

Introduction

There is growing agreement that patient involvement (PI) in medicines research and development (R&D) provides value for all stakeholders, including patients, researchers, industry, regulatory bodies, payors, and policy makers.[1-5] A literature review undertaken by PatientPartner—a 3-year project within the 7th Framework programme funded by the European Commission—summarizes potential benefits[6] (Table 1): more relevant research priorities from the outset, patient-relevant research methods and findings, and therapies healthcare interventions and therapies better targeted at patients' needs.

Despite little formal evaluation, PI is also thought to result in more meaningful outcome measures and may help to improve recruitment and retention in clinical trials.[3,8] In the rare disease setting, inclusion of patient groups in fundamental and clinical research as equal partners has been reported to contribute to the success of research applications and the research conducted.[9] In addition, funding bodies increasingly demand the involvement of patient organizations in grant applications and applicants' consortia. The new revised CIOMS international ethical guidelines for health-related research involving humans have also addressed this topic.[10]

However, the "when, where, why and how" of meaningful PI across all stages of medicines R&D remains a subject of debate and lacks clear practical guidance. Given the increasing costs of medicines development and the financial consequences of market failure,[11,12] incorporating PI early in biomedical research may reduce waste of R&D resources.[7,13,14,15-17]

PI can also support preventive and effective use of medicines post-approval. Adherence to therapy is a major factor for treatment effectiveness in many conditions, especially in chronic diseases. Studies indicate that therapy adherence correlates with the management and long-term effects of side effects as well as the impact on work and social life,[17-20] highlighting that reflecting contextual concerns of patients in the design of clinical studies may have a positive influence on study recruitment, retention, data quality, therapy adherence, and outcomes. A recent literature review exploring patients' and the public's knowledge, beliefs, and understanding of medicines R&D recommended that patient and public involvement becomes an integral part of the medicines development process

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Table 1. Benefits of Patient Involvement in Clinical Research.[7]

Benefits Described for Patients	Benefits Described for Research
Making sure research and research outcomes address patients' genuine unmet needs	Making sure research and research outcomes address patients' real unmet needs, and not professionals' perception of patients' needs
Gaining knowledge and research skills	Changes in information material given to patients
Greater self-esteem and confidence of patient representative involved in the process	Increased recruitment and better recruitment strategy
Utilizing patient experience and knowledge on their condition	Increased response rates
Acceptance of patients as equal partners in the clinical trial process and increased sense of ownership of the research	Changes in study design or elements (eg, methods of data collection, analysis of qualitative data, research questions, tools, priorities, and outcomes
Access to funding for bringing researchable topics to the research agenda that otherwise may not be taken into consideration	More patient-relevant research findings and methods
Increased understanding of the nature and purpose of a clinical trial	Challenged the assumptions made by researchers
Better understanding between patients and researchers	Wider dissemination of findings
Development of health care and therapies that are more representative of patient's needs	
Data and information exchange between users and industry on realities of use and management (phase IV postmarketing pharmacovigilance commitments)	

with PI approaches across all stages.[21] We describe a practical roadmap for PI across the whole medicines R&D life cycle developed through a collaborative venture that brings together existing good practice and guidance.

PI also is increasingly having a role to play beyond R&D such as in health technology assessment (HTA) and has been recognized as particularly important for assessment of orphan medicines where value and benefit uncertainties prevail.[22] An early PI in R&D may therefore help PI in HTA as well.

