# Patient involvement in the development, regulation and safe use of medicines

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Please note that the layout will be improved in the final version, and best efforts will be made to correct remaining typographical and/or grammatical errors, as well those pertaining to references.

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# Acknowledgements

(to follow)

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# Abbreviations

| | |
|---|---|
| ACE-inhibitors | angiotensin-converting enzyme inhibitors |
| AGREE Instrument | Appraisal of Guidelines for Research and Evaluation Instrument |
| AIDS | acquired immunodeficiency syndrome |
| ARBs | angiotensin receptor blockers |
| aRRM | additional risk minimisation measure |
| AusPAR | Australian public assessment report for prescription medicines |
| CAB | community advisory board |
| CAT | Committee for Advanced Therapies (of the EMA) |
| CDER | Center for Drug Evaluation and Research (of the FDA) |
| CHMP | Committee for Medicinal Products for Human Use (of the EMA) |
| CIOMS | Council for International Organizations of Medical Sciences |
| CMI | consumer medicine information |
| CoI | conflict(s) of interest |
| COMP | Committee for Orphan Medicinal Products (of the EMA) |
| COVID-19 | Coronavirus disease |
| CPG | clinical practice guideline |
| DHPC | direct healthcare professional communication |
| DTC | direct-to-consumer |
| EEA | European Economic Area |
| EFPIA | European Federation of Pharmaceutical Industries and Associations |
| EHR | electronic health record |
| EMA | European Medicines Agency |
| EPAR | European public assessment report |
| ePI | electronic product information |
| ETASU | elements to assure safe use |
| EU | European Union |
| EUPATI | European Patients' Academy on Therapeutic Innovation |
| EURORDIS | European Organisation for Rare Diseases |
| FAQs | frequently asked questions |
| FDA | U.S. Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FMEA | failure mode and effects analysis |
| GIN | Guidelines International Network |
| GVP | good pharmacovigilance practices |
| HCP | healthcare professional *or* healthcare provider |
| HEOR | health economics and outcomes research |
| HIV | human immunodeficiency virus |
| HTA | health technology assessment |
| IAPO | International Alliance of Patients' Organizations |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IMI | Innovative Medicines Initiative |
| INN | International Nonproprietary Name |

| | |
|---|---|
| MAA | marketing authorisation applicant |
| MAH | marketing authorisation holder |
| MG | Medication Guide |
| MHLW | Ministry of Health, Labour and Welfare (Japan) |
| MHRA | Medicines and Healthcare products Regulatory Agency (UK) |
| NHANES | National Health and Nutrition Examination Survey |
| NHC | National Health Council (US) |
| NHWS | National Health and Wellness Survey |
| NICE | National Institute for Health and Care Excellence (England) |
| OTC | over-the-counter |
| PAES | post-authorisation efficacy study |
| PAG | patient advocacy group |
| PARADIGM | Patients Active in Research and Dialogues for an Improved Generation of Medicines |
| PASS | post-authorisation safety study |
| PCI | patient-centred initiative |
| PDCO | Paediatric Committee (of the EMA) |
| PDP | product development partnerships |
| PEMAT | Patient Education Materials Assessment Tool |
| PFDD | patient-focused drug development |
| PFMD | patient focused medicines development, *also* an international collaboration called Patient Focused Medicines Development |
| PICS | post-intensive care syndrome (related to COVID-19) |
| PICS-F | post-intensive care syndrome-family (related to COVID-19) |
| PIL | patient information leaflet |
| PL | package leaflet |
| PM | Product Monograph |
| PMDA | Pharmaceuticals and Medical Devices Agency (Japan) |
| PMI | Patient Medication Information |
| PPI | patient and public involvement *or* Patient Package Insert (US) |
| PPS | patient preference studies |
| PRAC | Pharmacovigilance Risk Assessment Committee (of the EMA) |
| PREM | patient-reported experience measure |
| PRO | patient-reported outcome |
| PROM | patient-reported outcome measure |
| QoL | quality of life |
| R&D | research and development |
| RCT | randomised controlled trial |
| REMS | risk evaluation and mitigation strategy |
| RiskMAPs | Risk Minimization Action Plans |
| RMM | risk minimisation measures |
| RMP | risk management plan |
| RWD | real-world data |
| RWE | real-world evidence |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |

| | |
|---|---|
| SDM | shared decision making |
| SMA | spinal muscular atrophy |
| SMOG | Simple Measure of Gobbledygook |
| SmPC | summary of product characteristics |
| TGA | Therapeutic Goods Administration (Australia) |
| UK | United Kingdom of Great Britain and Northern Ireland |
| UN | United Nations |
| US | United States of America |
| USPI | US Prescribing Information |
| WHO | World Health Organization |
| YPAG | young persons' advisory group |

# Preface

The involvement of patients in medicine development, regulation and use is a dynamic and evolving area of public health. The CIOMS IX Working Group's 2014 report, *Practical Approaches to Risk Minimisation for Medicinal Products*, devoted only a small section in one chapter on the role of patients in developing medicine safety programmes. Now, less than a decade later, CIOMS has dedicated this entire report on patient involvement, not only in risk management, but in all aspects of medicine development, regulation, and safety.

As with all CIOMS reports, this one is a pragmatic handbook: a 'how to' of sorts, for involving patients in the development and safe use of medicines. Wherever possible, it recommended 'best practice'. What does that mean? Best practices are those which have been distilled to date from the published literature and the combined experience and expertise of members of the CIOMS XI Working Group, a diverse collective of patients, patient advocates, regulators, academics, and industry representatives. These best practice recommendations can serve as a guide only – it is not expected that the best practices set out in this report will, or should, necessarily be adopted in their entirety. Rather, our report should prompt readers to review and select those which best fit their current organisational needs.

This CIOMS XI report is not likely to be the last word on pragmatic approaches to patient involvement in medicine development. As patient involvement evolves and expands across different countries and regulatory jurisdictions, much more will be learned. Sharing the lessons widely among diverse audiences (*e.g.* through professional conferences, social media, and peer-reviewed publications) will advance patient involvement and firmly entrench it in the development, regulation and safe use of medicines.

To date, research on the impact of patient and public involvement is sparse and it is not known which strategies are most appropriate. Qualitative and quantitative research is needed to better understand what constitutes meaningful patient and public involvement and how to optimise processes and strategies to obtain the best and most impactful input from patients and members of the public.

Patient and public involvement rests mainly on ethical and democratic principles. So even if we do not yet know what works best in different settings and for each different goal, there is no doubt that strengthening patient involvement in all healthcare contexts and taking every effort to make it meaningful is the way to go.

Views on patients' role in medical decision making, let alone in medicine development and safety, differ enormously across the globe. While the value of patient involvement has gained increasing recognition in many countries with well-developed economies, elsewhere in the world it is still very much an 'emerging phenomenon', as noted in the report of the CIOMS Working Group XI.

From the CIOMS XI Editorial Team

February 2022, Geneva, Switzerland

# Foreword

## Ethical principles for patient involvement

The development of good medicines benefits people who need them for treating, preventing or diagnosing a medical condition or for maintaining their health and wellbeing. But these people should not be regarded simply as research subjects or users of medicines; they can also be involved in decisions on the development and regulation of these medicines, and as consultants to medicine developers, payers, regulators, or other such stakeholders. Increasingly, those likely to take the medicines are involved as sponsors of investigational medicines, the funders of medicines research.[1]

Codes of conduct, laws, and other forms of policy list many ethical issues relevant to clinical research and to the practice of medicine outside of research.[2,3] Here, we focus on the broad ethical principles on engaging patients during the development of medicines and during their use. The reasons for engaging patients and the scope and outcomes of engagement vary according to circumstances.

These ethical principles are drawn from the Belmont Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in the US.[4] Released in 1979, the Belmont Report was the foundational document for 'principlism', the dominant approach to modern bioethics in research regulation. Principlism involves examining moral dilemmas by applying relevant ethical principles.

The Belmont Report summarised three ethical principles that should underlie research on humans. They provide an analytic framework to guide the resolution of ethical quandaries on biomedical and behavioural research. Since the publication of the Belmont Report over 40 years ago, these principles have been recast; for example, 'respect for persons' is now commonly called 'autonomy', 'beneficence and nonmaleficence' are frequently separated into two individual principles, and 'justice' is often used alongside 'equity' and 'solidarity'.

We use the Belmont Report's original framing of principles. More important than the name of the principles or their precise definitions are the questions they raise about how best to engage ethically with people who use (or are expected to use) medicines.

We outline several fundamental ethical principles on the involvement of those expected to use medicines in the development and use of these medicines. It is for national bodies and other entities to decide which of the rules and recommendations in our report they should developed. The recommendations are likely to require nuanced interpretation according to prevailing circumstances.

## Key message

Many principles fundamental to bioethics – the ethics of medical and biological research – regard those likely to use medicines as expert partners who can meaningfully contribute their preferences, concerns, understandings, and lived experiences of a medical condition to improve medicine development and use. Such engagement offers:

- pragmatic benefits including research, development and use of a medicine better suited to the patient's needs and preference (which can lead to better effectiveness)
- adherence to ethical principles including respect for persons, beneficence and nonmaleficence (protection of the person's welfare), and justice.

### Respect for persons

The Belmont Report states that the principle of respect for persons is based on at least two ethical convictions:

- individuals should be treated as autonomous (having ability to make independent decisions)
- persons with diminished autonomy are entitled to protection.

The Belmont Report states that individuals should be treated as 'capable of deliberation about personal goals and of acting under the direction of such deliberation' and if they are incapable of such self-determination, they should be protected from exploitation, abuse, or ill-treatment. Although these tenets relate to research on human subjects, they are equally important in medical care.

The contemporary view is that individuals should be informed about their treatment options and permitted to make their own decisions and act on them. This is a shift in thinking from deference to clinicians (a paternalistic approach) to shared decision-making approach: clinicians contribute medical knowledge of a given condition and patients contribute their experience and understanding of living with the condition, as well as what outcome is most important to them. In shared decision making, clinicians and patients are viewed as experts of their different domains.

Shared decision making is described as the patient-as-partner approach to medicine.[5] This approach is embodied in international publications such as the World Medical Association's International Code of Medical Ethics.[6] But the paternalistic model of medicine still persists; in clinical research, those enrolled into studies have been described as 'research subjects', suggesting a passive role. However, in many cases people in studies are now regarded as 'research partners who can help shape the research goals and protocols'.[7] By accepting patients (or patient communities) as expert partners, their biases and potential conflicts of interests can be openly noted and considered, just as for other expert partners like clinicians and investigators.[8,9]

The views of people expected to use authorised medicines should complement those of science and business experts involved in medicine development: users of medicines should not be relegated to the role of passive recipients. Input should be solicited from likely users of medicines at all stages of development – from laboratory and clinical development to the medicine's marketing authorisation and beyond.[10] As expert partners, medicine user' preferences can influence decisions about their treatment (for example, on acceptable formulation of the medicine and how it is to be taken). Likewise, during development, their concerns and understanding of how the medicine is used can influence decisions ranging from identifying relevant endpoints in clinical studies to assembling instructions on a medicine's storage or use.

Engaging with patients and other anticipated users of medicines can result in better medicines and better systems for informing individuals about using them safely.[11] This provides a utilitarian argument for the involvement of patients. But even if there were not pragmatic reasons to engage with likely users of medicines, doing so upholds the ethical principle of respect for persons.

