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THE ROLE OF PATIENTS AND COMMUNITY REPRESENTATIVES IN VALUE-BASED ASSESSMENT OF HEALTH TECHNOLOGIES AND RESPECTIVE DECISION-MAKING PROCESSES WITHIN HEALTHCARE

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***Purpose** – to conduct a complex analysis of the existing approaches to assessment of health technologies' value by patients and community representatives, and their role in respective decision-making processes within healthcare.*
***Methods**: bibliosemantic (review of 63 sources – 35 literature sources and 28 web-resources) and expert opinion.*
***Results**. The four key areas were identified for the analysis: unmet patient needs; discovery and development of a health technology; PRO and PCO measurement; HTA and regulatory procedures, decision-making. Existing patient engagement frameworks, experience and practices were analysed and consolidated.*
***Conclusions**. Over the last decade the significant progress has been made by patient organisations and other healthcare stakeholders in actualisation and identification of patients' role in value-based assessment as well as implementation several patient-centric initiatives across discovery, clinical development, PRO/PCO, HTA and authorisation. A lot of constructive efforts within methodology and governance took place very recently (2014–2016); however at this stage it's rather impossible to identify any tangible outcomes which could demonstrate good level of evidence.*
***Key words**: patients, community representatives, patient engagement, value, patient-centric healthcare, value-based assessment.*

INTRODUCTION

Over the last decade patients, or people living with the certain medical condition/conditions, have been considering as paramount healthcare stakeholders at different levels: from the global scope to regional and national healthcare systems. The patient voice is usually represented by caregivers, treatment activists, advocates and several types of patient organisations: patient advocacy groups (PAGs), community based organisations (CBOs) and other non-government organisations (NGOs).

Before the current period patients weren't really empowered to present their unmet needs and expectations from healthcare systems and providers; their insights and feedbacks didn't play any significant role in decision-making and weren't taken into consideration either at public health policy level or individual disease management level. Healthcare providers (HCPs) used to transfer patients' vision on health technologies with significant changes, self-interpretation and modification, or even presented that vision on behalf of patients. Such paternalistic approach led to procedural bias assessing value of different health technologies, systematic exaggeration or under-estimation of their impact to patient health and wellbeing. Evidence shows that HCPs' vision on several morbidities and related complications, health technologies value and research priorities differ from those of patients [55, 56]. For example, patients at high risk for atrial fibrillation placed more value on the avoidance of stroke and less value on the avoidance of bleeding than did physicians who treat patients with atrial fibrillation. Patients traditionally pay more attention to safety profile and quality of life when taking the dedicated health technology/group of technologies. Other divergences in priorities for health research between HCPs and the public were found in the areas of diabetes, arthritis, Alzheimer disease, and mental health [31, 55].

A lot of national healthcare systems still rely on HCP insights analysing patient perspectives; the patient movement and influence in those countries can be characterised as minimal, if exists. In such cases professional associations and healthcare organisations as well as separate activists take a role of main patient advocates and policy influencers. Some governments prohibit any patient movement at all.

On the other hand, patient empowerment may face some obstacles due to subjective reasons: expecting and exploring medical instead of preventive model of care; disempowering nature of illnesses; easy access to medical services etc., therefore people's behaviours and practices often seem to reinforce the dependency and passivity [19].

Despite above limitations, the general trend is moving towards truly patient centric approaches within above country and national healthcare systems with the significant impact of the following factors:

– healthcare transformation at all levels;
– growing public scrutiny to processes taking place within healthcare;
– growing health literacy, educational level and awareness on health-related issues;
– age of information and digital excellence;
– sophistication of health technology assessment (HTA) systems, wider scope/objectives and more complexity in value assessment to achieve better robustness and transparency in decision-making;
– more active patient movement in line with the widely accepted principle «Nothing about us without us» as health-related manifestation of community freedom and growing role of public sector within healthcare;
– improved balance and collaboration between public, governmental and private sectors;
– diversified technical and environmental support provided by global organisations and regulators (WHO, IAPO, US FDA, NICE, EMA etc.).

The unique role of patients as final customers in healthcare cannot be overestimated. Patients or people living with certain medical conditions and therefore having medical needs should be considered as end-users of different health technologies: medicines and medical devices, processes and operations, preventive measures, information and facilities [48, 50]. Other healthcare stakeholders have a transitional user's role providing the end-user with technologies in different ways. They are more or less connected with patients and each other; such connectivity depends on national regulatory environment, legislation, traditions, healthcare and general infrastructure, behaviours and many other factors. Governments try to monitor and determine to what extent that connectivity can be allowed and take place being beneficial for patients; for example in some healthcare systems any communication between biopharmaceutical industry and patients is prohibited; other systems encourage HCPs to diversify ways of working with patients improving collaboration and ensuring shared decision-making (SDM) on treatment. Ideally, every transitional user must commit to end-user's benefit providing value through better diagnostics, prevention, treatment and rehabilitation, affordable prices and flexible access policy, optimal management solutions, good laboratory, manufacturing, distribution, clinical, publication and other practices (GLP, GMP, GDP, GCP and GPP respectively), highest ethical standards, relevant skills and knowledge [22, 47, 52, 61]. Patient-centred healthcare comprises such complex stakeholder's commitment and putting patient interests first (Fig.).

