DEEP DIVE

PPI ABROAD: A PATIENT ADVOCACY PERSPECTIVE

THE EVOLVING PRACTICE OF PATIENT AND PUBLIC INVOLVEMENT IN EUROPE AND THE UNITED STATES

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Patient and public involvement (**PPI**) in academic human research has been evolving in the United States and Europe since the early 1980s, when it was jump-started by activists responding to the HIV pandemic. This article provides a brief look at the development of PPI in academic human research in the US and Europe, highlights the PPI initiatives of several US and European organisations, discusses how PPI is gaining momentum in health technology assessment bodies, and provides recommendations for various stakeholders on how to incorporate more PPI into academic human research.

THE DEVELOPMENT OF PPI IN THE UNITED STATES AND EUROPE

Similar to health systems, the academic research environment was not originally planned around the patient. With the Declaration of Helsinki adopted only in 1964, we are still struggling to make patients' and society's needs the ultimate arbiter of what is *acceptable*, *reasonable*, and a *priority* for patients in academic human research. The change in the historical relationship between healthcare professionals and patients became evident during the HIV pandemic in the early 1980s, a time of increased political activism towards social acceptance. HIV activists used their existing advocacy know-how to successfully lobby public health authorities such as the US Food and Drug Administration (**FDA**). Activists' main argument was that the regulatory process should serve patients' interests and thus enable faster approvals and early access to life-saving medication. As a result of their efforts, the FDA started collaborating with patients in 1988 and, ultimately, promising HIV drugs were released on a parallel track before approval.

In Europe, it was again HIV patients in the 1990s knocking at the doors of the newly established European Medicines Agency (**EMA**) who inspired the regulator to adapt European legislation and lay the groundwork for involving patients in all its processes and decision-making. This activism established a precedent for collaboration with patients with all indications, accelerated approval processes, and introduced expanded access pathways.

Today, PPI is becoming increasingly integrated into academic human research. Stakeholders beyond medicine – including those in the areas of digital health and data, medical devices, and health systems – better understand the value of patient involvement; however, fragmentation remains an obstacle to replicability, scaling, and adoption across health systems. This often results in a gap in patient-centred outcomes addressing unmet needs, in lower performance of healthcare stakeholders, and in increased costs to society. Improved patient involvement can drive the development of innovative medicines, devices, digital health, and care services that deliver more relevant and impactful patient outcomes. Patient involvement can also make medical product development faster, more efficient, and more productive. In addition, it leads to a better understanding of patients' needs, better prioritisation of early research, improved decision-making and resource allocation, and trial protocol design that better reflects patients' needs. Consequently, PPI lowers potential barriers to patient participation, enhances recruitment, and increases retention.

Historically, the US has been the main driver of PPI because of the FDA's active role in writing its own legislation. Recently, the UK has become a European leader in PPI in terms of its number and range of initiatives. And although generally, little legislation directly related to PPI exists in Europe, there are several examples of European and national guidance and initiatives as well as many initiatives from individual organisations (see **Box 1** at the end of this article for a selection of PPI legislation, guidance, and initiatives in Europe and North America). The following organisations demonstrate several of the efforts being made to achieve more patient involvement in academic human research in the US and Europe.

A SELECTION OF ORGANISATIONS IN THE US AND EUROPE WITH PPI INITIATIVES

US Food and Drug Administration (FDA)

Since 1988, the FDA has taken several measures to engage patients in its processes (see its summary Evolution of Patient Engagement at the FDA). It has shaped the most recent efforts to advance the patient voice in regulatory processes through the Patient-Focused Drug Development Program with the development of four FDA guidances articulating how stakeholders should collect and submit input from patients to contribute to medicine development and regulatory processes. There is an increasing expectation that the FDA will make patient engagement mandatory in regulatory documents (e.g. patient experience data). This is only the beginning of a series of public health authority efforts to build better patient voices in development and decision making.

European Medicines Agency (EMA)

At its creation in 1995, the EMA had no formal policy for talking to patients. Members of the European AIDS Treatment Group (**EATG**) approached the EMA in 1996 and asked the agency to accept running pivotal studies with biomarkers instead of clinical endpoints to shorten the time to approval. Regulators understood that patients had something important to say and agreed to meet and start discussions with them. The EATG was also the first to alert the EMA about worrying side effects observed in HIV patients under combination therapy in 1997 – an observation that resulted in regulators changing their pharmacovigilance strategy from reactive to proactive, especially in fast-track approved medicines.