Listening to people and interacting with them is the simplest way of demonstrating respect for them. Numerous patient groups and others have adopted the disability rights movement's slogan, 'nothing about us without us'. It encapsulates their entitlement for a stake in medical research and medicine development and, at the very least, for their perspectives to be recognised and heard. Failure to solicit these perspectives and acting on them indicates lack of respect for medicine users as persons. Also, using patient data without due attention to matters such as privacy, confidentiality, and patient concerns about the data represents failure to respect patients as persons.

However, partnership with likely medicine users in the development and use of medicines may not truly uphold the principle of respect for persons if there are significant structural, medical, or other barriers to proper engagement with patients, despite an appearance of upholding it.[4] Similarly,

engaging with patients superficially may appear to uphold the principle of respect for persons, but this will be an empty gesture if no value is placed on patients' input.

One example of respect for persons in medicine development and use comes from an understanding of patients' tolerance or acceptance of risk. FDA, other regulators, and an increasing number of pharmaceutical companies are engaging with potential users of the medicine to understand what levels of safety and efficacy they would accept.[12] Another example of the industry's respect for potential users of medicines is a recognition they are not a monolithic group. When developing a product for global distribution, demonstrating respect for persons requires learning about the various contexts in which the product will be used and by whom. This learning allows industry to be responsive to the needs of a range of users.

### Beneficence and nonmaleficence

The aim of beneficence is to promote wellbeing. It is often paired with nonmaleficence – to avoid harm. Together, these principles oblige developers, researchers, regulators, and clinicians to increase benefit while minimising possible harm – an obligation that is central to the development, regulation, and use of medicines. A clinician must weigh the possible benefits against potential risks when choosing treatments for patients. Regulators, sponsors, and others involved in developing and using medicines must also contemplate the possible benefits and harm of their activities.

To evaluate a medicine, it is essential to have as complete an understanding of its potential benefits and risks as possible. Therefore, beneficence and nonmaleficence oblige stakeholders to share research findings and other data and to review all this information before making decisions. But medicines' possible risks and benefits are not solely pharmacological: there may be logistic, psychological and financial implications, social impacts, and opportunity costs. To understand these wider implications of medicines, it is essential to engage with expected users and to learn from them. While this engagement upholds the principle of respect for persons, it also fulfils the principles of beneficence and nonmaleficence because the interactions can result in safer and more effective approaches to the development, regulation and use of medicines.

The principles of beneficence (sustaining and improving wellbeing) and nonmaleficence (preventing harm) create an obligation to provide medicines to all who can benefit from them. Unhappily, not all who can benefit from medicines have access to them. The obligation to provide medicines competes with other obligations, such as providing shelter, protection, food, and meeting other fundamental needs. While principles help us understand which actions are good or bad, they cannot always carry societal consensus, as individuals' views about which principles should prevail vary. Thus, despite understanding the ethical obligation to provide medicines, individuals or institutions may not necessarily act to fulfil this obligation.

### Justice

The principle of justice creates an obligation to treat people equally and calls for justification for any apparent inequality. In research, justice creates the obligation to select research subjects with care, to ensure that certain individuals or groups are not disproportionately enrolled into studies or excluded from them. Justice in the development and use of medicines means ensuring that activity does not concentrate on certain conditions to the exclusion of others and that there is fair access to the medicines and to knowledge about them. For example, it would be unjust to communicate on safe storage or use in language that is inaccessible to many who may use the medicine.

Upholding the principle of justice is often hindered by conflicts over distribution. If people are to be treated equally, then what constitutes fair distribution must be defined. Should access, be it to a medicine or a chance to participate in a clinical trial, be on a first-come, first-served basis? Should access be prioritised to those with the greatest medical need? Should selection be random (as

through a lottery)? Should priority be given to those who can afford to pay or to those who are members of, say, a certain nation, occupation, or private insurance company? Should research and medical care funding be allocated equally to all diseases or conditions with the largest impact on wellbeing or fatality?

These questions are often resolved through policy; however, individuals may not always consider the solutions just because the concept of justice varies between individuals. When they view policies as unjust, patients have historically engaged in advocacy to secure policies that align with their views. Such advocacy work cannot be done, however, if patients and other stakeholders do not know what research is underway, what medicines exist and who has access to them, or the comparative efficacy and safety of different treatments. The principle of justice, when applied to medicines development and use, requires engagement with likely users so they can advocate for changes they deem necessary. Failure to engage restricts access to information necessary to evaluate a situation and, if deemed unjust, to seek remedy.

## Conclusion

Excluding patients and expected medicine users from the development and use of medicines beyond the role of passive recipient fails to respect them as persons. Such exclusion can reduce benefit and increase harm; this runs counter to the principles of beneficence and nonmaleficence. Furthermore, the failure to engage raises concerns about justice as it limits people's ability to learn about, seek access to, and stake a moral claim to medicines that are currently out of reach or are not being developed.

Engaging as partners with people likely to receive a given treatment aligns with the ethical principles of respect for persons, beneficence and nonmaleficence, and justice. It is wise. These principles also align with better research design, good research conduct, and an open exchange of perspectives, which benefit all stakeholders.



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# Executive summary

This CIOMS report describes and promotes the idea that patients should be involved throughout the life journey of medicines – from their development, through regulation to ongoing safe use in everyday healthcare. It describes where we are, and a path to where we need to be.

Many people and organisations work closely together to make sure that each medicine is fit for purpose. This involves long research to develop medicines that will meet regulatory authorities' demanding requirements for quality, safety and efficacy. For as long as a medicine is used, it is important to keep monitoring for any new effects, and this is how some very rare side effects are identified. It is right that patients' views are taken on board throughout the medicine's lifetime - from development to product retirement.

## What we mean by 'medicines' and 'patients'

Medicines can cover a wide range of products that are approved for use by medicines regulators. They can be used to:

- treat medical conditions
- prevent illness
- maintain or alter the way the body works and
- diagnose changes and abnormalities.

'Medicines' covers, for example, vaccines and medicine-device combinations. The development of a medicine is a complex and lengthy process.

In this report, when we say 'patients', we are generally talking about a wider group of people than just those taking the medicines. The patient community also includes the patient's family, caregivers, patient organisations, and patient representatives in various situations where medicines are discussed.

## Involving patients

Opportunities to involve patients start with a proper engagement to find out where treatments are needed. Only patients – who live every day with their health condition – can really say what causes them the greatest problems and what benefit of treatment they value most. However, even though this is an obvious idea, it is often overlooked. This makes it so important to engage patients at the very start of developing treatments. Then, for as long as a medicine continues to be used, patients can help to detect any new effects of the medicine. This builds up a fuller picture of the medicine's benefits and risks.

Engagement with patients can be achieved by working with relevant patient organisations – some of which came out of patient activism movements. The barriers to overcome for successful patient engagement include legislative and regulatory burdens as well as language and communication obstacles. Above all, there needs to be a cultural shift to see patients as partners in the development, regulation and safe use of medicines.

## What are the principles for involving patients?

Principles to guide medicine developers and regulators to involve patients include asking for and then respecting patients' views – since patients know most about how their condition affects them.

To make such involvement fair, sustainable and ethical, patients should be properly reimbursed for their time – and taking part should be made as convenient as possible. In this way they can play their full part.

The independence of patient organisations must be protected – so that their views are not influenced by those of other stakeholders. It is most important that there is an open, trusting, long-lasting, and respectful relationship with patients. Clear communication is vital for the relationship.

Digital technology can support communication and enables telemedicine. Smart technology – wearable and mobile devices – increases the depth and breadth of patient participation. It does this by enabling easy two-way communication and instant transmission of health data.

Importantly, diverse and special groups of patients, as well as family carers and other caregivers should be considered in all decisions. Their rights to make informed choices and get information in an accessible and appealing way must be considered. This gives a voice to the very old or very young, pregnant women as well as those facing particular barriers in society.

### Training for involving patients

Patients, and those who wish to involve patients, should have appropriate training to get the best out of this involvement. For patients, the training can involve:

- medicines-related sciences
- ethics of health-related research
- clinical trial methodology and interpretation and
- medicines legislation and regulation.

Patient organisations can offer, support and coordinate training. The training should be relevant to how individuals will be involved. This could be in development, regulation and monitoring use of medicines – to the construction of clinical practice guidelines.

### Medicines research

Patients should be drawn into providing an input into research on candidate medicines. They can work closely with healthcare professionals, academics and pharmaceutical companies on:

- defining the research goals and what treatment benefits to look out for
- getting patients involved in clinical trials planning and design, and
- circulating emerging research information that it is clear, relevant, and timely.

Patients' input in setting up and running clinical studies can improve the quality of the studies. Patients should also be involved in the design of a medicine and have a say on how it is formulated and packaged.

The research programme should explore patients' perspective on their medical conditions and on the treatment (or prevention) of these conditions through well-designed 'patient preference studies'. These studies can help identify what factors patients consider important and relevant. This type of research is particularly valuable when there are many treatment options and also when opinions vary between people.

### Licensing medicines

Regulators should continue to increase patients' involvement in:

- decisions on assessing the benefits and risks of medicine and
- continuous monitoring for new information on their side effects.

In some parts of the world, patient representatives are members of formal scientific and decision-making committees. They are also part of working groups on specific scientific aspects of medicine regulation. This trend must continue – to make sure that patients have a meaningful impact on the licencing of medicines – and their long-term monitoring after approval.

### Real-world data

After a medicine is approved, we get a greater understanding of a medicine's place in treatment from information on the medicine's effects on patients. This information is routinely collected in day-to-day medical practice – it is called 'real-world data'. To get most value from this, patients, health professionals, industry and regulators need to work together. Programmes called 'patient-centred initiatives' give patients the chance to provide their health information for research.

Patients must be fully involved in planning and decisions on how real-world data is:

- collected
- stored and managed, and
- released.

Patients must also be involved in making sure their privacy is protected.

Digital technology helps with the collection, exchange and analysis of real-world data. It also increases the opportunity for patient to play an active role.

### Information for patients about medicines

Once a medicine has been approved for use, it is the patient-facing information – mostly the patient information leaflet - that provides patients with the 'official' information on how to use the medicine, what precautions to take, and what its side effects might be. This information can also help healthcare providers and patients during shared decision making.

Patient involvement in designing and drafting this information can improve its relevance, clarity and, above all, take-up of the advice. Patients provide important context about how the information is used. They can provide information on local customs and traditions, health literacy, and healthcare structures. Patients should also be involved in developing regulations on how such information for patients is produced and evaluating the effectiveness of such patient information.

### Additional risk minimisation measures

The usual information given to patients about a medicine might not be enough for some medicines – where there are certain risks. In such cases additional risk minimisation measures for a medicine are needed. These may include the patient having regular tests or the need to take extra care over the use of certain medicines.

Because these measures often create an extra burden on patients, they should be involved in decisions about the design of the measures. This can include input into:

- the need for the risk minimisation measure
- the design and development of the measure
- how the measure is communicated
- how feasible it is to put the measure into practice (using digital technology where appropriate)
- helping with evaluating how well the measure works.

### Urgent safety information

Sometimes there is the need for urgent safety communication after a medicine has been licensed. This may be about a new concern over the use of a medicine or a group of medicines. This information is usually for healthcare professionals – but sometimes it may need action from patients.