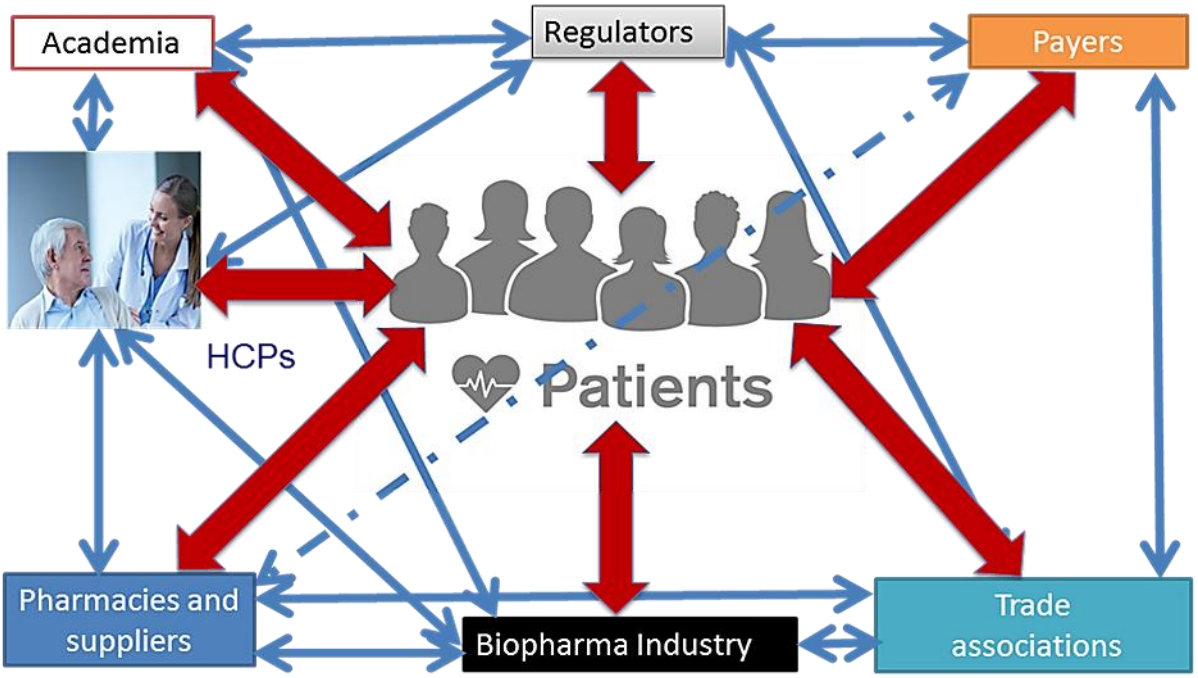

Fig. Patient-centric healthcare (by author)

The essence of patient-centred healthcare is that the healthcare system is designed and delivered so that it can address the needs of patients [22]. There are a lot of definitions of patient centricity and patient-centred healthcare; majority of them mention the core place of patients and serving roles of other stakeholders to address patients' unmet needs, preferences and expectations. Analysis of more than 30 definitions of patient-centred healthcare and patient centricity developed over the last three decades shows that the authors have been changing their focus from collaborative efforts and stakeholders' role to value for the patient, patient-centred outcomes (PCOs) and value-based decision making [2, 22, 34, 48, 49, 52]. This reflects the transformation of HTA systems around the world and implementation of newest methodologies aimed to embed patient-assessed value of health technologies into the consolidated HTA tools.

The ***purpose*** is to conduct a complex analysis of the existing approaches to assessment of health technologies' value by patients and community representatives, and their role in respective decision-making processes within healthcare.

MATERIALS AND METHODS

Taking the relatively fast transformation of healthcare systems and increased focus on patient centricity over the last decade, we analysed 63 sources (35 literature sources and 28 web-resources); 50 (79,4%) of them were published throughout the period of 2011–2016 with the following key selection areas/key words: patient-centred (-powered, -driven) medicines [drug] development; addressing unmet patient (medical, social, psychological) needs; patient-reported/-centred outcomes (PROs/PCOs); patient-centred care; patient-centred HTA and regulatory procedures; information-education-communication (IEC) mix targeted to patients; value for patients; patient safety and reported adverse events; social listening; shared decision-making; patient-centred decision-making and patient centricity (several aspects).

In addition, the best practice examples and experiences gained by different healthcare stakeholders, namely, PAGs, CABs, NGOs, academic institutions, biopharmaceutical and R&D companies, HTA agencies and regulators, were analysed and reflected in this review. The above information was obtained from individual and group conversations with stakeholders, generated reports and summaries on events and meetings available on public domain.

Author analysed and consolidated several approaches to patient involvement in value assessment of health technologies within the unified continuum from discovery and clinical development to long-term surveillance trough maturity, obsolescence and withdrawal:

– identifying unmet patient needs;
– discovery and development of a health technology;
– PRO and PCO measurement;
– HTA and regulatory procedures, decision-making.

RESULTS AND DISCUSSION

In 2006 the famous investigators of the value in healthcare, Michael Porter and Elizabeth Teisberg in their work «Redefining healthcare: creating value-based competition on results» stated that achieving high value for patients must become the overarching goal of health care delivery, with value defined as the health outcomes achieved per dollar spent [47]. Although the key principles of cost-benefit analysis and methodology of ICER (incremental cost-effectiveness ratio) calculation had been developed before that time, the goal to achieve higher value for patients was quite innovative. Value of health technologies was usually considered as an integrated measure based on objectively evaluated compounds such as effectiveness and safety, transferred and interpreted by HCPs with minimal or no input from patients [16, 27]. Later the number of compounds/dimensions was increased to achieve better objectivity and complexity in HTA: alongside effectiveness and safety of a technology, investigators put their attention to therapeutic compliance and adherence, cumulative social and economic burden of illness and related methods of its management, ethical and other aspects of a technology [1, 11, 20, 36]. However, the share of patient voice was almost undetectable among those compounds/dimensions and therefore didn't contribute to decision-making in any way.

At that time a lot of investigators rose the points that patients must be considered as key customers of healthcare system and value should always be defined around the customer, e.g. patient. Value itself cannot be a virtual measure with no relation to whom it may be important and beneficial from practical point of view. Hence, healthcare must create and maximise value for patients as well as related persons – loved ones, relatives and caregivers [49, 50, 59].

As an outcome of the above mentioned discussions, the largest national healthcare systems (US, Europe Top-5, Canada, Australia, Brazil) has widely accepted this fundamentally new strategy of achieving the best outcomes at the lowest costs moving away from the supply-driven healthcare organized around what HCPs do toward patient-centric healthcare organized around unmet patient needs. Albeit drivers of this strategy faced some stakeholders' resistance and implementation challenges (environmental, legal, cultural, infrastructural, financial, organisational etc.), a lot of stakeholders recognised its advantage for all sides alongside patients [4, 48, 51].