From 2000 onwards, the EMA made patient representatives full members of its Committee for Orphan Medicinal Products (**COMP**). The agency realised it required legislation enabling further integration of patients in its processes. Regulation (EC) No. 726/2004 of the European Parliament and of the Council of the European Union, in particular Article 78(1), gives the EMA additional responsibility to develop contact with patients and consumers. On this basis, the agency established its Patients' and Consumers' Working Party (**PCWP**), a platform for patients and consumers to exchange information and information with the EMA. In 2005, the EMA introduced a well-balanced framework for its interaction with patients and consumers, which has been improved and updated over the past 15 years (see revised framework). This framework has further inspired many external parties, such as the European Patients' Academy on Therapeutic Innovation (**EUPATI**), the FDA, and the pharmaceutical industry, to establish or improve a structured, balanced, and meaningful approach to interacting with patients and the public.

Today, patients are fully active members on almost all of the EMA's working parties and decision-making committees. In 2020, the EMA reduced its activities due to the COVID-19 pandemic. Nevertheless, patients were involved in 102 scientific advice procedures, 42 scientific advisory groups, 228 committee consultations, and 203 document reviews (see the EMA's website for more PPI initiatives).

European Patients' Academy on Therapeutic Innovation (EUPATI)

The EUPATI project was launched in 2012 and funded by the Innovative Medicines Initiative (**IMI**). The driving force of EUPATI is the idea that involving patients in medicines research and development has important benefits. To enable patient involvement, it is essential that the processes and methods are understood by patients and that patients learn where and how they can make a meaningful impact.

Today, EUPATI is a non-profit foundation that is structured as a multistakeholder public-private partnership. The EUPATI approach is now gaining ground within academic research as we understand patient involvement increases the impact of research and enhances its acceptance by society. A quarter of EUPATI's partners are academic research institutions. One of them is the European infrastructure for translational medicine (**EATRIS**), representing over 100 academic centres. Another collaboration was launched with ERA PerMed, a funding scheme for research in personalised medicine. Through these collaborations, EUPATI seeks to enhance patient involvement and promote patients as active partners in the processes of academic research (see **EUPATI** article on p. 22).

Currently, the pool of EUPATI patient experts exceeds 200 individuals. They have been engaged in advisory roles, acted as trainers and speakers, supported patient organisations, reviewed trial protocols, and contributed to trial designs. Their involvement in academic research is increasing, as expressed by one EUPATI Fellow: "[I have been] involved in research activities and doing research and writing a scientific medical article, assessing proposals for medical research on the patient perspective."

Patient Focused Medicines Development (PFMD)

Back in 2015, key stakeholders involved in the life cycle of medicines agreed that more effective patient involvement was needed to ensure that patients' needs and priorities are identified and met. Patient engagement was very productive in some areas but somehow isolated, inconsistent, and fragmentary within organisations, between organisations, in different stakeholder groups, and in different regions. This led to the creation of the Patient Focused Medicines Development (**PFMD**) initiative, a global network that includes over 35 partners from patient organisations, industry, hospitals, and the regulatory area with the aim of promoting a more patient-centred healthcare system that benefits patients and health stakeholders.

Progress toward a shared, replicable, scalable, and adoptable model for patient involvement requires a joint, precompetitive, open, and international approach by all stakeholders, including academic researchers. It is necessary for them to work in true partnership to map, analyse, and consolidate good practices, to identify gaps, and to develop a comprehensive suite of methodologies, tools, and frameworks. This is the purpose of PFMD's Patient Engagement Suite, which is a global hub of practical tools that can be used to plan, assess, and execute PPI initiatives.

In addition, the growing need from various stakeholders to consult the patient community for respective decision points has led to several multistakeholder initiatives aimed at harmonising the understanding of the patient experiences, and turning it into patient-centred, relevant data for various decision points across systems and stakeholder groups. One example of this is the PFMD's Patient Engagement and Patient Experience Data project, which helps better integrate stakeholder-specific needs and patient engagement in decision-making. Another example of such a project is the Patient Centered Core Impact Set (PC-CIS) initiative, launched by the US National Health Council (a founding member of the PFMD).

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (**ICH**) published a Reflection Paper on patient-focused drug development in March 2021. The paper articulates key areas where the incorporation of the patient's perspective could improve the quality, relevance, safety, and performance of drug development and inform regulatory decision-making. This paper is a first step towards new ICH guidelines aiming "to provide a globally harmonized approach to inclusion of the patient's perspective in a way that is methodologically sound and sustainable for both the regulated industry and regulatory authorities".