Involving patients in setting up the process for such communication can make sure that patients' needs have been taken into account. Specifically, they can help to decide what issues need urgent communication, which groups of patients need to be informed, and how the information can designed for patients. Patient organisations can help to make sure important messages get to

patients quickly. They can also advise on ways to improve take-up of the message – such as using social media and bulletin boards.

### Clinical practice guidelines

Clinical practice guidelines describe how medicines should be used in day-to-day healthcare. The patient perspective is important in these guidelines, and patients should be involved in guideline development – by sharing their views and experiences. This is important because the benefits that patients think most important – and their acceptance of risks – may be different from what healthcare professionals think.

Just as with medicine research and development programmes, it is possible to involve patients at many points in developing guidelines. This can make sure they take into account patients' needs and that recommendations reflect patients' goals from treatment. The way in which effective patient and public involvement is put into practice will depend on the guideline developer's goals and resources.

### Low and middle-income countries

There are many barriers to patient involvement – such as lack of opportunity and training, inconvenience, time commitment and financial outlay. These barriers are even greater in low and middle-income countries. Patients in these countries also have additional problems of:

- poverty and high level of disease,
- less developed regulatory and healthcare infrastructure, and
- low health literacy (and healthcare providers' paternalistic attitude to patients).

In these countries, patient involvement can be improved by encouraging local research and development initiatives and working closely with international institutions and patient organisations. Also, involvement can be improved by raising health literacy – and by training health providers to look upon patients as partners in the delivery of healthcare.

### Patient engagement in pandemics

Like the HIV pandemic, the SARS-CoV-2 pandemic has highlighted the scope of patient engagement to improve outcomes. The ongoing pandemic has given patients the chance to become involved at all stages of medicine and vaccine development and their use in practice.

Some specific concerns have come to light, including:

- dealing with misinformation,
- quickly identifying and addressing public concern about vaccination,
- providing comprehensive information for patients to make an informed decision on vaccination, and
- making robust preparations for future pandemics.

### Conclusion

This report describes the issues around the involvement of patients throughout the life journey of medicines. It gives many examples and recommendations to improve patients' participation in matters that ultimately affect their own health. It is very important to make use of the many good practices described in this report. In this way we can continue improving engagement of patients in the development, regulation and safe use of medicines.

# Chapter 1: Introduction

We have seen the steady advance in the application of science and technology to the diagnosis, treatment, and prevention of disease. However, in recent years there has also been a related breakthrough that can further boost the success of new medical technology. That breakthrough has been the increasing recognition and recruitment of the unique expertise and perspective of people who live with a serious or long-term disease and of those who care for these people.

The glossary (Appendix 1) describes how we use certain terms in this report. However, below, we describe some that are widely used throughout the report.

### Medicine

In this report, we use medicines for products that are used to treat, prevent or diagnose medical conditions as well some used to restore, correct or modify how the body works. For the purpose of this report, these are products that fall within the scope of national and regional medicines regulatory authorities' activities. Vaccines and medicine-device combinations fall within our description of medicines. Other terms that are used interchangeably with medicines include drugs, medications, and medicinal products.

### Patients

In this report, we often apply a broad meaning to 'patients'. It can take in patient organisations, patients' families, patients' carers and patient representatives in various forums. All of these are said to make up the 'patient community'.

## 1.1 Opportunities to incorporate the patient's perspective

Regulators, medicine developers, health technology assessors, health care practitioners, payers, and others have increasingly engaged with patients, and they report gaining new insights into the burden of disease and what constitutes burden as well as value of new therapies. These lessons and their impact on decision making can occur at multiple points during the medicine's life, starting as early as drug discovery and continuing through all phases including safety management of the medicine during routine use.

The awakening of awareness of patients' role of patients has been driven by increased activism of the patient community coupled with recognition that patients often live with their disease every hour of every day, as do family members who care for them. This gives them their unique first-hand perspective and expertise on the burden of disease, including its defining symptoms and severity, and the nature and pace of disease progression. They can similarly comment on how well treatments work and on side effects and other treatment burdens.

Patients are able to identify which symptoms most impact their ability to live their lives and what would be the most valuable benefit that a new therapy might bring. They are uniquely positioned to help define what constitutes a meaningful improvement in how they feel or function as a result of therapy. These considerations are critical for regulatory assessment of the benefits and risks of a new therapy as well as for discussions on choice of treatment.

Since patients with a particular disease are the ones medicine developers target for enrolment in clinical trials of investigational therapies, they have a unique perspective on how best to make other patients aware of trial enrolment opportunities and what might be

an attractive opportunity to participate in research (*e.g.* in terms of potential benefit and risks of the investigational therapy). Patients with the disease are also uniquely well positioned to inform sponsors of the likely feasibility and acceptability of a study protocol, and the convenience of the proposed location of the study site. These factors can directly affect study sponsor costs and success in reaching enrolment targets, retaining study participants, and minimising changes to study protocols.

When an investigational medicine presents both potentially meaningful benefits and potentially serious harms, patients' direct and daily experience of living with the disease can enable them to provide uniquely qualified and credible information on the levels of risk that patients would accept in exchange for a specific expected benefit. This information, collected through well-constructed studies, can inform regulators' assessment of a new therapy's benefit and risk.

As the target population for the new medicine after approval, patients living with the disease are a primary audience for information on the safe use of a new product. This information is typically provided in product labelling for the patient. If additional measures are needed to manage risk so that benefits outweigh risks, the perspective of patients living with the disease must be considered critical to the success of risk management.

Similarly, patients should be considered critical to the design of a medicine, including formulation to enable easier use, package and container design, and any other drug delivery system features. These design considerations will be key not only to the safety of the medicine but its real-world effectiveness which, in part, depends on patients' adherence to therapy. Consultation with patients not only for the initial design and development of a medicine, but after authorisation will provide sponsors the opportunity for continued learning to inform further refinement of product designs.

Patients with a serious disease are constantly aware of the harm and inconvenience of the disease and of the risks of their treatment. Nonetheless, unexpected and unwanted effects or crises may emerge that require medical intervention and action. This may occur, for example, as an emerging side effect in a clinical trial or a new concern during the use of a marketed product. In these circumstances, patients living with the disease can provide a perspective and expertise critical for developing effective communication to manage the risk.

## 1.2 Increasing engagement and incorporating the patient's perspective

This CIOMS report regards patients living with the disease as the primary motivator, the intended recipient, and a vital partner in the development and use of new medicines. Recognising a wide array of opportunities for broadening and improving patient engagement and incorporation of the patient's perspective throughout the medicine's life, this report covers many related issues and ongoing activities.

Enhancing engagement and integration of the patient's perspective in medicine development and managing use of the medicine after authorisation opens a rich area of new ways of working and new opportunities. This report tries to reflect and bridge what is happening and what is suggested or recommended across the global medicine development ecosystem; it does not impose its own set of terms and definitions.

The approaches, constructs, and related terminology in this field are still evolving and they have not yet been internationally adopted or harmonised with standard definitions. Nonetheless, the report includes a glossary of the terms used in the report. The report employs these various terms and others currently used in the important effort of

incorporating patients' perspectives into the work on developing, regulating and using medicines intended to be so relevant to patients' lives.

During the drafting of this report, CIOMS organised various events to gather viewpoints from across the globe (see also Appendix 4, CIOMS Working Group membership and meetings):

- Open meeting – an open meeting was held in Geneva, Switzerland on 30 April 2019 to gather input from the public, patient organisation representatives, regulators, drug development experts, industry, academia, health professionals and other stakeholders concerned with the development and safe use of medicines.
- Workshop – a workshop was held in Kampala, Uganda on 27 August 2019 involving a not-for-profit civil society organisation, Community Health and Information Network (CHAIN), Uganda, and co-hosted with the National Drug Authority, involving local bioethics committee members, patient organisations, and researchers.
- Public consultation – an online public consultation was promoted and carried out in early 2022 to collect feedback from stakeholders likely to have an interest in the report.

This report largely reflects the perspectives of its contributors variously working in academia, the pharmaceutical industry, patient advocacy community and medicines regulatory agencies. It will be useful to a wide range of readers with an interest in broadening and improving integration of patients' perspectives. The contributors represent worldwide perspectives, giving insights from the European Union (EU), Japan and the United States of America (US), as well as other regions. Regrettably, it has not been possible to provide more comprehensive global viewpoints.

**Chapter 2,** Landscape, addresses the history and current landscape of patient engagement in the development and safe use of medicines.

**Chapter 3,** Guiding principles, sets the stage for planning and undertaking patient engagement activities by discussing guiding principles for patient engagement. With an intended audience that includes sponsors, these guiding principles ensure that patients' input produces meaningful value, is independent and credible, and is obtained through effective, clear and non-burdensome engagement processes.

**Chapter 4,** Advancing treatments, discusses opportunities for patient involvement throughout drug development beginning at the earliest stages identifying unmet needs and potential targets through pre-clinical and clinical development. It suggests how sponsor activities at each stage can be better informed with the patient's perspective, as well as the challenges that need to be addressed. The chapter also addresses how to engage patients in key activities throughout the medicine's life.

**Chapter 5**, Use of real-world data, considers guiding principles for patient engagement in collecting or using data sources that may be developed or used after authorisation of a medicine. These sources include medicine adverse event data, post-approval studies, registries, patient preference studies, patient surveys, focus groups, and social media. The discussion includes factors affecting patient engagement, patient consent, patient data protection, data quality, data sharing agreements, and rules of engagement.

**Chapter 6,** Product labelling, transitions the discussion to post-authorisation opportunities and considers patient involvement in patient product labelling. This chapter provides helpful background on available sources of medicine benefit-risk information for patients and efforts under way to improve the quality of patient labelling. It also provides recommendations for patient engagement in the development of patient labelling.

**Chapter 7,** Rapid safety communication, covers patient involvement in the development of urgent safety communications related to medicines. Beginning with the scope of urgent time-bound communications that are the focus of discussion, the chapter then describes ways in which patients can be engaged and involved in the development of these communications, providing examples of emerging issues in clinical trials, marketed medicines, and related to generic drug products.

**Chapter 8,** Additional risk minimisation, addresses patient involvement in drawing up measures beyond the usual ones to minimise risks – additional risk minimisation measures. After describing risk minimisation measures and regulatory aspects across the EU, Japan and US, the chapter outlines opportunities for patient involvement in the design, development, and implementation of additional risk minimisation measures as well as in evaluating their effectiveness.

**Chapter 9,** Clinical practice guidelines, deals with patient involvement in clinical care and discusses principles for patient participation in clinical practice guideline development. Drawing on international guidance on patient involvement, the chapter outlines clinical practice guidelines definitions, describes strategies for patient and public stakeholder involvement in the guideline work; it suggests opportunities for patient involvement and their recruitment. It also covers training patients, supporting their involvement, managing conflict of interest, and the value and impact of patient engagement in clinical guideline development.

**Chapter 10,** Low- and middle-income countries, discusses the opportunities and challenges for patient involvement in low- and middle-income countries (LMICs), describing the challenges that affect patients' ability to engage or be engaged. This chapter also describes ongoing initiatives in LMICs and makes recommendations for improving patient involvement.

**Chapter 11,** Pandemic considerations, concludes the report by considering the impact of the COVID-19 pandemic on patients, the voice of the patient, patient care, and healthcare systems. Although this report has been prepared in the midst of the pandemic, lessons from it are already emerging, and goals for the future can be identified.

Finally, for readers less familiar with how medicines are developed, regulated, monitored and improved, an overview of the key milestones in the product lifecycle, below, may help.