Patient organisations, such as PAGs, caregivers and independent activists strongly supported this game changing strategy and encouraged other healthcare stakeholders to recognise unique role of patients within healthcare collaboratively creating value for them [5, 14, 57]. International Alliance of Patients' Organisations (IAPO) has summarized the paramount principles of patient centricity in the Declaration on Patient-Centred Healthcare. There are the principles of 1) respect; 2) choice and empowerment; 3) patient involvement in health policy; 4) access and support; 5) information. By IAPO, healthcare must be designed and delivered to meet the needs and preferences of patients. Greater patient responsibility and usage will lead to improved quality of life, a more cost-effective system and, ultimately, better healthcare for everyone [22].

The recent publications, expert opinions and separate case studies have supported effectiveness of patient-centric approaches for healthcare stakeholders; however authors highlighted the lack of metrics for their qualitative and quantitative evaluation as well as consistency for establishing robust return-on-investment (ROI) criteria [17]. Other investigators disagree with appropriateness of the ROI-like measurements evaluating patient-centric initiatives across healthcare as it's rather impossible to measure value quantitatively; for qualitative analysis the term «Return of Relationships» was proposed as alternative [61].

On the other hand, it has become obvious that value of certain health technologies for patients could practically be measured with the related health outcomes, which is the subject of HTA [32, 34, 45]. Leaving behind health outcomes assessed and interpreted by HCPs, we, however, analyse existing methodologies and approaches to getting patient's vision/insight on a health technology value and further its perspective within a healthcare system/health market. We propose more holistic analysis instead of considering only PRO/PCO as a part of health outcomes evaluation: the value of potential technology can be assessed starting from identification of an unmet patient need and early discovery; throughout pre- and clinical development; at the stage of HTA and regulatory approval; routine usage and administration (for example, identification of hidden/undetected by HCP safety signals).

Identifying unmet patient needs

Identifying unmet patient needs is the first, important step towards real understanding on what characteristics potential health technology must have to tailor these needs/meet expectations and therefore provide the desired value.

Usually patients cannot articulate sophisticated points on therapy targets and clinical outcomes, improved mechanism of action or advanced safety requirements, but they can easily provide scientists with information on natural history of their illness and dynamics of symptoms, especially symptoms that are the most bothersome for them, personal goals for daily activities, expectations regarding quality of life receiving treatment, preferences for treatment delivery methods, desired formulations, parameters of medical devices, experience with ongoing treatment(s) including side

effects and how that treatment impacts their daily activities, physical functions, and quality of life [18, 42].

Having that patient-provided information (PPIN) physicians and scientists can «translate» unmet medical needs, symptoms and manifestations to pathways and targets to be focused on throughout the discovery procedures, better understand causality of adverse reactions and heterogeneity of treatment effects across patient population [56, 57]. It is also important for regulators. US FDA has recently started to implement patient-focused drug development initiative – a commitment under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) that aims to more systematically gather patients' perspectives on their condition. Within the frame of this project the regulator has carried out more than 20 «Voice of the Patient» meetings with the focus on the specific disease areas reflected by patients [57]. The first impression after reviewing reports from those meetings was that patients have unique disease vision usually different from traditional clinical vision. Such approach will help US FDA to inform further decision-making, especially assessing benefit-risk profile, identify any existing treatment challenges and understand how the health technology under review addresses them.

Prior starting any cycle of a technology development biopharmaceutical/medical device industry and academia should ensure they took into consideration the voice of patients and understood unmet medical needs to prevent avoidable misalignment between these needs and development decisions and processes, interim and final results. The «snowball effect» of systemic bias and misalignment throughout a health technology development may have catastrophic consequences from both financial and reputational perspectives. The industry knows some cases of disinvestment, closure of ambitious R&D programmes, termination of licences and technology withdrawal from healthcare markets due to fundamental reason – failure to tailor unmet patient needs [23].

A lot of discussions are currently taking place around the methods for collection PPIN and then crystallising unmet patient needs. Many of well-established methods and tools exist representing both common and special approaches, which depends on the purpose and project specifics, scope and target population, stakeholder's resources and timing. Healthcare stakeholders can explore a lot of them not just for identifying unmet patient needs, but also for getting their insights and input to discovery and clinical development, PRO measurements development and validation, detection of hidden safety-related issues/signals, HTA/regulatory procedures and decision-making. Several stakeholders have expressed a big interest and readiness to invest to digital technologies for collecting PPIN, in particular user-friendly mobile applications and tools [29, 30].

US Patient-Centered Outcomes Research Institute (PCORI) has summarised several approaches and methods for collecting PPIN including, but not limiting to: individual interviews, collecting comments from the public, conducting surveys, conducting focus groups, hosting open forums, conducting workshops/working groups, advisory boards, crowdsourcing (obtaining input from a large number of individuals) [34, 45]. The similar analysis was conducted by the Medical Device Innovation Consortium (MDIC) in 2015 called «A Framework for Incorporating Information on Patient Preferences Regarding Benefit and Risk into Regulatory Assessments of New Medical Technology» – predominantly focussing on value of patient preferences in medical devices' assessment [33].

Notably, unmet medical needs may be aligned with unmet psychological, social and other patient needs which a health technology may address, therefore stakeholders should consider holistic approach and comprehensiveness collecting PPIN [13, 27, 38, 42].

Discovery and development of a health technology

This area is a most complex covering different stages from early discovery to phase IV interventional and observational trials, where patients can assess value of a technology/combination of technologies under development and provide significant input to this process [23, 41, 56]. Although a lot of healthcare stakeholders have already accepted/supported Patient-focused drug/medicine development – PFMD/PFDD (use as synonyms: patient-driven (PDDD/PDMD), patient-powered drug/medicine development (PPDD/PPMD) doctrines which clearly articulated holistic engagement of patients and community representatives throughout the continuum, in fact such engagement is very inconsistent and sporadic yet [26, 29].

Meanwhile, successful identification of unmet patient needs informs productive discovery. At this stage discoverers can get answers, even preliminary, to the questions like «What value gap exists within this therapeutic area/available treatments?»; «What are the possible options to potentiate/modulate/minimise this effect mentioned by patients?»; «Any new options with unknown mechanisms of action?» etc. Answering these important questions can generate new scientific hypothesis and also open the way to incremental innovation, which, for example, advances medicines by expanding therapeutic classes, increasing the number of available dosing options, discovering new physiological interactions of known medicines, and improving other properties of existing technologies [6, 24, 38]. However, even more significant discoveries – radical (new technologies/groups of technologies) and revolutionary (new therapeutic/preventive models) can be made based on the input from patients.