Roadmap Development Process

The roadmap of patient involvement in medicines R&D is the result of a collaborative undertaking of the authors and based on multistakeholder discussions that took place between 2013 and 2016. As a first step, reports from the PatientPartner project were reviewed, focusing on the *Sponsors and Investigator Guide Patient Involvement in Clinical Research* to identify guidance relevant to PI across medicines R&D. Outputs from this review were further developed (based on the European Patients' Academy on Therapeutic Innovation [EUPATI] Syllabus, which covers all areas of medicines R&D) at various workshops and meetings held between the 33 EUPATI consortium members, including patient organizations, academia, nongovernmental organizations, and industry. Findings from these workshops and meetings were discussed and refined during five European Patient Advocacy Leadership Council Oncology (EPALCO) workgroups involving representatives from Novartis Oncology and patient organizations, The Organisation for Professionals in Regulatory Affairs (TOPRA)/European Medicines Agency (EMA) Annual Review conference, DIA EuroMeetings, and at Amgen Europe workshops. As a final step, the report from 2 EUPATI workshops ("Patient Involvement in Industry R&D" in July 2014 and workshop on the "Interaction of Patients, Regulators and Industry" in July 2016) and the accompanying 28 case reports of practical PI in medicines R&D were reviewed and the recommendations and guidance within these incorporated into the roadmap. Appendix A provides details of key workshops and meetings that informed development of the roadmap. The general approach for review of PI material and reports that were used for development of the roadmap is outlined in Figure 1.

Through review of existing reports and guidance, the R&D life cycle was categorized into 4 key stages: research priority setting; research design and planning; research conduct and operations; and dissemination, communication, and post-approval activity. Specific opportunities for PI within each stage were identified (summarized in Figure 2).

A Practical Roadmap for PI in Medicines R&D and Life Cycle

Opportunities for PI at each stage were reviewed and expanded with specific examples of how patient input can be sought and integrated to produce a practical roadmap of PI across the R&D life cycle (Table 2; Figure 3).

Stage 1: research priority setting

PI has a vital role at the very early stages of medicines development to ensure that research priorities align with patient needs to ensure the relevance of outcomes. Involving patients will help to ensure that development of novel therapies or interventions is focused on areas of patient care that require improvement as defined by patients themselves. The experiential knowledge that patients can bring to priority setting adds value to discussions, for example, in assessing whether the potential benefit of the proposed intervention is commensurate with the level of commitment and resources expected from all stakeholders—including patient participants and funders.

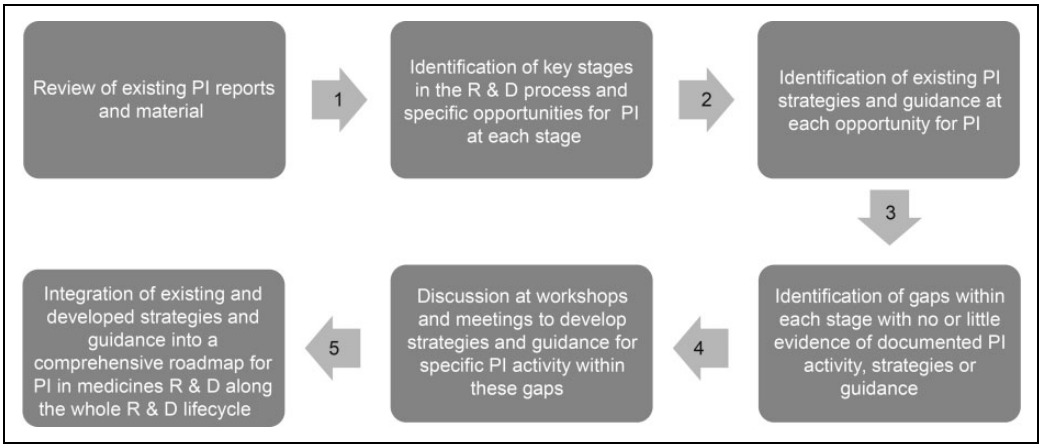

Figure 1. General approach for review of patient involvement (PI) material and reports.