## Product lifecycle

The development of a medicine is prompted by an unmet need: the gap between what is available and what is desired for preventing, diagnosing or treating a medical condition or maintaining a desirable state of health. Figure 1a depicts an unmet need, which persists in the absence of a satisfactory solution. It affects individuals in different ways, and may evolve as the individual ages and as expectations of a satisfactory outcome change. Typically, the unmet need continues to drive improvement to existing medicines and initiatives to increase access to affordable medicines.

***Figure 1a: Stages of the product development lifecycle: the unmet needs***

Source: CIOMS Working Group XI

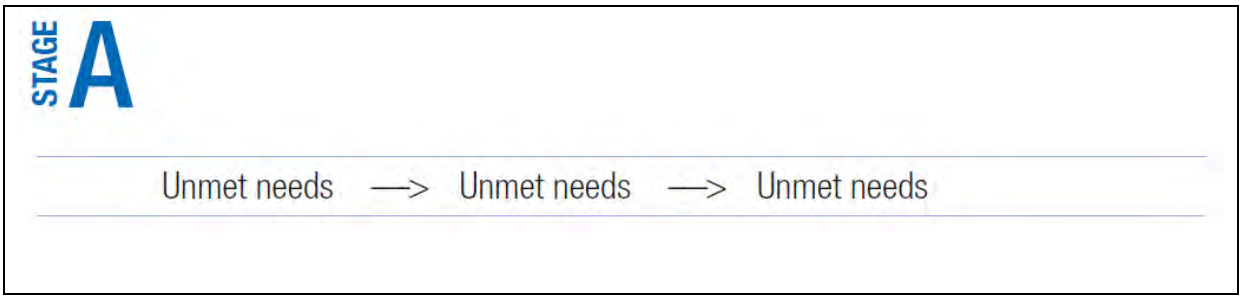



Figure 1b shows how key medicine development steps can be superimposed on the timeline. The process starts with research and the involvement of pharmaceutical companies who seek authorisation of their candidate medicine from a regulatory authority. The pre-authorisation phase includes assembling evidence from pre-clinical (laboratory) development of the medicine followed by clinical development, which involves studying the medicine in humans. Phase I, II, and III clinical trials involve the study of what the body does to the medicine and what the medicine does to the body.

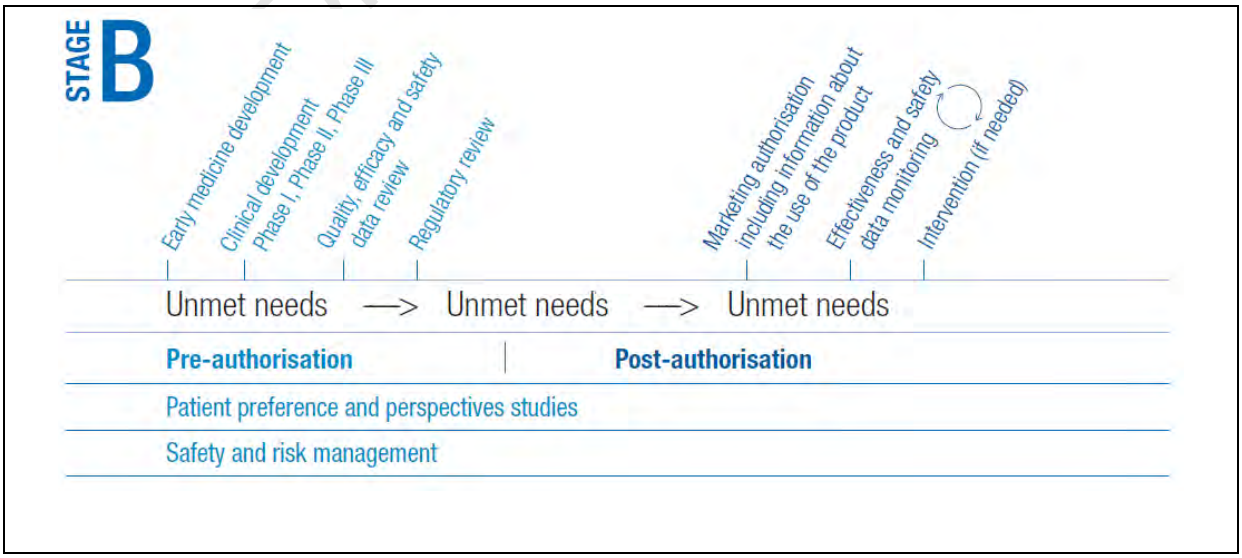
The company then passes a dossier of all the pre-clinical and clinical evidence to the regulatory authority, which comprehensively reviews the data on quality, efficacy and safety of the medicine. All going well, market authorisation is granted for the medicine, together with approval of the information (for health professionals and patients) on how to use it to best effect.

Once authorised, the medicine can be used routinely in the community and the post-authorisation phase begins. The effectiveness and safety data are monitored throughout the medicine's life, and any measures to mitigate risks are planned and implemented.

Right through the medicine's development and routine use, patients' input – including patient preference studies – can inform the medicine's development, regulation and safe use. Patients and all who help to make the patient voice heard can engage in countless ways: the topic that is at the heart of this CIOMS report.

***Figure 1b: Stages of the medical product development lifecycle***

Source: CIOMS Working Group XI



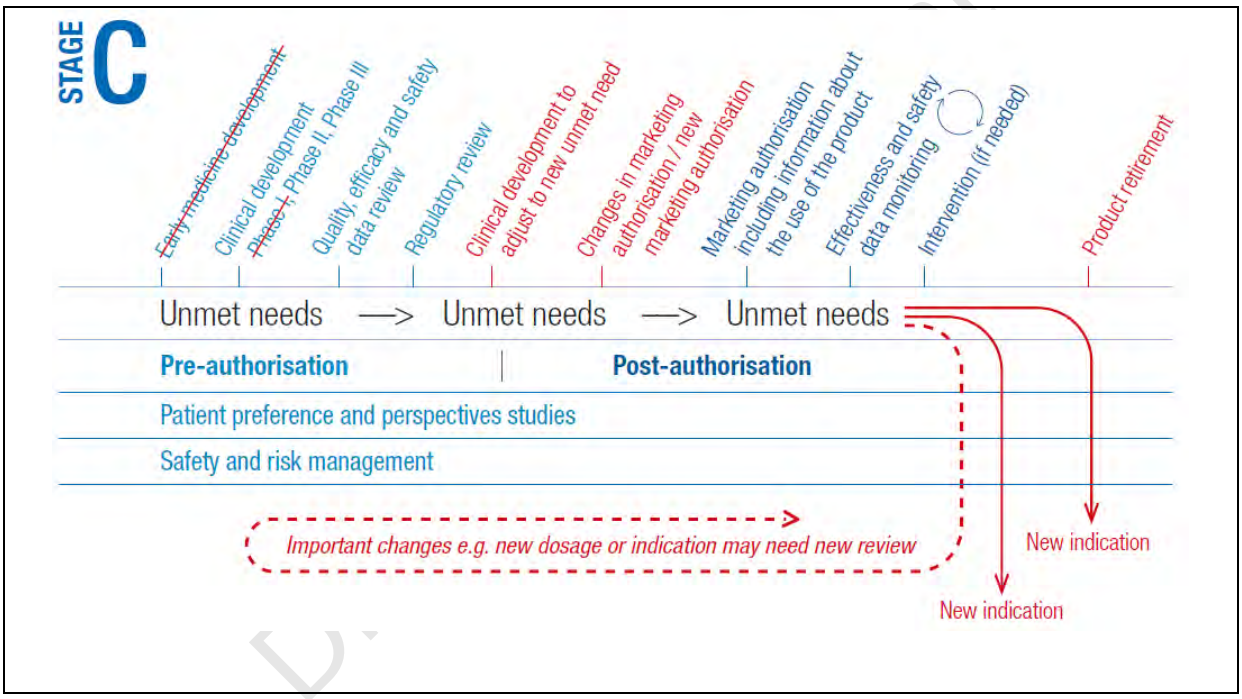
A successful medicine may have a long life. But it is also a stepping-stone for better addressing remaining unmet needs. Figure 1c shows, in red, the extra steps that the changes can involve with red strike-out (in red) of early steps that are not necessary for authorising improvements to an existing medicine.

Changes to a medicine can involve: extension of its use to cover additional conditions; development of new dosage forms which allow the medicine to be used by a wider range of people (*e.g.* very young children); and development of generic versions that make the medicine more affordable.

Making these changes to an authorised medicine is far less cumbersome – and cheaper – than developing a new one since much of the preclinical and clinical evidence from the first authorisation still applies. As ever, any change to the medicine's use, including the introduction of new dosage forms, must undergo a regulatory review and the granting of an adjusted marketing authorisation.

***Figure 1c: Stages in the potential improvement of medicines***

Source: CIOMS Working Group XI




In the ideal world, the unmet needs will eventually diminish thanks to the new and improved medicines arriving on the market.

# Chapter 2: Landscape

This chapter outlines the rise of patient-centricity, which has been defined in the following terms:[1]

> Putting the patient first in an open and sustained engagement of the patient to respectfully and compassionately achieve the best experience and outcome for that person and their family.

The chapter also covers the history and current landscape of patient engagement in the development and safe use of medicines. We review the historical context of patient engagement with regulators and medicine developers, highlighting the groundwork laid by the HIV/AIDS and rare disease patient communities and the evolution towards patient-centred outcomes. We then turn to a broader movement towards patient-focused medicine development and safe use of medicines in the 2010s.

**Key points**

1. Patient advocates, especially members of the HIV/AIDS and rare disease communities, advanced the role of patients in the development and regulation of treatments.
2. Patients, pharmaceutical companies and medicine regulators have collaborated to overcome real and perceived regulatory, cultural and communication barriers to patient engagement in medicines development.
3. Case examples of patient involvement in the development, regulation and use of medicines demonstrate considerable benefit to all parties: a win-win situation.
4. The cultural shift to greater involvement of patients needs to continue by deepening involvement of patients in areas such as identifying patient-related treatment outcomes, participating in regulatory review, contributing to constructing, reviewing and disseminating medicines information, and monitoring medicines safety by making direct contribution to reporting and assessing side effects.

## 2.1 Opportunities for patients to engage

In Europe and North America, early involvement and action was prompted by patients and patient groups representing diseases for which no treatment options were available. In particular, members of the HIV/AIDS and rare disease communities organised effectively and demonstrated a model for how patient groups can affect policy.

### 2.1.1 Patient organisations

Patient organisations, which collectively represent patients, are now recognised as a key stakeholder in health – harking back to the 1978 Alma Ata declaration that proclaimed people's 'right and duty to participate individually and collectively in the planning and implementation of their health care'.

Beyond the individual, there is a growing trend towards collective patient engagement in different aspects of healthcare. Patient organisations have an important role as they can represent their patient communities' views on specific issues.[2] Patient organisations typically have experience of navigating the medicine research and regulatory environments.

Section 5.1.4 describes how patient groups can increase their engagement in medicines research, development and use.