Health technology assessment (HTA) bodies

Health technology assessment (**HTA**) bodies are also looking to promote a more systematic approach to patient engagement. The UK's National Institute for Health and Care Excellence (**NICE**) and its National Institute for Health Research (NIHR) Centre for Engagement and Dissemination as well as the Canadian Agency for Drugs and Technologies in Health (**CADTH**) and the international Health Technology Assessment international (HTAi) Interest Group for Patient and Citizen Involvement in HTA (**PCIG**) have delivered and are working on guidance or initiatives to better involve patients in decision-making and evidence generation. The pioneers of this approach were the pan-Canadian Oncology Drug Review agency (**pCODR**), which called for written input from oncology patient groups, and NICE, which established an early PPI team. Processes have been further enhanced by the HTAi and adopted by many of the world's leading HTA bodies, including France's Haute Autorité de Santé (**HAS**) and the Scottish Medicines Consortium (**SMC**). A standard set of questions are now used by most HTA bodies to gain input on patient-relevant unmet needs and patients' experience of current healthcare practices. HTA bodies and regulatory agencies such as the FDA and the EMA are also progressing to more systematically incorporate the voice of the patient and patients' lived experience through the use of patient experience data (**PED**) in their review and approval processes for new drug submissions and value assessments (see related EMA report). These agencies are also adopting patient involvement practices within their early dialogues (scientific advice) with medicine developers.

RECOMMENDATIONS FOR FUNDING INSTITUTIONS, APPLICANTS, AND PATIENTS TO INCREASE PPI IN ACADEMIC RESEARCH

The contributions of patients, caregivers, patient advocates, patient experts, and patient organisations to the design of clinical research and development have been well established through frameworks, tools, and educational resources by organisations and networks such as EUPATI, PFMD, and INVOLVE UK. However, applicants for research grants as well as funding bodies have experienced challenges putting systematic engagement with the patient community in collaborative research projects into practice. One exception to this is the Patient-Centered Outcomes Research Institute (**PCORI**) in the United States, which involves patients by design.

Patient representatives can play different roles when research projects are being designed, when collaborative groups apply for funding, and when research projects are being implemented. Within projects, patient engagement can be established in the funding framework, partnering concept, project design, grant application, application review, project implementation, and dissemination of project outcomes. Furthermore, funding institutions can engage patients to make sure that calls for proposals are focused on patients' unmet needs and that the quality of patient engagement is one of the criteria used when grant applications are evaluated.

The EU-funded IMI is a pioneer in this area, involving patient advocates in the definition of call topics as well as requiring patient involvement in some call texts. More recently, an IMI pool of patient experts was created with 157 patients and caregivers in order to further PPI. The IMI has also funded projects which were either led or co-governed by patient organisations (see IMI's website for a selection of projects). The European Commission has involved patient experts for years in independent review panels of their funding programme Horizon 2020. However, the absence of a clear, cohesive PPI strategy for the EU has led to some dissatisfaction on many sides and needs to be developed.

To address the gaps in practical methods and models for how researchers and patients can engage in the different phases of collaborative research projects, the Switzerland-based Rising Tide Foundation and the think tank Patvocates Network have developed recommendations and checklists for funding institutions and applicants. These guidance documents include recommendations on how to involve the patient community before a collaborative research project starts, during the review of project applications, and during the implementation of a research project. They also describe how to bring researchers and the patient community together during the application phase, which practical engagement models and roles in the governance and implementation are feasible in collaborative projects, and how to measure the quality of patient engagement and compensation models.

In addition to an effective approach, patient engagement often requires technical knowledge like medical expertise, methodological expertise, and systems expertise. Therefore, it is essential to provide training for patient advocates so they can understand research and contribute to research projects effectively. Moreover, researchers need to receive training on how to involve patients in the most effective manner. Both EUPATI and the Workgroup of European Cancer Patient Advocacy Networks (**WECAN**) are examples of organisations that provide such training.

Some of the most important PPI initiatives in Europe and the United States are discussed above. Like every fundamental change, such developments take time, and established systems and processes need to adapt. Initiatives have proven most successful when they were carefully planned, included a long-term perspective, and legislative changes were made proactively. The progress in PPI that has been achieved so far can inform future efforts to promote and coordinate PPI in academic human research – with the goal of providing even greater benefits to patients and the public.