The authors of the 2013 update of «Priority medicines for Europe and the world» have identified three categories of motivations drive the several stakeholders' efforts to involve patients and citizens in priority setting for pharmaceutical innovation: 1) political and stems from the desire to promote democratic ideals of legitimacy, transparency and accountability; 2) health-related motivations that stem from the need to better align pharmaceutical innovation with the unmet needs of patients, and 3) arguments of transparency and trust [51]. The forth, quite pragmatic category of motivations has been crystallised over the last two-three years – there is an intent to improve productivity/ROI of discovery and clinical development programmes [6, 8].

There are a lot of frameworks proposed by different healthcare stakeholders for patient involvement to Research& Development (R&D) processes: from conceptual to practically implemented at the corporate/private, community or governmental (national healthcare system) level. Albeit

several healthcare stakeholders have been demonstrating their ability to develop and maintain such frameworks, they didn't really demonstrate collaborative approach and good alignment between each other; therefore the efforts made were inconsistent and unfocussed [5, 10]. Patients and their advocates have been observing such situation over the last time taking pro-active position and encouraging better cross-sectoral coordination and partnerships (governmental/public/private) within R&D [41, 59, 62].

Hereinafter we briefly overview the most promising frameworks and cross-sectoral initiatives developed and implemented over the last years.

US FDA Patient-Focussed Drug Development Initiative has been launched under the 5-year implementation of the Prescription Drug User Fee Act (PDUFA) with the key goal to get patient perspective on certain disease areas and related needs in new/improved health technologies based on benefits/risks assessment of current treatment options available [14]. The regulator shares outputs from workshops with patients on public domain to ensure earlier understanding unmet patient needs and better identification of discovery& clinical development directions. Eventually that information is a critical element of FDA's decision-making as it establishes the context in which the regulatory decision is made [57, 63].

UK Research Governance Framework for Health and Social Care with the technical support provided by NICE and NHS has made the main focus on including the perspectives of a wide range of people and groups in research as well as overcoming the main information, methodology, resourcing and other barriers to involving them (INVOLVE Initiative). The framework has addressed the issues on how to involve a diverse range of people in research (special medical conditions, ethnic minorities, age) developing guidance for researchers and other healthcare stakeholders [25].

Clinical Trials Transformation Initiative (CTTI) is a wide-scale public-private partnership with involvement of more than 70 healthcare stakeholders, aimed to transform existing practices within R&D to more efficient and patient-oriented. The separate focus has been made on the collaboration with patient organisations improving quality of clinical trials through advisory activities, sharing best practice examples, joint efforts developing study-related documentation, policy and advocacy activities [5, 6]. In 2015 the CTTI recommendations for all stakeholders (with particular focus on patient groups, academia and industry sponsors) on effective engagement around clinical trials were developed and broadly presented [8]. Additionally, some practical tools for PAGs'/CBOs'/other NGOs' capabilities evaluation were developed to help other healthcare stakeholders with targeted engagement [6, 8]. Some self-explanatory cases come from the area of orphan (rare) diseases, such as Friedreich's ataxia, Wiskott-Aldrich syndrome (WAS) etc., where PAGs play paramount role in driving R&D agenda as well as ensuring appropriate investments/budget allocation for that purpose. CTTI has been providing the great environment for such cross-sectoral collaboration and patient engagement [5].

Patient Focused Medicine Development is a recently presented cross-sectoral initiative aimed to build efficient, well-coordinated, measurable and reliable framework that involves patients as partners, acting as a catalyst and facilitator to achieve synergies and fill the gaps in the current patient engagement landscape [41]. In 2015–2016 the following two work streams run within the initiative: 1) delivering landscape analysis covering needs, gaps, stakeholder map and recommendations and developing «strawman» proposal for the framework on patient involvement in drug development, and 2) building the operational structure that will deliver the landscape analysis above and the subsequent recommendations for positioning and strategy with guidance from the Advisory Committee.

European Patients' Academy on Therapeutic Innovation (EUPATI) is a wide scale partnership which provides scientifically reliable, objective, comprehensive information to patients and the general public on the research and development process of medicines. It increases capacity of patients and the community representatives to be effective advocates and advisors, e.g., in clinical trials, with regulatory authorities and in ethics committees. In January 2016 EUPATI successfully launched a new educational toolbox with the key objectives to improve literacy/awareness on R&D processes and increase patient involvement to clinical development programmes both as experts and participants [12].

Corporate initiatives/projects driven by either biopharmaceutical/medical device companies as R&D sponsors or academic institutions had predominantly been aligned to corporate R&D strategies and business planning processes before the launches of the cross-sectoral initiatives mentioned above, when academia and the industry stakeholders have had an opportunity to join [10, 23, 30]. Although the industry and academia can provide a lot of best practice examples of successful engagement with proven outputs and real benefits for patients, the challenge remains the same: lack of consistency and coordination with other healthcare stakeholders. For example, running some investigator-sponsored studies (ISSs) or collaborative studies the parties (manufacturer/license owner, investigator, third party CRO) don't have the same vision on getting patient advice/insights on clinical protocols or informed consent forms (ICFs), hence, don't rise these points, discuss them and reach an agreement on actions required. Therefore, the expectation is that all involved parties have to be «at the same page» getting patient insights on a technology value and providing input to clinical development programmes [6, 8, 41, 61].

There are a vast majority of topics and formats to be explored getting patient insights, advices or information within discovery and development stages. A lot of really helpful recommendations have been developed over the last years on how to organise/facilitate advisory boards, individual interviews/consultations, focus-groups or run discussions and workshops with patients, caregivers, advocates and representatives of patient organisations [8, 21, 34, 54]. From the governance perspective, it's crucial to comply with the ethical principles of engagement with patients outlined in the industry Codes – IFPMA, EFPIA, ABPI as well as corporate codes, and GCP and National/Federal regulations (for example, the draft of FDA's Guidance on Patient-Focused Drug Development is under review now). Prior any type of engagement healthcare stakeholders should clearly understand the intent, timing, planned outputs, appropriateness of activity/event and agenda. Industry and

other stakeholders must not use the discussion platform on health technology's value for any promotional purposes.