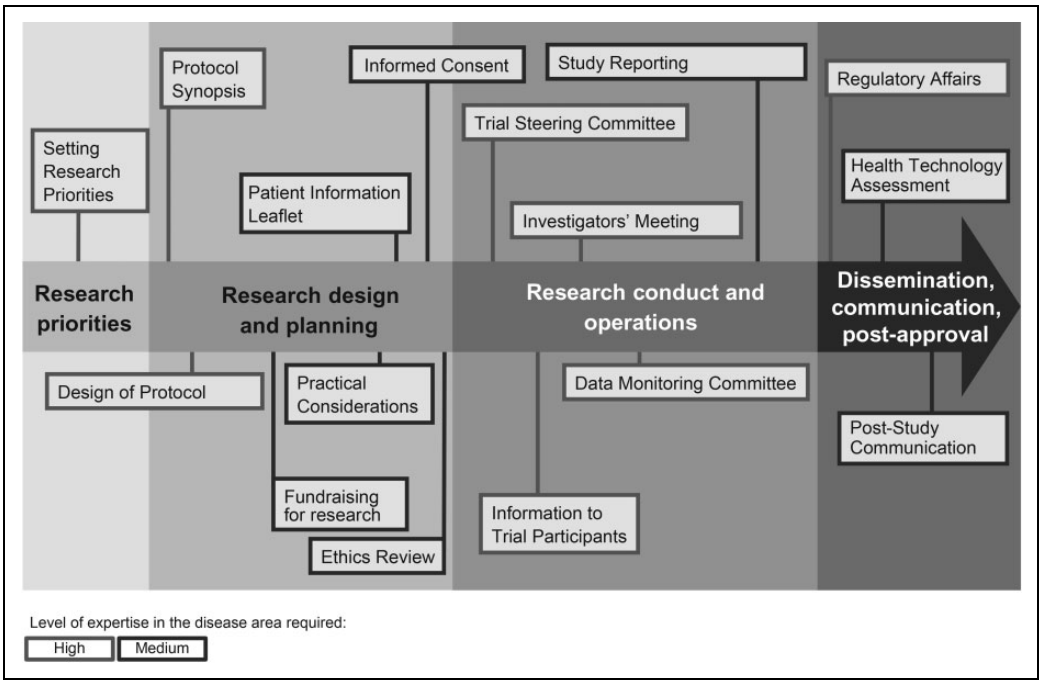

Figure 2. Key areas and opportunities for patient involvement across the medicines R&D process.

Stage 2: research design and planning

PI in protocol synopsis and design can identify acceptable comparators (eg, best care vs placebo, or pharmaceutical intervention vs nonpharmaceutical approaches); relevant endpoints (eg, treatment-free, progression-free, or overall survival); acceptable risk versus potential benefit from the patient perspective; and relevant target population. Working with patients can help to identify appropriate exclusion and inclusion criteria that do not prevent those at greatest need or most likely to benefit from the intervention from participating in clinical trials. It might also help to generate real-world data by including patients with characteristics that better reflect that of the "unselected" target population. PI can also facilitate selection of relevant patient-centered outcomes such as quality of life or other patient-reported outcome measures (PROMs). Patient input can help in identifying potential issues such as data protection that need to be addressed to provide adequate assurance that patient concerns are addressed early in the trial design process and do not become barriers to trial participation. Other issues, such as frequency of visits or the availability of remote monitoring are operational factors that can impact the ability or willingness of patients to take part in trials, can also benefit from timely PI.

The introduction of the EU Clinical Trials Regulation coming into effect in 2018 will further drive patient involvement in clinical trial design, given the trial protocol is required to describe "where patients were involved in the design of the clinical trial, a description of their involvement," which may

Table 2. Specific PI Activities Across the Medicines R&D Process.

Stage	Specific PI Activities
Setting research priorities	• Gap analysis • Early horizon scanning • Matching unmet patients' needs with intended research outcomes • Defining patient-relevant added value and patient-relevant outcomes
Research design and planning	• Protocol design and synopsis: relevant endpoints, inclusion and exclusion criteria, target population; diagnostic procedures; patient-reported outcome / quality of life measures; risk-benefit balance; crossover; ethical issues; mobility issues; data protection • Fundraising • Informed consent and patient information: content, visual design, readability, language • Ethics review
Research conduct and operations	• Investigators Meeting: patient perspective on trial, recruitment, challenges, opportunities, can trigger amendments • Trial Steering Committee and Data Monitoring Committee: eg, for risk/benefit, drop-out issues, amendments • Information to participants: protocol amendments, new safety information • Improving patient access to trials
Dissemination, communication, postapproval	• Regulatory affairs: EPAR summaries, package leaflets, updated safety communications and other finding in real world use (eg, how to inform and communicate issues or opportunities based on real world usage with a non–clinical trial setting population) • Establishing/designing phase IV (pharmacovigilance) studies data collection and communications • Creation of lay summaries (as required by the EU Clinical Trial Register) • Contribution to publications and dissemination of research results to patient community and professional communities • Health Technology Assessment: assessment of value, patient-relevant outcomes, priorities