### 2.1.2 HIV/AIDS activism

AIDS – acquired immunodeficiency syndrome – was described in the 1980s and information began emerging on the role of human immunodeficiency virus (HIV). Untreated, HIV infection can progress to AIDS when severe damage to the immune system puts the patient at risk for life-threatening infections. Patients facing grim prognoses challenged traditional regulatory approaches and assumptions of risk tolerance.[3]

ACT UP, the AIDS Coalition to Unleash Power, led gatherings and protests across the United States, including at the Food and Drug Administration (FDA) and National Institutes of Health. Advocates argued that 'in the case of AIDS, no drug could have a graver endpoint than the untreated disease itself'.[4] They pushed FDA to establish accelerated approval procedures to help HIV/AIDS patients to access emerging treatments.[5] FDA also created the Office of AIDS and Special Health Issues to build relationships with the patient community; at least one patient representative served on their advisory committees.[5]

In Europe, advocacy efforts resulted in the formation of the European Community Advisory Board (ECAB), a working group of the European AIDS Treatment Group, a patient organisation for people living with HIV and AIDS. Established in 1997, ECAB serves as a forum for interactions with the pharmaceutical industry and regulators.[6]

### 2.1.3 Rare disease patient advocacy

In 1962, the US Congress passed the Kefauver Harris Amendment, which required pharmaceutical manufacturers to demonstrate safety and efficacy for all new medicines. Because the clinical development programmes to meet these new FDA requirements were expensive, pharmaceutical companies were less inclined to invest in research and development programmes for rare diseases.

In the 1970s, rare disease patients and their families started an informal coalition which was instrumental in the passage of the US Orphan Drug Act of 1983. The Act established a regulatory framework for the development of medicines for rare diseases. By formally defining rare diseases and their prospective treatments – called 'orphan drugs' – it attracted unique financial incentives including grants or public contracts.[7]

The European Commission introduced similar regulations in 1996, creating a favourable financial and scientific environment to develop medicines for rare diseases. To support passage of the new regulation, the French Ministry of Health gathered patient perspectives from large patient organisations, including the AFM-Téléthon (neuromuscular diseases), National Cancer League, Aides (as AIDS-related opportunistic diseases are rare disorders), and Vaincre La Mucoviscidose (a cystic fibrosis organisation).

## 2.2 Patient-centricity in medicine development

In the 2000s a movement began which promoted patient-centricity in the development, evaluation, and reimbursement of medicines. This section highlights some key issues.

### 2.2.1 Patient-centred outcomes

In 2009, the FDA published Patient-Reported Outcome (PRO) Measures: Use in Medical Product Development to Support Labeling Claims. It stated:[8]

> … an instrument will not be a credible measure without evidence of its usefulness from the target population of patients. Sponsors should provide documented evidence of patient input during instrument development.

This was an important cultural shift among regulators and others in the medicine development community. PRO measures that did not consider patient input in their development were considered insufficient. While the FDA guidance was limited to PROs, it was interpreted to apply to all clinical outcome assessment measures.

### 2.2.2 Patient-focused medicine development

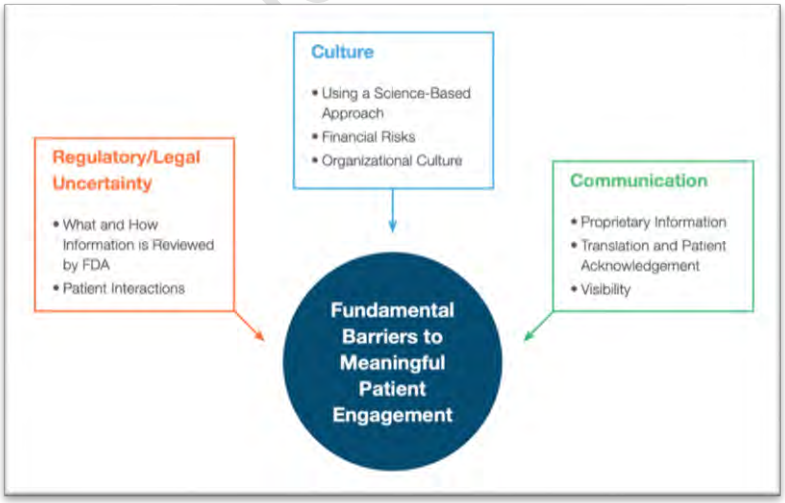
Subsequently, as part of the Prescription Drug User Fee Act (PDUFA) V reauthorization (2013–2017), the FDA committed to hosting 20 meetings with patients about specific diseases.[9,10] The purpose of the patient-focused drug development (PFDD) meetings was to 'more systematically obtain the patient perspective on specific diseases and their treatments'.[11] As of 2021, FDA hosted more than 25 disease-specific meetings and established a process for 'externally-led' meetings.[11] Importantly, PFDD meetings and the corresponding 'voice of the patient' reports helped demonstrate that patients are experts on living with their disease and can contribute valuable information to medicine development.[10]

### 2.2.3 Barriers to meaningful engagement

By 2015, many stakeholders were considering how to increase the scope of PFDD and enhance patient engagement.[12] Despite substantial interest among stakeholders to better leverage patient expertise to enhance medicine development, there were a variety of perceived barriers to engaging patients. Barriers cited included regulatory/legal uncertainty, culture, and communication (Figure 2).[13]

***Figure 2: Barriers to meaningful engagement in medicine development identified at National Health Council/Genetic Alliance Dialogue (2015)***

Source: [13] (Figure reproduced with permission)



### 2.2.4 Overcoming regulatory and legal uncertainty

Despite success of the PFDD programme, stakeholders were uncertain regarding how regulators would evaluate insights from patient engagement activities during regulatory review. It was not clear if patient engagement data would ultimately impact approval decisions.[12–14] Furthermore, there was concern that without formal guidance from regulators encouraging patient engagement, even meaningful engagement could be perceived as pre-approval promotion.[15]

To overcome this, in the US, the 21st Century Cures Act and PDUFA VI committed FDA to develop a four-part PFDD guidance, *Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making*.[16] The first part was released in June 2020. In addition to providing stakeholders with information on patient engagement methods and applications, the guidance series is a formal signal that FDA encourages early patient engagement, and when done appropriately, is not considered pre-approval marketing.

In parallel, in June 2021, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) released a reflection paper on 'key areas where incorporation of the patient's perspective could improve the quality, relevance, safety and efficiency of drug development and inform regulatory decision making'.[17]

In Europe, patient engagement was further bolstered by the requirement that all clinical trials conducted in the European Union must include patient engagement: the 'protocol shall at least include... where patients were involved in the design of the clinical trial, a description of their involvement'. Passed in 2014, this requirement is effective as of December 2021.[18]

In Japan, patient engagement in medicine development is supported by the government, a related regulatory agency, and a funding agency. The Ministry of Health, Labour and Welfare (MHLW) has held a study group since 2010 on unapproved and off-label medicines of high medical need.[19] This group documents medical needs and encourages pharmaceutical companies to develop medicines approved in Europe and the United States, but not yet in Japan. Patient advocacy groups can submit requests for medicine development to this study group via the MHLW.

The Japanese related regulatory agency, the Pharmaceuticals and Medical Devices Agency (PMDA), launched the Patient Centricity Working Group in May 2019.[20] The group facilitates outreach to patients and released the guidance on patient participation for the relationship between patients and the PMDA in 2021.[21] The funding agency, the Japan Agency for Medical Research and Development (AMED), has been conducting activities related to patient and public involvement (PPI) in research since 2017. The *Patient and Public Involvement Guidebook*, published in April 2019, covers PPI in medical research and clinical trials mainly for researchers.[22,23]

In addition to formal rules and regulations, patient groups, regulators, and industry trade organisations have collaborated to establish codes of practice for appropriate interactions.[24–28] There has also been collaboration to develop tools, principles, and forums to support patient involvement which are described in other chapters.

### 2.2.5 Promoting culture shift

Cultural barriers to advancing PFDD included the perception that information from patients is 'anecdotal, emotional, and in many cases subjective as compared to clinical outcomes data obtained in clinical trials'.[13,29] Scepticism about the benefits and return on investment of patient involvement is also a significant hurdle. Part 1 of FDA's PFDD guidance,[16] describing methods for collecting comprehensive and representation views, help overcoming this barrier.

Capacity building initiatives were established to help researchers and patients collaborate effectively. For example, the European Patients' Academy (EUPATI) developed patient education to train formal 'patient experts'.[30] EURORDIS, an alliance of European patient organisations, established an Open Academy that 'empowers patient advocates to have the confidence and knowledge needed to bring their expertise to discussions on health care, research, and medicines development'.[31] An international collaboration called Patient-Focused Medicines Development (PFMD) developed a Patient Engagement Management Suite, which includes training for professionals in the pharmaceutical or medical technology industries.[32] Through a capacity-building funding mechanism, the Patient-Centered Outcomes Research Institute (PCORI) has supported development of extensive patient-friendly training and tools.[33–35]

There has been a strong push to change the terminology in clinical research. For example, replacing 'subject' with 'participant', to acknowledge the patients' central role in clinical trials.[36] It is also important to note the role of health technology assessment (HTA) bodies in advancing the culture shift toward PFDD. Several HTA bodies, including the Scottish Medicine Consortium, developed pathways for patient involvement in the early 2000s.[37]

### 2.2.6 Open communication and information sharing

An early barrier to PFDD was the dearth of information on guiding practices or case examples. Given medicine development is highly competitive, stakeholders were reticent to share methods, lessons learned, or successes related to patient engagement that could guide best practice or demonstrate return on investment to encourage uptake.[13,14] However, more recently, several public-private initiatives have raised awareness and provided forums to share examples and to collaborate on developing best practice. Many of these initiatives are described in Chapter 6. Publicly available case examples of how patient engagement contributes to clinical development have also led stakeholders to recognise the value of patient engagement (see Table 1 and the case studies in Appendix 2).

***Table 1: Real-world patient-focused medicine development: examples from the National Health Council's Case Example Repository***

Source: [38]

| | | |
|---|---|---|
| **Patient trade-offs between effectiveness and safety'** | In partnership with FDA, RTI Health Solutions conducted a preference study to evaluate the trade-offs patients make between effectiveness, safety, and other attributes of weight-loss devices. This allowed researchers to estimate the maximum mortality risk patients were willing to accept for a certain amount of weight loss, and the minimum amount of weight loss sufficient for patients to take on the risks of a weight-loss device. | **Key point**: FDA stated that this was the first time a patient-preference study impacted a new device approval. |
| **Patient views on convenience of medication use'** | Rituxan Hycela, a medicine for treating lymphomas, contains the active substance rituximab together with hyaluronidase, which helps with the absorption of rituximab. FDA approved Rituxan Hycela on the basis of clinical studies that found that giving it subcutaneously (under the skin) resulted in rituximab levels in the blood comparable to those from giving rituximab intravenously, and it was no less effective. Importantly, one of the clinical studies found that the majority (77%) of patients preferred Rituxan Hycela over intravenous rituximab, with the most common reason being that Rituxan Hycela required them to spend less time in the clinic. These findings are reflected in section 14.4 'Patient Experience' of the product label. | **Key point**: This appears to be the first example where a US product label includes a 'Patient Experience' section. |
| **Patient input into formulation and packaging** | When considering various formulations for a new skin medicine, the pharmaceutical company Dermira ran a focus group of patients for whom the medicine was designed. Dermira had expected patients to favour the most sophisticated formulation. However, patients preferred a traditional formulation – stating they could feel the cream being absorbed into their skin.<br>Patients preferred a plastic tube over a traditional metal tube. Patients want to squeeze all the cream out of the tube, but when the metal tube is folded over, it can become sharp and cause cuts on hands.[39] | **Key point:** Patient input was useful in determining a medicine's formulation and user-friendly packaging. |

### 2.2.7 Patient engagement in advancing medicine safety

While patient-focused medicine development is an emerging activity, patients have been involved in safety-related activities for several decades (see also Chapter 8).