Herein we consolidate the possible agendas and aspects in focus of patient engagement throughout discovery and clinical development continuum which have already been broadly established and based on experience of regulators, academia and the industry. The list isn't exhaustive and can be updated in line with the newest milestones of PFMD programmes:

– «Voice of the Patient»/Patient vision of illness;
– Providing data on unmet patient needs and disease/therapeutic burden;
– Incremental innovation: what does it mean for patients within the dedicated disease area;
– Input regarding interest of research question to patient community;
– Fundraising priorities, investment directions and direct funding for research to identify target molecules;
– Helping define study's population/ensuring better enrolment of female population, ethnic minorities and key affected populations (KAPs)/sub-populations;
– Providing patients/community feedback on study design/concept and protocols;
– Protocol simulation journey;
– Device simulation/testing sessions;
– Natural history database and patient registry support;
– Input on meaningful clinical endpoints/outcomes;
– Developing PRO/PCOs, advisory/insights on their collection and measurement;
– Review of study documentation: informed consent form (ICF) and patient/participant leaflet (PL);
– Working with regulators/HTA bodies on benefit-risk evaluation;
– Assistance in feasibility assessment: selecting and recruiting optimal clinical sites; clinical/laboratory infrastructure support/advocacy;
– Providing patient feedback on study participant experience;
– Serving on Data & Safety Monitoring Board;
– Serving on Ethics Committee members;
– Input for any trial adaptations or modifications;
– Accompanying sponsor to milestone meetings, providing interim feedback on the development programme;
– Providing public testimony at a regulator's advisory committee and other hearings;
– Serving on post-market surveillance initiatives;
– Input on study results and end-points' interpretation;
– Co-presenting results (with sponsors and/or academia);
– Publications/communications on study results (in particular, development of plain language summaries – PLSs);
– Supporting development/optimisation/testing digital tools for patients and study participants to help them with providing feedback within R&D programmes (ePRO, electronic health records – EHRs, e-registries etc.).

The safety-related issues and clinical outcomes must be taken seriously by a study sponsor and regulator at any stage of discovery and clinical development. Despite strict national regulations based on GCP standards and an investigator's obligation to report any adverse event/reaction within 24 hours upon detection, some safety-related issues may remain hidden and therefore unreported. Alongside HCPs any patient, patient-related individual or community representative has a right to report about an adverse event/ reaction happen in a patient using health technology including adverse drug reactions (ADRs), medical device adverse incidents, cases on defective (with inappropriate quality) medicines, counterfeited or faked medicines or medical devices. As an example, the Yellow Card Scheme in the UK managed by MHRA, may be considered [58].

Social listening as an innovative method for getting public insights was recently explored within healthcare for alternative detection of safety related-signals/issues and pharmacovigillance procedures [46, 60]. Although the good technical solutions such as filtering and sorting-out have successfully been implemented, technology owners face some methodological challenges with data robustness, validation and interpretation as well as follow-up difficulties with clarification and making further contacts [44]. Very recent ideas reflect a growing interest to social listening from healthcare stakeholders and encompass broader value-getting purposes, when any information regarding unmet patient needs, care gaps and expectations from R&D and regulators will be appreciated and considered as important, even from anonymous/indefinite community representatives [9, 44]. The expectation is that social listening tools will be filling out some existing gaps (not addressed yet by market research agendas) with understanding health technologies value at post-authorisation/surveillance stage.

Patient-reported and patient-centered outcomes measurement

Up to date PRO and PCO measurement can be considered as an impactful and valuable tool for HTA and decision-making within healthcare. The methodology and practices for PRO/PCO collection and analysis has become more advanced and sophisticated over the last years; they have widely been embedded into different clinical development programmes and research projects within healthcare; regulators and HTA agencies consider PRO/PCO as mandatory part of health outcomes analysis what reflects patients vision of health technology's value and determinates further access- and reimbursement-related decisions [4, 18, 34].

US FDA, UK NICE and other regulators recommend separating PROs from other subsets of PPIN. Overall, PPIN means a range of information that comes directly from patients such as, but not limited to, views, experiences, preferences, needs, opinions, expectations and priorities. PPIN has the subsets listed and defined below:

– Patient-perspective information – information regarding the attitude or the point of view of the patient, including informal comments in correspondence to a regulator or testimony at advisory committee panel meetings or PFMD/ PFDD meetings, patient opinions expressed publicly including through social media, patient responses to qualitative *ad hoc* surveys, quantitative measurements and quotations [14, 57].

– Patient preference information – qualitative or quantitative assessments of the relative desirability or

acceptability of attributes that differ among alternatives, e.g., alternative therapeutic strategies. Attributes of a drug or biologic include characteristics such as effectiveness, safety, route of administration, dosing regimens, duration of effect, duration of use, and other product features about which patients express preferences [35].

– Patient-reported outcomes (PROs) – a measurement based on a report that comes directly from the patient (e.g., study participant) about the status of the patient's health condition without amendment or interpretation of the patient's response by a HCP or anyone else. A PRO can be measured by self-report or by interview provided that the interviewer records only the patient's responses [18].

Patient-Centered Outcomes Research Institute (PCORI) uses the term Patient-Centered Outcomes (PCOs) in relation to the programme of patient-centered outcomes research (PCOR) as a particular approach to comparative effectiveness research (CER). PCORI explores this approach by emphasising research that examines choices and clinical outcomes that are meaningful to patients. This research, which takes into account patients' values and preferences, helps individuals and their caregivers make informed healthcare decisions [34, 45].

Taking the definitions above, PROs and PCOs must be measurable and therefore assessable either qualitatively or quantitatively. The DhpResearch and other health outcomes consultants propose the term of PRO measure, or PROM. PROMs are the tools to gain insight from the perspective of the patient into how aspects of their health and the impact the disease and its treatment are perceived to be having on their lifestyle and subsequently their quality of life (QoL). They are typically the questionnaires in different formats (paper, touch-pad devices, ePRO apps etc.), which can be completed by a patient or individual about themselves, or by others (relatives, caregivers) on their behalf [30, 32, 43].