Abbreviations: EPAR, European public assessment report; PI, patient involvement; R&D, research and development.

thus be seen as a quality criterion when application dossiers are being assessed by regulatory bodies and ethics committees.[23]

Securing patient advice for communications around trials can ensure clarity of material such as patient information leaflets and consent forms, especially materials that may be used in initial approaches to potential trial participants. Patients are also best placed to identify practical considerations that reflect the diversity of the patient population and their differing situations, such as the need for travel expenses, support for family members, or other obligations that need to be addressed. PI can also contribute to securing funding for research, for example, through fundraising or by facilitating access to new funding streams through identification of novel research topics that would otherwise not be identified without the unique insight and perspective of patients. In terms of ethics, PI can aid in evaluating the relevance of a study to the proposed target population, its potential to deliver meaningful outcomes, and assess that it is conducted in a way that is sensitive to the needs of participants. It may also uncover ethical dilemmas that need to be addressed and is increasingly important in the era of more personalized treatments requiring collection and storage of potentially sensitive patient information. Furthermore, ethics committees in several countries routinely request evidence that end users have been involved in the development of the research and in the development of material intended for patients. This involvement, however, usually asks for a lay person to be involved, not specifically an expert patient.

Stage 3: research conduct and operations

For research conduct and operations, patient representatives as members of trial steering committees and participants at investigator meetings could ensue a timely integrating of the patient perspective to anticipate, for example, trial recruitment challenges or opportunities—potentially highlighting areas of concern to trigger protocol amendments. When protocol changes are implemented, PI in communicating what these changes are and why they have been made is valuable—especially if resulting from new safety information where participant concerns need to be allayed. Working with data monitoring committees, patient input can help to evaluate the impact of study results on real patients, facilitate assessment of side effects, and also identify underlying issues related to formulation and administration, adherence, as well as study retention and drop-outs. Dissemination of interim results at predetermined study milestones should be an integral part of the communication strategy for clinical trials. Implementing PI in this process can aid communication of results and their relevance to the wider patient community and may encourage retention.

Stage 4: dissemination, communication, and postapproval activity

A role for PI has also been identified in regulatory affairs, HTA, and post-study communication. This includes involvement of patient representatives in European Medicines Agency (EMA), with pilot involvement in CHMP[24] and in some