European Union (EU) regulations that came into force in 1999 mandate patient leaflets in medicine packaging. The leaflets conform to a template and must be approved by regulatory authorities.[40] In 2005, further regulation required 'consultation with target patient groups', largely through 'user testing' the leaflets.[41] This major step in patient engagement in the EU meant that at least 20 lay people tested the leaflets to ensure they were fit for purpose. Some regard this as a landmark change because it altered the perceived importance and value of information given to patients in the package leaflet.

The EU pharmacovigilance directive and regulation which came into force in 2012 further highlighted the importance of the patient's voice in pharmacovigilance.[42,43] As a result, the Pharmacovigilance Risk Assessment Committee (PRAC) – EMA's safety committee – was established to monitor and assess data on medicines safety before and after authorisation.

The PRAC includes a patient representative member. The patient representative plays an 'invaluable role in ensuring that regulators remember for whom they are working, and in contributing to decisions about the wording and timing of risk communications which play

a fundamental role in ensuring medicines safety'. A 2013 EMA report also notes that involving patients in this capacity results in clearer communications about the benefits and risks of medicines to patients organisations and wider civil society.[6] Box 1 gives an example of the PRAC engaging stakeholders, including patients, in their work.

The PRAC has four main patient engagement mechanisms to support their assessments:

1. written consultations;
2. dedicated meetings (non-public);
3. patient representatives at Scientific Advisory Group meetings; and
4. public hearings.

As part of an ongoing effort to systematise and improve the impact of the PRAC's pharmacovigilance activities, efforts are underway to adapt the International Risk Governance Council (IRGC) framework to guide regulators in selecting patient engagement mechanisms for specific risk assessment procedures.[44,45]

***Box 1: Pharmacovigilance Risk Assessment Committee vignette***

Source: [46]

PRAC held its first public hearing in 2017 to review the risk minimisation measures for valproate medicines when used during pregnancy. It heard 32 testimonies, 15 from people representing valproate patients and their relatives. Five key themes emerged regarding the valproate risk minimisation programme:

1. low level of awareness and uptake of the risk minimisation measures by healthcare professionals
2. limited dissemination of risk information to patients
3. insufficient attention to programme implementation
4. lack of stakeholder input on the design and implementation of risk minimisation materials
5. absence of a robust feedback process regarding program implementation.

Subsequent EMA policy changes substantially reflected those proposed by participants at the hearing (extra restrictions on valproate use in pregnancy and a warning symbol and patient alert card affixed to the external packaging). Additionally, participants called for improved programme implementation and coordination within and among countries, and for improved targeting and distribution of risk minimisation materials. The hearing was generally regarded successful in gaining extensive feedback from an array of stakeholders, including patients, regarding their experiences with the valproate risk minimisation programme.

The 2012 EU pharmacovigilance legislation also mandated all member countries to accept patient reports of adverse events to their spontaneous reporting systems, a major step in acknowledging patients' perspective on adverse drug reactions (see also Reporting adverse events in section 5.2.1).

Globally, as with information on the use of medicines (section 4.8.5 and Chapter 6), patients are also involved in developing safety communications (see Box 2, section 7.7 and Appendix 2 C).

***Box 2: Patient involvement in developing and distributing safety communications: vignettes***

*Developing safety communications*

Health Canada partnered with representatives of patient groups to develop 'i-messages' (tweets, posters) as part of the educational programme around potential side effects of a medicine in high dosage

*Distributing alerts*

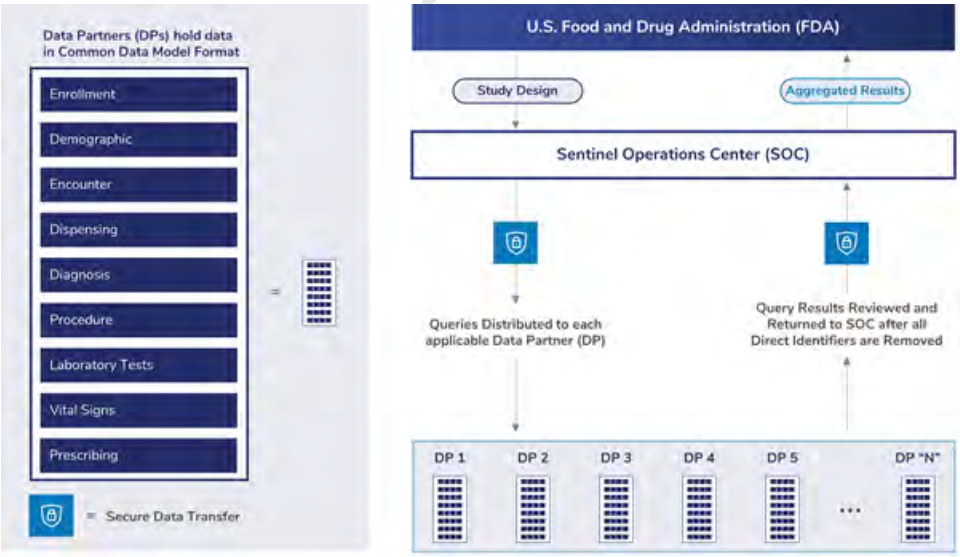
Health Canada has also involved patients in disseminating alerts, for example, when it is important to reach patients, mothers, caregivers, etc about a medicine recall. Health Canada's Communication and Public Affairs Branch posted the message on Facebook to help disseminate the information widely. The alert was also distributed to patient groups and groups with a large patient base for them to disseminate it among their membership. The main benefit of integrating patients into the dissemination is to reach a wider group of patients (including potentially impacted patients) more effectively and quickly than the regulator on its own can.

*Expanding access to safety monitoring technology*

The US FDA's national electronic system to monitor the safety of medical products, Sentinel, has established a Community Building and Outreach Center to further increase awareness of Sentinel. The Sentinel Building and Outreach Center is creating a webinar series geared towards patient advocates and informaticists with a range of skills levels. To further increase awareness of Sentinel, the Coordinating Center is also distributing a quarterly newsletter highlighting upcoming events (such as workshops), recent publications, and updates to the Sentinel System. The Community Building and Outreach Center also creates graphics (see below) to help explain the role of Sentinel. [47]

*A Combined Collection of Datasets: the Sentinel Distributed Database*

Source: [47]




## 2.3 Continuing culture shift

Countries across the world are at varying stages of adopting patient involvement in the development of medicines. In many countries, regulators have signalled an interest in patient involvement in medicine development, but formal processes are evolving only gradually. Where patient involvement has taken hold in the development and regulation of medicines, there continues to be a cultural shift. Patient involvement has by and large

occurred in a collaborative environment where the broader healthcare community and civil society develop solutions to barriers or challenges.[48]

The following chapters introduce new challenges and propose solutions for meaningfully engaging patients in medicines development and safety.

## Chapter 2 – References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# Chapter 3: Guiding principles

In this chapter, we describe the guiding principles for patient engagement. These apply to medicine developers, regulators and academics who plan patient engagement activities.

**Key points**

1. The patient voice offers a valuable perspective throughout the development of a medicine. It should be fully integrated into decision-making.
2. Patients have expert knowledge and understanding of their diseases and conditions. This means they have equal credibility as those who are scientific and medical experts.
3. Reimbursement of expenses and compensation for patients' time and contribution should be considered."
4. Consider training of all stakeholders during the planning for patient engagement activities.
5. Patients' independence must be maintained.
6. Transparency and open communication are key. Written agreements should be clear and easy to complete.

The guiding principles for patient engagement in this chapter apply primarily to those who plan and participate in patient-engagement activities. They include medicine developers, regulators, health technology assessment (HTA) bodies, payors, academics as well as patient representatives and patient organisations.

## Methods for drawing up guiding principles on patient engagement

The guiding principles set out in this chapter were derived from an analysis of key documents provided by CIOMS XI working group members supplemented by an online search. Eligible documents had a focus on meaningful patient engagement in the development and safe use of medicines, were from internationally recognised institutions or initiatives, and were in English. The institutions and initiatives span a variety of different perspectives and their documents are intended for a varied audience, encompassing regulators, medicine developers and patients.

All selected documents were analysed for underlying concepts and other key statements to serve as a basis for this set of guiding principles for patient engagement. The search and analysis followed a 'snowballing-approach' that was continued until new documents did not reveal new concepts to include.

No conflicting statements or values were identified, indicating consistency in the guiding principles on patient engagement for different stakeholders and for different parts of the world. Results were grouped into clusters of related concepts and subsequently turned into overarching principles. Annex 1 to this chapter includes an overview of principles and associated sources.

## Terminology

The initial guiding principles recommended in this chapter refer to patients and the patient perspective in different ways. The terms *patient voice* or *patient* refer to the patient perspective in general, irrespective of the individual's specific role or profile. Subsequent principles deal with patients or their representatives in specific roles or functions as partners during the medicine development process. Details on background and profiles are provided when relevant. 'Patient representatives' includes patient organisations, and formal or informal caregivers, or relatives. The Glossary describes how 'patient' is used in this publication.

## 3.1 The patient voice is vital

**Guiding principle.** The patient voice offers relevant and valuable perspective throughout the medicine lifecycle (see Chapter 1) and it should be fully incorporated into decision making to extract meaningful value.

### 3.1.1 Clarifying goals that are important to patients

Patient engagement activities should include goals and outcomes that are important to patients as well as to those who engage them. Patients' goals or priorities may be different from those of medicine developers, regulators, and other stakeholders. Only patients or those who represent them can validate patient-centred or patient-prioritised outcomes.[1,2]

Goals should be determined by considering how each patient engagement activity will ultimately improve patient health or outcomes and benefit the patient population as a whole.[3,4]

### 3.1.2 Inclusive patient engagement

In addition to patients themselves, patient representatives or patient organisations are relevant intermediaries for incorporating the patient voice throughout the medicine lifecycle.[5,6] Umbrella patient organisations, like EURODIS, have based the code of practice for their members on this basic objective of nominating representatives that have thorough and genuine understanding of the patient voice.[7] Various sources have published criteria for selecting representative patient organisations in a transparent way; such sources include European Medicines Authority (EMA) framework, European Patients' Academy on Therapeutic Innovation (EUPATI) guidance and National Health Council (NHC) standards of excellence.

Inclusiveness and diversity of those to be involved in patient engagement activity are important to consider. Inclusiveness relates to how the patients involved (or those representing the patient voice) fit the needs of the activity while representing those intended to benefit from the output of the activity: the larger patient population.

In determining inclusiveness, diversity of patient sub-populations, stages of diseases, demographics, and other relevant criteria should be evaluated [1,2]. Those wishing to either involve patients or speak on behalf of a patient group, should take every care not to exclude specific subgroups of patients (*e.g.* by the methods or communication channels they choose).

Patients who are not members of patient organisations need to be involved so that as many patient views as possible are included. Community representatives and people who work with underserved patient groups can bring a wider range of patient perspectives into treatment development.

The 2016 *International ethical guidelines for health-related research involving humans*[8] points out that for research to benefit all patients equitably, it should not focus disproportionately on patients who are most convenient to include in medicine development. Diverse groups of patients should be included in research to represent the universe of patients with the disease, or the stages and aspects of the disease appropriate to the treatment. For example, clinical trials should include people of appropriate genetic profile, stage of disease, ethnicity, or age for which the new treatment is intended and should strive to include people of all economic circumstances, and in rural as well as urban settings.