Questionnaire design is usually developed on visual analogue scale (VAS) or Likert scale methodology. VAS measures a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured (for example, answering to the question «How severe is your pain today?» a patient shall place a mark on horizontal or vertical line from «No pain» to «Very severe, intolerable pain»). Many researchers prefer to use a method of analysis that is based on the rank ordering of scores rather than their exact values, to avoid reading too much into the precise VAS score [7]. The Likert Scale measures attitudes directly, accounting for both the cognitive and affective components of attitudes. It assumes strength/intensity of experience is linear i.e. on a continuum from strongly agree to strongly disagree. Respondents offered a choice of five to seven responses with the neutral point being neither agree nor disagree [28]. Diversity/heterogeneity of patients' answers to open questions requires content-analysis or other qualitative PROMs.

There are at least three groups of ongoing PROM concepts: common, special and public health oriented concepts. Common concepts are applicable to almost all health-related conditions and health technologies; they include health status, health-related quality of life (HRQoL), quality of life (QoL), well-being measures, treatment satisfaction, symptoms and functioning [32]. Those measures have been widely accepted in clinical practice and used by healthcare stakeholders. Special concepts are applicable to the dedicated illness/group of illnesses and correspondent technologies. For example, for HIV/AIDS area and related health technologies the following PROM have been developed: HIV Impact Score, HAT QoL, HIV symptom Index, AIDS-HAQ, HOPES, ACTG QoL, Medication Attribution Scale (MAS), Living With HIV Scale (LWH) and others [15]. Special PROM concepts are also widely accepted and applicable for clinical practice within the dedicated disease/therapy area. Albeit substantiated and actualised, the third group of public health oriented PROMs is still under development; there is a lack of consistency among experts regarding their validation and practical implementation. Public health oriented PROMs reflect patient's satisfaction with healthcare infrastructure, operations, logistics, HCP qualification and expertise, some aspects of adherence and retention in care, provided technical support and excellence in shared decision-making (SDM) throughout the individual disease and care journey [1, 2, 13, 53].

Patient community, regulators and other healthcare stakeholders strongly encourage R&D sponsors to embed PRO/PCO into design of clinical trials and discuss that with patients as earlier as possible, ideally at the stage of identification of unmet medical needs and initial planning of a clinical development programme [4, 18, 32, 45]. Quite eloquent cases came from oncology where survival-based end-points are routinely used in clinical trials' design. The general trend is that patients live longer with cancer, therefore they must increasingly choose among technologies with varying efficacy-toxicity balances as a treatment usually affects their QoL much more than an illness itself. Patients understandably want to know how their peers felt during and after a treatment; progression-free survival (PFS) or overall survival (OS) outcomes don't address that question [4]. Moreover, payers increasingly seek information about patients' comparative experiences with different products, because patients with worse symptoms or functional status utilise more supportive services [13].

From the practical perspective Meadows (2012) recommends R&D sponsors to develop a clear measurement strategy based on the following steps: 1) Identifying key treatment effects and key outcomes; 2) Select outcomes relevant to the treatment and intervention (e.g. heath technology; 3) Develop endpoint model and, finally, 4) Select PROM [32]. Other authors (Basch, 2013) proposed more explanatory algorithm with the following steps upon PRO/PCO identification (with some our adaptation) [4]:

– PROs/PCOs identification.

– Discussion of plans for measuring and analysing PCOs at structured meetings between R&D team and regulatory agency.

– Development or selection of measures to evaluate outcomes using established qualitative and quantitative methods.

– Inclusion of PROs/PCOs alongside other measures in pivotal trials, with protocol-specified plans for statistical analysis as well as minimizing and handling missing data.

– Engagement with community representatives or the target population/KAP.

– Inclusion of PROs/PCOs in drug labels to help patients and HCPs with decision making.

The last point can be considered as a «must be» practice for health technology owners and regulatory/HTA agencies, as in accordance to the analysis of PROs/PCOs inclusion rate in US drug labels only 24% were granted PRO claims throughout the period of 2006–2010; 86% among them were for symptoms [3]. The procedure of compulsory PROs/PCOs inclusion in drug labels hasn't been established yet in a lot of countries, whilst the statistics of voluntary inclusion is absent.

HTA and regulatory procedures, decision-making

Regulation, governance, decision-making processes and final decisions made regarding health technologies' reimbursement/access have been under the permanent public scrutiny. Policy and advocacy efforts of patient organisations have also been endeavouring across those important areas with recognisable results: patients and/or their representatives/ advocates have become more empowered parties in HTA and regulatory discussions; they have got more influence on decision-making; a lot of cross-sectoral public/ governmental partnerships have been established around; regulatory and HTA operations have become more transparent and clearer for healthcare stakeholders, first and foremost for patients [4, 14, 21, 35–37, 39, 40, 51].

However, even across EU countries (UK, France, Spain, Italy, Poland and Germany) where HTA and regulatory spheres are well-established, only 19% of respondents self-indicated their knowledge about HTA aspects as good; 15% – as good about pharmacoeconomics and 18% – as good about the regulation; more than 30% of respondents expressed an interest to learn more about pharmacoeconomics and regulation, more than 40% – about HTA; there was a strong correlation between previous experience of medical research and greater interest in the mentioned aspects [62]. Access to health technologies remains the main challenge within emerging healthcare markets; in particular, in the less developed countries (LDCs), hence, the public interest in regulatory and HTA procedures is generated by access-related issues, if HTA system exists. In some countries PAGs and/or CBOs take a role of key drivers of a HTA system development, optimisation of reimbursement procedures and changes within national healthcare legislation and regulatory area.

Although a lot of national HTA and regulatory systems demonstrate their openness and readiness to build mutually beneficial partnerships with patients and community representatives, to work in collaborative way and to utilise patient vision of health technologies' value, there are a limited number of cases/evidence of truly holistic approach, diversified engagement agenda and long partnerships history. The question remains open on how an input from patients does inform a final decision on reimbursement and access within those systems. We haven't found any relevant analyses of correlation between a level of patient engagement or established partnerships and a number of patient-driven/-lobbied HTA/regulatory decisions. The evidence is only supported by the separate case studies. Taking the dynamics of patient-centric initiatives implementation across HTA and regulatory area as well as a growing interest expressed by PAGs and CBOs, such consolidated analyses can be expected at the nearest future.