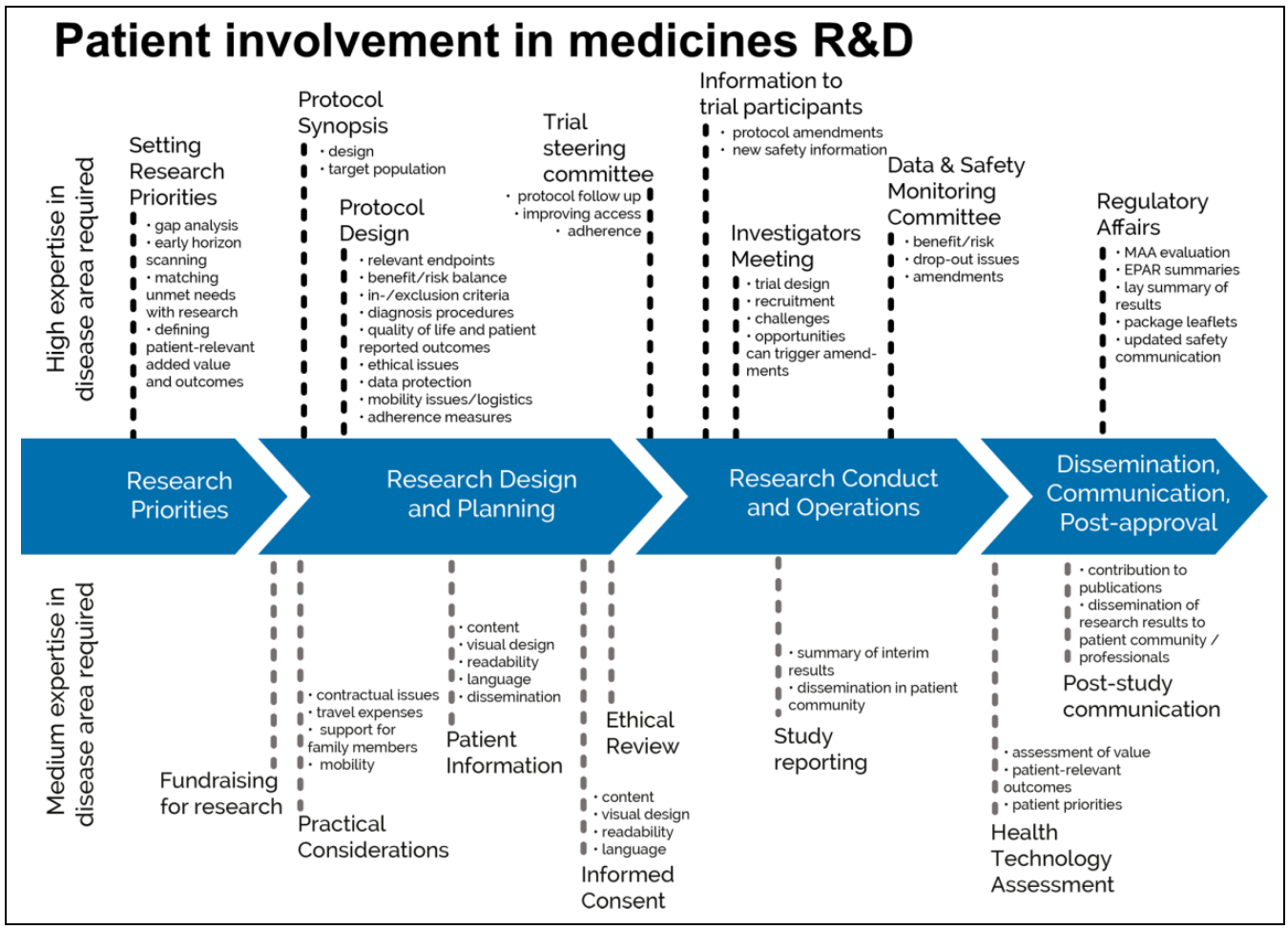

Figure 3. Practical roadmap for patient involvement in medicines R&D.

European National Competent Authorities' advisory groups; evaluation of regulatory approval applications for marketing authorization, although not yet formally regulated; development and revision of European public assessment report (EPAR) summaries as well as lay summaries of results; development and revision of unambiguously written package leaflets; and development and revision of updated safety communications that clearly describe and put into context for patients any new safety signals observed in clinical trials. PI should additionally be incorporated into post-study communication strategies, for example, in development of updates, feedback and "thank-you" letters to participants, and development of synopsis of results for nonexpert or lay audiences with clear explanation of the potential benefits and risks for patients. This information exchange across communities on the practicalities, issues or challenges encountered during real-world use of medicines can be used to improve patient experience and outcomes. Finally, PI during HTA will help with evaluation of whether identified patient priorities and patient-relevant outcomes have been appropriately addressed within the trial and ensures that HTA discussions are aligned with the needs and experience of patients as end users of the technology. Through public consultations, EUPATI has published guidance documents on patient involvement across the entire process of medicines research and development with regulatory agencies, health technology assessment (HTA) bodies, ethics committees, and the pharmaceutical industry recently published on the EUPATI website.[25]