Box 1: A selection of regulations, guidance, and initiatives on PPI in academic human research in Europe and North America

Location, Year	Regulation, guidance, or initiative	Related organisation	Purpose
USA, 1988	Investigational new drug, antibiotic, and biological drug product regulations	US Food and Drug Administration (FDA)	Interim regulatory procedures to speed up the availability of new therapies to desperately ill patients; applicable to AIDS, some cancers, and other life-threatening diseases
USA, 1991	FDA Patient Representative Programme	FDA	Mechanism for advocates to provide formal input to the FDA's decision-making process as medical products are regulated; first patient representative serves on the Antiviral Drugs Advisory Committee and receives voting rights in 1993
USA, 1993	Office of AIDS Coordination (est. 1988) renamed Office of AIDS und Special Health Issues	FDA	Build relationships with patient communities; broadened to include patients with cancer and other serious illnesses
European Union, 1996	Informal dialogue with (HIV) patients	European Medicines Agency (EMA)	Consider patients' perspectives regarding endpoints in pivotal trials to speed up approval
UK, 1999	Patient and Public Engagement Policy	National Institute for Health and Care Excellence (NICE)	Involve patients, service users, caregivers, and the public – including voluntary, charitable, and community organisations – in its work
European Union, 2000	Patients become members of the EMA's Committee for Orphan Medicinal Products (COMP)	EMA	Include patients' perspectives on the committee
European Union, 2004	Regulation (EC) No. 726/2004 of the European Parliament and of the Council of the European Union	European Commission (**EC**), EMA	Article 78(1) gives the EMA additional responsibility to develop contact with patients and consumers
European Union, 2005	Framework created for the EMA's interactions with patients and their organisations (revised version)	EC, EMA	Explain and consolidate the EMA's PPI methodology
European Union, 2006	Patients' and Consumers' Working Party (PCWP)	EC, EMA	A discussion platform for patients and consumers to exchange information and ideas with the EMA
European Union, 2012	European Patients' Academy on Therapeutic Innovation (EUPATI)	EU, Innovative Medicines Initiative (IMI)	Improve patient and public education and empowerment in order to improve medicines research
USA, 2012	Patient-Focused Drug Development (PFDD) initiative	FDA	More systematically obtain the patient perspective on specific diseases and their currently available treatments
European Union, 2014	EMA's Public Engagement Department created	EC, EMA	Facilitate the EMA's engagement with the public
International, 2015	Patient Focused Medicines Development (PFMD) initiative	Pharmaceutical industry, medical devices industry, patient organisations, patient networks, and individuals	Promote a more patient-oriented healthcare system
USA, 2015	Patient preference information (PPI) and guidance	FDA, Center for Devices and Radiological Health (**CDRH**)	Incorporate the patient perspective in CDRH's regulatory decision-making
USA, 2020	Final patient-focused drug development (PFDD) guidance released	FDA	Provide a systematic approach to collecting and submitting input and data from patients and caregivers for medical product development and regulatory decision-making
UK, 2020	Report of the Independent Medicines and Medical Devices Safety Review (Cumberlege Review)	The Crown	Provide guiding principles for responding to and including patients' perspectives in improving the safety of medicines and medical devices and; recommend structural changes
European Union, 2020	EMA pandemic Task Force with patient involvement	EMA	Provide a strategy for managing the COVID-19 crises and include patients in crisis management
International, 2020	New guidance, templates, and processes for patient summary information	Health Technology Assessment international (HTAi)	Improve patient information; in use in Scotland and being piloted in England, Canada, Australia, and other countries
International, European Union, 2020	Tools and resources for HTA bodies	HTAi via PARADIGM-IMI	Enable HTA bodies to quickly and effectively include patients early in the dialogue process
International, 2021	Reflection Paper on patient-focused drug development	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)	Promote PPI for improving drug development and regulatory decision-making; lay a foundation for new ICH PPI guidelines
UK, 2021	Innovative Licensing and Access Pathway (**IALP**)	Medicines and Healthcare products Regulatory Agency (**MHRA**), NICE, Scottish Medicines Consortium (SMC)	Improve patient access to medicines by accelerating the time to market
UK, 2021	Proposed Patient and Public Involvement Strategy 2020–25	MHRA	Develop and introduce clear PPI processes to ensure teams have a systematic means of engaging and involving patients and the public in their work
UK, 2021	MHRA pilot project on patient involvement in new applications	MHRA	Place patient involvement at the heart of clinical trials and medicine development
Canada, 2021	Guidance for Providing Patient Input	Canadian Agency for Drugs and Technologies in Health (CADTH)	Revised guidance to increase patient input in decision-making processes
Canada, 2021	CADTH Framework for Patient Engagement in HTA (revised)	CADTH	Revised framework to promote PPI in HTA
UK, 2021	The NICE strategy 2021 to 2026	NICE	Develop partnerships across the health and social care system, including with regulators and patient groups; introduce new PPI approaches to inform the evidence base for guidance development