We identified two traditional formats of patient engagement explored by majority of national HTA agencies and regulatory bodies: members of an advisory committee/ board (sometimes there is a board/panel comprised of patients/community representatives only) and members of a working group [21, 31, 37, 40, 63]. The last format is more typical for development of clinical guidelines and several technical documents. Having no objection to analyse patient engagement within every national HTA system, hereafter we focus on the two biggest and most comprehensive ones in terms of history and diversity of patient engagement approaches: US FDA and UK (predominantly NICE).

US FDA considers patient insights or PPIN as a valuable source for any decision-making during the technology review process; this approach seems the most holistic comparing with other regulators. In 1988 FDA formed an office to work with the patient advocates, focusing mostly on the HIV/AIDS community. In 1990 cancer patient advocates were firstly recruited into the Patient Representative Program and in mid-1990s it expanded to include serious and life-threatening diseases. In 1991 the first patient representative served on the Antiviral Drugs Advisory Committee for HIV. After 2000 patient representatives received privileges as members Advisory Committees within the dedicated disease/health technology areas. FDA's Centre for Drug Evaluation and Research (CDER) has established the Professional Affairs and Stakeholder Engagement (PASE) department with a significant focus on patient engagement programmes [21, 63]:

– Patient Representative Programme (Advisory Committees).

– Patient Network: «FDA For Patients».

– Patient Focused Drug Development (PFDD, please, see above).

– Professional Affairs and Stakeholder Engagement (PASE) – wider multi-stakeholder engagement and cross-sectoral partnerships.

– Patient Perspectives in Benefit-Risk Determinations for Medical Devices.

– Device Patient Preference Initiative.

– Patient Engagement Advisory Committee (PEAC).

Within the frameworks of the Patient Representatives Programme over 200 patients or community representatives took part in 190 Advisory Committees across 300 disease areas/conditions. The format of those meetings allows CDER to bring patient voice to discussions about new and already approved drugs, to get advice on drugs, devices, and biologics considered for approval, to ensure earlier input in medical product development and review, to expand and sustain communication with patients and their community, to educate patients, advocates, and HCPs on medical product regulations and to allow for comment on proposed regulatory/ clinical guidelines and prescribing information (PI).

The Patient Network «FDA for Patients» has been created as a «one-stop-shop» of FDA resources aimed to help patients learn more about FDA and interact with the regulator. The resource provides an opportunity to find out about FDA public meetings, submit comments to FDA and comment on proposed regulatory guidelines. With the aim of continuous

service improvement CDER conducts the public workshops to help community representatives and PAGs gain a better understanding of how to effectively engage CDER [21].

UK regulators have traditionally been considering patients as important stakeholders within HTA, regulatory procedures and decision-making. A lot of public/governmental partnerships were established over the long period of NHS evolving with methodology optimisation and improvements.

A significant transformation of patient's role in value assessment has been taking place over the last five years within the framework of VBP (value-based pricing)/VBA (value-based assessment) implementation [20]. In December 2010, UK Department of Health launched a consultation on VBP. With participation of patients and wide community representatives it was suggested a higher cost for each QALY gained could apply for drugs that: tackle a disease for which there was high «burden of illness», demonstrate wider societal benefits such as a patient's ability to return to work or contribute to society (such benefits may vary, for example, with age, gender, disease and quality of life), show greater therapeutic innovation or improvements compared with other technologies. Albeit the feedback to this consultation was largely positive, there were a lot of concerns expressed, in particular, by patient advocates and PAGs: how to determine price, including how to price a drug that can be used to treat different conditions or patient populations (for which its value could be varied); potential discriminatory effects and how unmet needs, innovation and real world evidence could be taken into account [11].

These discussions preceded the next step: in 2014 UK government introduced the concept of VBA with clarification that NICE would conduct the VBA of the technology and the Department of Health would use it as the basis of price negotiations with industry [36]. NICE produced proposals for amending its appraisal methods to take into account such characteristics as burden of illness (BoI) and wider societal impacts (WSI). Even after more than 900 consultations the agreement on the unified VBA methodology wasn't gained due to inputs heterogeneity; however the consultations raised much wider scope of the proposed VBA methodology and allowed to consider more flexible approaches for data/insights collection from patients to inform technologies appraisal:

– on the proposed patient access schemes (PAS);
– on technologies addressed unmet needs within orphan and ultra-orphan diseases;
– on outcomes (including PROs)-based appraisal schemes when limited or no data are available;
– on patient preferences research;
– on early access to medicines and adaptive licensing etc. [20, 35, 37].

Those considerations have also been reflected at the recent reform of the Cancer Drug Fund (CDF) and new ways of working with public [39]. NICE has established the following formats of patient and community engagement through medicines evaluation and appraisal:

– The citizens council;
– Advisory committees and working groups:
  – Accreditation Advisory Committee (AAC);
  – Clinical Guidelines Updates Standing Committee (CGU);
  – Diagnostics Advisory Committee (DAC);
  – Highly Specialised Technologies Evaluation Committee (HSTEC);
  – Indicator Advisory Committee (IAC);
  – Interventional Procedures Advisory Committee (IPAC);
  – Medical Technologies Advisory Committee (MTAC);
  – Public Health Advisory Committee (PHAC);
  – Quality Standards Advisory Committee (QSAC);
  – Technology Appraisal Advisory Committee (TAC).
– NICE public board meetings;
– Technology appraisal appeal panel.

The Citizens Council provides NICE with a public perspective on overarching moral and ethical issues that NICE has to take account of when producing guidance. The Council's recommendations and conclusions are incorporated into a document called «Social value judgements» and, where appropriate, into NICE's methodology.

Patients and/or their representatives are serving as advisory committee or working group members with influence and responsibility on decision-making. NICE's advisory committee meetings, technology appraisal appeal hearings, public board meetings and a range of other meetings are also open to the general public and press to observe [37].

In addition to NICE initiatives, Scottish Medicines Consortium (SMC) established unique value assessment practice running Patient and Clinician Engagement (PACE) group. PACE is a new stage to the SMC value assessment process. It can be used to allow a more flexible approach to considering medicines for either end of life treatment or orphan or ultra orphan medicines. The main part of the PACE process is a meeting which brings together patient representatives and HCP experts. The purpose of the PACE meeting is to gather detailed information which will allow a discussion on the benefits of a medicine, including how it can impact the quality of a patient's life. This information may not always be fully captured within the conventional HTA process [40].