Discussion

A roadmap has been developed through review and refinement of existing PI initiatives and related outputs to provide a structured framework for PI along the medicines R&D pathway (Figure 3). The roadmap identifies particular stages in R&D for PI and provides guidance in terms of specific opportunities or activities where PI can be sought. The roadmap applies to both academic and industry R&D processes and is relevant to preclinical and early phase clinical trials, as well as Phase IV / post-marketing / therapy optimization studies, which are often academic studies. The roadmap has been used to structure discussions around practical examples of meaningful PI when discussing with academic and industry research groups, and

has already proven valuable in transforming PI theory into practical reality.

It is worth noting that not all opportunities for PI have the same impact and there is a risk of selecting only relatively simple activities, such as review of patient material or informed consent forms. While valuable, other aspects of PI along the R&D pathway will have more strategic long-term impact but may be less straightforward to implement. For example, incorporating PI in research priority setting may require a change in culture within academia and industry but has the potential to yield substantial benefits in ensuring that resulting interventions more fully meet patient needs. Taking the example of clinical trials whether led by academia or industry, the main intent is to design better trials, not to increase participation in trials that have fundamental design flaws. Thus, the highest impact for PI would be in the design phase. Indeed, implementing early PI to drive "pragmatic" trial design can yield study results that more accurately reflect the real world setting and as such facilitate selection of the most appropriate therapeutic option.[26]

Lessons can be learned from other areas where PI has been successful. Thorough preparation, realistic expectations, and a systematic approach to learning from successes and failures will be critical to leveraging the potential of PI; we have seen from the highly successful HIV community that PI was not instantaneous, but grew and evolved over time. Initially, PI can potentially add not only time but also costs. For example, in companies, PI as described in Table 2 currently needs to be agreed with the investigators involved and internally approved, frequently causing delays as a result of a lack of streamlined processes and uncertainties around the PI process. Effective PI in medicines R&D will therefore require revision and, if necessary, implementation of new procedures for patient groups and experts, paralleling the existing ones for medical key opinion leaders.

Given the wide range of PI opportunities in R&D, there is a need to identify the elements and stages of PI along the medicines R&D pathway with maximum impact. This requires a clear understanding of the different stakeholders' goals of PI and what it should achieve in order to develop relevant metrics to evaluate success of PI implementation. Metrics could potentially cover degrees or depth of engagement/involvement as well as the impact that PI has ultimately had on factors such as: trial enrolment/speed; time saved in trial timelines; identification of meaningful clinical benefit; cost savings; impact on time to approval/ response of the regulators; and trial participant satisfaction. Different metrics will be important for different stakeholders—selecting those that are able to quantify or demonstrate the benefit and value of PI will encourage widespread implementation of effective PI that enhances medicines R&D processes and outcomes.

The proposed roadmap has both strengths and potential limitations. The strengths of the roadmap are that it provides practical examples of engagement, it has been developed through a collaborative approach with wide stakeholder involvement, and it is aligned with other PI activities, thus augmenting other PI projects and minimizing duplication of effort. However, we acknowledge that the search for documentation, literature, or evidence on PI in medicines R&D may not have captured all existing PI initiatives. There are many examples of patient engagement that have occurred that are not documented or even well understood or known within several companies and organizations that may have elements that have not been incorporated into the current roadmap.

We invite all stakeholders in medicines R&D—including those in academia and industry—to contribute to the refinement of the roadmap by evaluating and implementing the roadmap in their organizations and providing input and feedback.

The use of this roadmap, together with the implementation of the 4 guidance documents on patient involvement that were recently published by EUPATI,[25] are supporting regulators, academic researchers, pharmaceutical companies, HTA bodies, and ethical committees in identifying best possible approaches for receiving the most suitable expert patient input. To complement this, EUPATI already piloted a "match making process" that also facilitated to identify trained patient experts to contribute to specific engagement opportunities described in the roadmap.