Mermet-Bouvier and Whalen's review[9] mapped significant regulatory and ethical interpretations and their implications on how vulnerability affects the stakeholder ecosystem and its evolution as part of the overall protection for patients.

Before choosing patients for engagement, each patient-engagement activity should be thoroughly analysed for:

- specific type of input required, such as representative overview of patients' needs or expectations, in-depth advice on study protocol, patient story
- the role of patients in the activity such as co-creator, consultant, adviser
- the desired profile of the patient, including experience, expertise, language skills.[6,10]

**Example.** When designing communication strategies to promote safe use of medicine, 'real' patients should be involved for user testing to ensure meaningful outcome. See section 4.6 and section 6.6 for details on how patients can be involved.

Patients should be involved early (*e.g.* early in agenda setting and planning) to ensure that goals important to patients are incorporated and they can provide input on critical design components. Including patients early and having an open discussion can help define the scope of an activity, align the goals with patients' expectations, and determine what needs to be accomplished to achieve those goals and for the activity to produce meaningful value.[2,11]

Certain groups ('special patient populations') and patients considered potentially vulnerable have historically been excluded from many clinical trials and hence from directly participating in patient-engagement activities. Examples of these groups include children, the elderly (including the very elderly),[12] people with severe mental impairment,[13] and people in prisons.[14] Engaging these patients may be critical and highly valuable, as they are the ones living with the disease or condition. Their perspective and experience is unique and may differ from that of close relatives or carers.

The inclusion of children is particularly important as they are often capable of contributing to decisions made by their parents or legal caretakers on participation in clinical trials; as such, an informed assent can be applied. Informed assent means that the child is meaningfully engaged in the research discussion at a level that matches the child's capacities. Clinical trials and clinical studies involving children can gain insight from children who have previously participated in such studies; their perspectives or preferences may help improve study design.

Increasingly, new methodologies are emerging to successfully involve special patient populations. Consideration should be given to whether additional planning and fit-for-purpose settings are needed, preferably consulting or working with patient organisations which have expertise in the relevant patient population.[1,15]

## 3.2 Patients' expert knowledge and credibility

**Guiding principle.** Patients possess expert knowledge and understanding of their experiences, diseases and conditions, and have equal credibility as scientific and medical experts.

Patients should be considered experts in living with their condition, the benefits and side effects of treatments, as well as the impact of the condition and treatment on daily life. As such they have a moral right to contribute to the development of the treatments intended for them. Moreover, patients can contribute unique knowledge not only on the medical

aspects, but also related aspects such as work, school, and personal relationships, that may affect the outcome of treatment and quality of life. [1,2,6,15–18]

Patient representatives and patient organisations understand the worries, expectations and needs of their communities, and access to the broader patient perspective that informs this understanding. This expert knowledge should be given equal weight to that of others.[4,10,19]

**Example.** Huber *et al*. (2016) conducted a study to understand how different stakeholders, including patients, view and define 'health'. It found that patients often broaden the definition of health to more than just 'absence of disease'. This was in contrast to others, such as physicians, who viewed health significantly more narrowly, focussing on daily functioning and quality of life. The investigators therefore proposed the term 'positive health' with six dimensions that encompass the patient's perception of wellbeing. The six dimensions include physical functions, mental functions and perception, spiritual/existential dimensions, social and societal participation, and daily functioning. This illustrates how engaging with patients enables inclusion of their unique knowledge and expertise.[20]

## 3.3 Reimbursement of expenses and compensation for patients' time and contribution

**Guiding principle.** Reimbursement of expenses and compensation for patients' time and contribution are vital for meaningful engagement.

### 3.3.1 Reimbursing expenses for participation

Medicine developers, regulators and other stakeholders should reimburse patients for out-of-pocket expenses such as for travel, accommodations, conference fees, and meals. Additional expenses to consider include the cost of home or childcare to allow an individual to participate in an activity.[15,21]

The effect of a disease or condition on a patient and the ability to travel or participate should also be considered for reimbursement. For example, if a caregiver needs to accompany the patient and provide support for the patient to participate in the activity more effectively, then the caregiver's out-of-pocket expenses should also be considered for reimbursement.

Other expenses that should be evaluated for reimbursement are for patient representatives' or organisations' activities that assist in the understanding of the patient perspective and support contribution to a patient engagement activity. This can include expenses associated with conducting a survey, setting up and maintaining an online panel of patients, or conducting a patient focus group.

### 3.3.2 Compensation for patient's time and expertise

Compensation or payment to patients, in addition to reimbursement of expenses, should be considered during the design of a patient-engagement activity and evaluated in the context of local laws and regulations. Compensation should take account of the time patients invest in an activity and their expertise.

Compensation should be discussed with patients to understand their expectations and concerns on this topic (*e.g.* whether maintaining independence, potential impact on

healthcare benefits). Patients have the right to refuse compensation or have it paid to their patient organisation.[19,21]

At the very least, the following should be considered to determine an appropriate amount of compensation:

- Total time invested by patients and, if applicable, the time invested by their organisation for facilitation or support. The time directly participating and time spent preparing for an activity should be included.[21]
- What amount is reasonable and when appropriate it should be aligned with fair market value for the activity or contribution of work.[22] Fair market value for a patient or member of a patient organisation, should be determined in a similar way to determining compensation for key scientific leaders or consultants. It should take into account the individual's expertise and training, amount of time, complexity of work, and country of origin among other factors.[21]

Compensation for patient-engagement activities should take account of ethical considerations that apply to compensation for patient participation in clinical studies. This includes preserving voluntary participation (patients not being motivated to participate by the compensation), treating patients fairly (avoiding exploitation), avoiding deception by patients (*e.g.* about their eligibility to participate), and preserving public trust.[23]

To help determine fair market value, the National Health Council in the US developed a Patient Engagement Fair-Market Value Calculator for stakeholders that engage patients to use and customise for their own needs. The calculator has been developed for the US initially, with the intent of adding other countries in the future.[24,25]

Compensation can take other forms in addition to financial and include:

- public recognition of contribution (*e.g.* newsletter, awards);
- attendance at conferences;
- educational opportunities;
- speaking opportunities; and
- opportunity for co-authorship of publications and posters.

## 3.4 Training of stakeholders for patient engagement activities

**Guiding principle.** Training of all stakeholders should be considered during the planning for patient engagement activities.

### 3.4.1 Training and education of those who engage patients

Effectively engaging with patients requires specific knowledge, skills and experience. It should not be assumed that an organisation is ready to engage patients without first assessing current capabilities honestly. Organisational training and education are key for building these capabilities.

In addition to relevant regulatory, legal, and healthcare compliance requirements, and specific patient engagement approaches and methods (*e.g.* patient advisory boards), other topics for organisational training and education include: [10,15]

- Case studies and testimonials of the importance and value of patient involvement beyond trial participation in the medicine development lifecycle;
- Evaluation tools and metrics to assess the effectiveness and impact of patient engagement

- Understanding the nature of patient representatives, their organisations and how they operate;
- Dispelling preconceived notions about patient representatives and organisations (their abilities, their knowledge of medicine development, and their motives or intentions);
- Where to find patient representatives or organisations and how to determine who to work with;
- Listening skills to discern meaning from spoken and unspoken communications from a person or group of people;
- Communication skills to convey medical and technical concepts and transferring knowledge effectively to partners who do not have technical or scientific backgrounds;
- Cultural sensitivity to understand differences across cultures and subtle differences among social groups, patients, and those underrepresented or discriminated against;
- Interpreting, integrating, handling and protecting data generated from patient engagement into medicine development and regulatory activities.

Training for academia and biopharma industry professionals has been developed by the European Patients' Academy on Therapeutic Innovation (EUPATI) with a 1-day in-person training, and patient-focused medicines development (PFMD) with online trainings.[26,27]

In addition to assessing capabilities, an assessment of organisational readiness for patient engagement should include an evaluation of available resources and access to facilities to meet patients' needs for in-person engagement.

Resources on capabilities for patient engagement that may be helpful for medicine developers, regulators and others include:

- DIA Considerations Guide for Implementing Patient-Centric Initiatives in Health Care Product Development – link
- IMI-PARADIGM Deliverable 4.1, Recommendations on the required capabilities for patient engagement – link
- National Health Council Patient-Focused Medical Product Development Webinar Series & Case Examples – link
- National Health Council Rubric to Capture the Patient Voice: A Guide to Incorporating the Patient Voice into the Health Ecosystem – link
- PFMD Book of Good Practices – link
- PFMD Quality Guidance – link

### 3.4.2 Training and education of patients for patient engagement activity

Training and education are essential for building patients' capacity and capability to engage in decisions during the medicine lifecycle; they should be considered integral to any patient-engagement activity.[1,28]

Patients' knowledge of the medicine development and regulatory process can vary widely. To be effective partners and to add meaningful value, patients may need to be knowledgeable of these areas. Training and education can help fill these knowledge gaps and enhance patients' ability to collaborate effectively.[10]

Knowing the critical points for patient input, and how to influence them, is also crucial. This includes practical training on communication and negotiation skills preferably using real-world case studies. Information on resources (*e.g.* databases) that contain data on the patient perspective can be valuable for patients to support their role as representative of a larger community.

Examples of effective patient training include EUPATI's Expert Training Course, and the EURORDIS Open Academy, with its winter, summer, digital, and leadership schools.[29,30] The EURORDIS summer school on medicines research and development addresses scientific and regulatory topics tailored to the needs of the rare disease community and includes a specific module on benefit-risk assessment and pharmacovigilance, as well as the regulatory framework.[31]

The European Patients' Forum provides cross-cutting, non-disease specific capacity-building activities.[32] It has a dedicated youth programme, summer school for young patient advocates, and has published several resources including 'Transparency Guideline', a guide to Empowering leadership, a fundraising toolkit, and resources to support national coalition development, entitled 'Building National Coalitions of Patient Organisations'. The latter in particular highlights the benefits of joining forces at national level, learning from the expertise of others, transcending institutional boundaries, and fulfilling one's mission more quickly and in a sustainable way by collaboration and optimal use of resources.[33]

EMA has also developed training for patients and consumers working with the agency.[34]

The National Health Council has developed a Center of Educational Excellence for the US context, including patient community training on Health Technology/Value Assessment and Real-World Evidence.

## 3.5 The independence of patients

**Guiding principle.** Patients' independence must be maintained.

### 3.5.1 Patients' independence in patient engagement activities

The independence of patients is of particular relevance when patients partner or engage with medicine developers who may also be providing funding to patient organisations.[4,7,22]

Efforts should be made to enable and encourage patients to interact and work with different stakeholders, including multiple medicine developers, and not with only one or a few. Similarly, stakeholders who engage patients should aim to work with a variety of patient organisations and representatives, taking into account the operational needs of a given project.

When a patient organisation directly funds drug development, this may compromise the organisation's ability to remain independent for patient engagement activities throughout the development and regulatory process.

In addition to following legal requirements, medicine developers must ensure that they are not perceived to be inappropriately influencing patients or that patients are not perceived to be directly supporting commercial interests.