In-depth analysis on patient-centric initiatives and value assessment frameworks supported by HTA agencies and national regulators around the world is the subject of further public health research.

CONCLUSIONS

Over the last decade the significant progress has been made by patient organisations (PAGs, CBOs, and other NGOs), biopharmaceutical and medical device industry, academia, regulators and other healthcare stakeholders in actualisation and identification of patients' role in value-based assessment as well as implementation several patient-centric initiatives across discovery, clinical development, HTA and authorisation. A lot of constructive efforts within methodology and governance took place very recently (2014–2016) at the global, regional and national levels; however at this stage it's rather impossible to identify any tangible outcomes which could demonstrate good level of evidence.

We haven't found any relevant systematic reviews, analyses or publications on correlation between level/types of patient engagement or public partnerships established between stakeholders and a number of proved patient-driven/-lobbied

decisions within discovery and clinical development milestones as well as HTA/regulatory procedures. The evidence is only supported by the separate case studies and observations shared by healthcare stakeholders, including patients and community representatives.

Prior initiation of any technology development continuum it's crucial to identify unmet medical needs of patients to prevent avoidable misalignment between these needs and further decisions and processes. We found that this important step is predominantly out of scope and therefore missed at early planning stage.

Several patient engagement frameworks were founded and implemented capturing discovery and clinical development areas. Albeit the healthcare stakeholders have been demonstrating their ability to develop and maintain such frameworks, they didn't really demonstrate collaborative approach, joint focus, consistency and alignment between each other. More efforts needed within cross-sectoral collaboration and communication, sharing best practice examples/cases and implementation of the unified set of essential standards for all stakeholders. Truly innovative engagement agendas and formats aimed to getting more insights on R&D, such as social listening, should be better showcased and utilised.

Academia, sponsors, and regulators have demonstrated a good progress incorporating PROs/PCOs in to study design as end-points and establishing strong methodology pillars. A lot of common and illness-specific PROM concepts were widely accepted. However, taking constantly evolving healthcare environment, more public health oriented PROMs have to be considered and implemented. We found no or very limited practice with incorporating PRO/PCO data to drug labelling/prescribing information.

Although a lot of national HTA and regulatory systems are keen to build mutually beneficial partnerships with patients and community representatives, there are still a limited number of cases/evidence of truly holistic approach, diversified engagement agenda and long partnerships history. We reviewed the most diversified practices presented by the US FDA and UK regulators – NICE and SMC. In-depth analysis will be necessary to compare and identify best practices in this area all around the world.

Overall, we tried to review and consolidate a major part of existing approaches and identify research directions/further collaborative efforts needed to synchronise patient engagement frameworks and ensure better consistency assessing health technologies value with patients.

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Роль пацієнтів і представників громадськості в ціннісній оцінці медичних технологій та прийнятті відповідних рішень у системі охороні здоров'я

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Мета – провести комплексний аналіз існуючих підходів до оцінки цінності медичних технологій пацієнтами та представниками громадськості, а також їх ролі у прийнятті відповідних рішень у системі охорони здоров'я.

Методи: бібліосемантичний (огляд 63 джерел, серед яких 35 – літературні джерела, 28 – Інтернет-ресурси) та експертних оцінок.

Результати. Для проведення аналізу визначено чотири основні сфери: нагальні потреби пацієнтів; винахід та розробка медичних технологій, клінічні дослідження; результати, повідомлені пацієнтами; оцінка медичних технологій; прийняття регуляторних рішень. Проаналізовано та узагальнено існуючі програми, накопичений досвід та підходи до залучення пацієнтів у зазначених сферах.

Висновки. За останні 10 років пацієнтські організації та інші сторони охорони здоров'я досягли значного прогресу в актуалізації та визначенні ролі пацієнтів в оцінці цінності медичних технологій, а також у впровадженні різних пацієнт-орієнтованих ініціатив у сферах винаходу, розробки, клінічних досліджень, результатів, повідомлених пацієнтами, оцінки медичних технологій та реєстрації. Багато конструктивних зусиль у царині методології та організації зазначених процесів мали місце в останні роки (2014–2016), але наразі фактично неможливо ідентифікувати конкретні результати, які б мали належний доказовий рівень.

КЛЮЧОВІ СЛОВА: пацієнти, представники громадськості, залучення пацієнтів, цінність, пацієнт-орієнтована охорона здоров'я, ціннісна оцінка медичних технологій.

Роль пациентов и представителей общественности в ценностной оценке медицинских технологий и принятии соответствующих решений в системе здравоохранения

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Цель – провести комплексный анализ существующих подходов к оценке ценности медицинских технологий пациентами и представителями широкой общественности, а также их роли в принятии соответствующих решений в системе здравоохранения.

Методы: библиосемантический (обзор 63 источников, среди которых 35 – литературные источники, 28 – Интернет-ресурсы) и экспертных оценок.

Результаты. Для проведения анализа определены четыре основные сферы: актуальные потребности пациентов; открытие и разработка медицинских технологий, клинические исследования; результаты, сообщенные пациентами; оценка медицинских технологий и принятие регуляторных решений. Проанализированы и обобщены существующие программы, накопленный опыт и подходы к вовлечению пациентов в указанные сферы.

Выводы. За последние 10 лет пациентские организации и другие стороны здравоохранения достигли значительного прогресса в актуализации и определении роли пациентов в оценке ценности медицинских технологий, а также во внедрении различных пациент-ориентированных инициатив в сферах открытия, разработки, клинических исследований, результатов, сообщенных пациентами, оценки медицинских технологий и регистрации. Много конструктивных усилий в аспектах методологии и организации указанных процессов имели место в последние годы (2014–2016), но сейчас фактически невозможно идентифицировать конкретные результаты, которые бы имели достаточный уровень доказательности.

КЛЮЧЕВЫЕ СЛОВА: пациенты, представители общественности, вовлечение пациентов, ценность, пациент-ориентированное здравоохранение, ценностная оценка медицинских технологий.

ВІДОМОСТІ ПРО АВТОРА

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