The value of education of patients about the R&D process, way beyond individual experience and knowledge in their specific disease area, was demonstrated by the EUPATI Patient Expert Training Course in which 96 patient experts from 51 disease areas and 31 countries graduated in 2016 and which has again opened recruitment in early 2017. The EUPATI Toolbox on Medicines R&D, available in 7 languages, has been accessed by more than 100,000 individuals, evidencing the demand for lay-friendly education and training around PI.

Further data about the results and impact of PI should be collected in order to demonstrate the impact.

Key messages

- Currently ongoing initiatives involving patients in medicines R&D are numerous but lack consistency and a structured approach.
- Workshops and meetings have been used to collect existing good practice and guidance to provide a practical roadmap for patient involvement across the medicines R&D life cycle.
- This roadmap intends to stimulate further discussion. All involved parties—academia and pharmaceutical industry, patient organisations and patients, clinicians and researchers—will need to be involved in the identification of strategic PI points and their implementation to maximize the benefit for all stakeholders.

Appendix

Meetings and workshops involving roadmap discussions

- EUPATI Workshop: Interaction of Patients, Regulators and Industry: 20 July 2016, Berlin, Germany
- EUPATI Workshop: Patient Involvement in Industry R&D: 23 July 2014, Berlin, Germany.
- EPALCO workgroups: February 28, 2013; September 27, 2013; May 19, 2014; October 8, 2014; May 11, 2015. EPALCO is a forum bringing together leading patient organization representatives and Novartis Oncology Europe management to brainstorm and discuss the development of a patient-centric focus. Novartis involvement included senior managers of Region Europe Oncology representing all functions led by the Head of the regional Office. Organizations involved in EPALCO include Europa Donna (France, Austria, Cyprus); Sarcoma UK; International Brain Tumor Alliance (IBTA); Myeloma UK; Cittadinanza Attiva (Active Citizenship Network); Women Against Lung Cancer Europe (WALCE); Ensemble Contre Le Gist, France; A.I.G Italian Association Against GIST, Italy; GEPAC/AEAL, Spain; Aliva Poland; CML and General Cancer Association, Poland; CML Advocates Network; Sarcoma Patient Network Europe (SPAEN); KEFI Cancer Patient Organization, Greece; Dutch Cancer Patient Federation; Breast Cancer Organization (BRO) Sweden National and Regional Representatives; National Patients' Organization of Bulgaria (NPO).
- TOPRA/EMA Annual Review conference: November 20-21, 2014.
- Amgen Europe Workshops: December 2013 and November 2014. Participating organizations: Europa Donna; International Alliance of Patients' Organizations (IAPO)/Canadian Organization for Rare Disorders (CORD); European Patients' Forum (EPF); European Patients' Academy on Therapeutic Innovation (EUPATI)/CML Advocates Network; Melanoma Patient Network Europe (MPNE); Roy Castle Lung Foundation; and Genetic Alliance UK. Amgen Europe workshops with leading EU patient advocacy thought leaders and Amgen Europe senior leadership covered patient expert recommendation and guidance, not only on PI in R&D but also carefully considering phase IV pharmacovigilance and advising exchange, communication, and insights to real-world usage of medicines.

Other organizations involved in roadmap discussions

- Patient Focused Medicines Development (PFMD)

Declaration of Conflicting Interests

J.G. is Director of EUPATI (funded by the Innovative Medicines Initiative, receiving financial contributions from the European Union's FP7/2007-2013 program and 20 EFPIA companies) and Managing Director of Patvocates GmbH, Germany (a think tank providing a bridge between health policy, patient advocacy, and social media); B.R. has acted as a consultant on the patient perspective at various meetings and is founder of the Melanoma Patient Network Europe (MPNE) which receives balanced unrestricted grants from the pharmaceutical industry; S.L.P. was an employee of Novartis Farma S.p.A; M.U. was an employee of Amgen Europe GmbH during the time of development of the roadmap and is currently an employee of Shire.

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