### 3.5.2 Patient engagement must not result in promotion or endorsement of a medicine

Patient-engagement activities must focus on the medicine lifecycle and its objectives must not be promotional or commercially driven. Medicine developers must dissociate patient engagement from product promotion, and patients must ensure that none of their activities could possibly be associated with medicine promotion.[4,7,22]

Patient-engagement activities must follow the laws and regulations on medicine promotion; additionally, activities or actions that should be avoided include:

- medicine developers using patient engagement activities to promote a medicine to patients or requesting patients to promote a medicine (whether in development or marketed);
- patients sharing unbalanced, non-validated, or partial information about a medicine;
- medicine developers using quotes from patients in external communications that favour or deprecate a medicine; and
- patients appearing or testifying in promotional materials for a medicine.

### 3.5.3 Funding of patient organisations

Medicine developers should not dictate that a patient organisation receives funding from one company or other single entity (for either core activities or specific projects).[4,22]

Patient organisations should make every effort to diversify their funding sources. However, there may be situations where a patient organisation receives funds from only one medicine developer; this can happen when only a limited number of companies are conducting research and development *e.g.* for rare diseases. Transparency and diversifying funding will prevent conflicts of interest and help to maintain patient organisations' independence.[7]

If a company provides funds for the core activities of a patient organisation, it should not dictate how those funds are used. Similarly, if funds are provided for a patient organisation project or event, those funds should be accepted without conditions imposed on the project approach, or event agenda and content.[7] Importantly, patient organisations should transparently report their sources of funding.

By way of an example, the National Health Council Standard of Excellence 21 states:

> The organization maintains financial records and prepares financial statements in accordance with generally accepted accounting principles (GAAP), as certified by a qualified independent certified public accountant. The audited financial statements are reviewed by the Board and made available to the public online within six to 12 months after the close of the fiscal year.

### 3.5.4 Optimising patient organisation input

To be eligible partners, patient organisations may need to meet certain standards to ensure that their input is representative, meaningful, up-to-date and well-substantiated and is not driven by a single issue. In addition to enabling eligibility, meeting these standards may also result in patient organisations being more valuable partners through enhancing credibility and being more effectively able to represent their constituents.

Examples of specific criteria include those of EMA for involvement in the agency's activities, and those of patient umbrella organisations for membership such as the International Alliance of Patients Organizations, European Patients Forum, EURORDIS, and the National Health Council.[35–39]

## 3.6 Transparency, open communication and agreements

**Guiding principle.** Transparency and open communication are key. Agreements should be non-burdensome and clear.

### 3.6.1 Open and honest communication

Effective communication supports trust, integrity, honesty, and openness between stakeholders and helps to form productive partnership for patient engagement.[2,7] The

objectives and scope of any patient engagement activity should be transparent to all stakeholders, agreed upon, and documented.[1]

The mechanisms for communication between stakeholders need to be considered and agreed upon. This includes communication to manage the relationships or partnership, managing an activity or project directly, effective management of issues or problems as they arise, communicating important dates and events, and communicating updates or changes to an activity or programme.[10]

After a project is complete, it is good practice to communicate the project's outcomes to all stakeholders, including the value of their contribution and how it was used.[1,40]

All stakeholders (medicine developers, regulators, patient organisations) may consider appointing one or more dedicated contact persons for patient engagement activities – for general inquiries as well as for specific activities or projects.[1,10]

### 3.6.2 Disclosure of conflicts of interest

Any past or existing relationships, financial or non-financial interests, or other interactions that can influence participants' perspectives, decisions, or outcomes need to be disclosed.[7,21]

**Example.** A regulator may invite patients for their perspective on the benefits and risks of a medicine under review for approval. If those patients have participated in a study or patient engagement activity for that medicine or have any relationship with the medicine developer, that should be disclosed as a potential conflict of interest.[41]

### 3.6.3 Contracts and agreements need to be brief and clear

The working relationship between medicine developers, regulators, and other stakeholders with patients need to be formalised through a written agreement or contract. These typically cover aspects such as roles, responsibilities, confidentiality, intellectual property, data protection, expenses and compensation. Agreements are intended to legally protect all parties involved and can prevent misunderstandings. What must be included in contracts will vary with the scope of the relationship, as well as by the country's laws and regulations.[10,21]

A particular concern is that the contracts between medicine developers and patient groups are often overly long, difficult to understand, and contain ambiguous clauses. Patient groups often struggle with contracts since the majority do not have lawyers to assist them, and their capacity to review contracts and negotiate changes is limited. Therefore, medicine developers, regulators, and academia should make every effort to keep contracts short and easy to understand. To assist in this area, the Workgroup of European Cancer Patient Advocacy Networks (WECAN), comprising patient advocates and industry experts, was established to develop guidance to simplify contracts and make them more reasonable. The workgroup is being coordinated by Myeloma Patients Europe (MPE) in collaboration with Patient Focused Medicines Development (PFMD).[21] Resources and information can be found on the initiative website: https://www.mpeurope.org/legal_agreements/

A US adaptation of the agreements was led by the National Health Council: https://nationalhealthcouncil.org/additional-resources/patient-contracting-tools/

### 3.6.4 Transparency of stakeholder relationships while protecting privacy

For transparency, relationships and partnerships in patient engagement activities should be disclosed (*e.g.* on the organisations' websites); the public disclosure should be in line with relevant regulations.[7,16] It should also follow and respect the transparency and privacy policies of participating stakeholders. Furthermore, data or information from patients or other stakeholders must be respected, taking precautions to protect privacy and confidentiality.[4,16]

1527 # Chapter 3 – Annex 1: Sources of patient engagement principles

| Principle | Sources |
|---|---|
| 1. The patient voice offers relevant and valuable perspective throughout the medicine lifecycle and it should be fully incorporated into decision making to extract meaningful value. | • BIO Guiding Principles for Interaction With Patient Advocacy Organizations – link<br>• Bloom 2018, The Rules of Engagement – CTTI Recommendations for PE – link<br>• DIA Considerations Guide for Implementing Patient-Centric Initiatives in Health Care Product Development – link<br>• EMA Stakeholder Relations Management Framework – link<br>• EURORDIS Code of Practice Between Patient's Organisations and the Healthcare Industry – link<br>• FDA Guidance, Patient-Focus Drug Development: Collecting Comprehensive and Representative Input – link<br>• IAPO Consensus Framework for Ethical Collaboration – link<br>• IMI-PARADIGM D4.1 Recommendations on the required capabilities for patient engagement – link<br>• NHC Rubric to Capture the Patient Voice – link<br>• PFMD Book of Good Practices – link<br>• PFMD Quality Guidance – link |
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|---|---|
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# Chapter 4: Advancing treatments

In this chapter we talk about the important roles patients can play in developing treatments when working with other stakeholders.

**Key points**

1. Many stakeholders are involved in discovering treatments, developing them through the product lifecycle, and promoting their safe use.
2. Stakeholders include patients themselves, along with healthcare professionals, sponsors (academics, funders, and biotechnology developers), and regulators.
3. Patient participation is needed in planning, testing, reviewing, and approving treatments throughout the lifecycle of medicines.
4. Improving treatment development and delivery depends on transparent and evidence-based communications among all stakeholders.

Patients should be fully involved in developing therapies to treat their disease, beginning with describing what they would like a medicine to do for them and the difficulties of living with their disease. These unmet needs should be the most important endpoints to drive early development and clinical development. They should be the measures that decide whether a new treatment is approved for prescribing to patients. Patients from many walks of life should be asked about their needs and expectations of treatments so that the medicines help diverse groups of patients.

As patients use these new medicines, safety monitoring that began during the development phases will continue throughout everyday healthcare delivery. New information that is learned about the medicine and its effects on the disease or side effects should be clearly communicated to the public as well as to doctors and researchers. This information should support better care for patients and improve the next new medicines that are being developed.

Table 2 describes the key roles for each of four main stakeholders (patients, healthcare professionals, sponsors, and regulators) in introducing and improving treatments.

Patients should be involved starting from the definition of their needs in a dialogue between patients, developers and regulators. Patients may also be involved later in the R&D process:

1. Discussion on how to evaluate the impact of a medicine (choice of the patient-relevant outcome measure, or clinical assessment outcome);
2. Discussion on how to improve the practical aspects of a clinical trial, burden of procedures in a trial, how to enrol patients (sign them up to take part in a study), how to retain them (have them want to stay in a study rather than leaving), any substantial amendment to the protocol;
3. Discussion on when a compassionate use could be envisaged, for which population, and its practical arrangements;
4. Emergence of an unexpected adverse drug reaction that requires communication with patients;
5. Placing the product on the market;
6. Shortages on supplies of medicines.

Therefore, the table below illustrates the process from the point of view of a medicine's development. Patients may be involved in many key points. Ideally, they should be involved early and repeatedly throughout the process, rather than only being engaged in later or limited activities.

1571 ***Table 2: Stakeholder collaboration on introducing, improving, and using medicines***

1572 Source: CIOMS Working Group XI

| >> Stage: Unmet need | >> Early development | >> (continued) Clinical development |
|---|---|---|
| **Patients*** | ▪ Form patient organisations<br>▪ Produce information for patients about their disease<br>▪ Conduct / contribute to early research<br>▪ Create patient registries<br>▪ Create biosample banks<br>▪ Develop research priority setting partnerships, e.g. James Lind Alliance | ▪ Establish research priorities<br>▪ Describe living with disease<br>▪ Describe standard of care – may not be treatments available (likely to be some variability)<br>▪ Describe being treated<br>▪ Describe needs, goals and wants | ▪ Develop patient-relevant outcomes<br>▪ Contribute to protocol design<br>▪ Co-create / review research plans<br>▪ asterix<br>▪ Co-create / review information for patients<br>▪ FDA MyStudies App |
| **Health care professionals** (HCP) | ▪ Establish clinical guidelines<br>▪ Characterise disease<br>▪ Develop natural history studies | ▪ Talk with / listen to patients about their needs, goals, and wants | ▪ Inform patients about clinical trials and ensure they are making an informed choice<br>▪ Talk with patients about interest / eligibility for clinical trials<br>▪ Support patients throughout the trial and give regular feedback<br>▪ Talk about standard treatment |
| **Sponsors** (academia, funders, pharma) | ▪ Joint research priority partnership, e.g. The,James Lind Alliance | ▪ Talk with / listen to patients about their needs, goals, and wants<br>▪ PFMD | ▪ Co-create / request patient review of research plans; incorporate needed changes<br>▪ EUPATI R&D<br>▪ Co-create / request patient review of information for patients; incorporate needed changes<br>▪ Developers contact patient organisations to recruit for clinical trials (should not be the first interaction with patients)<br>▪ Provide clinical trial feedback to patients (make accessible) |
| **Regulators** | | ▪ Invite / attend public discussions of patients' diseases, treatments, needs, goals, and wants<br>▪ FDA CDER PFDD<br>▪ EMA multistakeholder workshops<br>▪ Talk with sponsors and patients about development plans | ▪ Co-create / provide guidance on including patients' input in treatment development<br>▪ FDA CDER PFDD<br>▪ EMA patients & consumers<br>▪ EMA scientific advice<br>▪ Talk with sponsors and patients about development plans and risk minimisation<br>▪ Include patients as members of scientific committees, e.g. EMA paediatric committee PDCO, committee for orphan medicine COMP |



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* Patients should be involved throughout the lifecycle; may begin interactions at any stage

1574 Table 2 (continued)

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| | >> Stage: Regulatory review | >> Ongoing: **Healthcare delivery Safety monitoring** | >>Ongoing: **Health & data communication** |
|---|---|---|---|
| **Patients** | ▪ Contribute to dossiers / reviews<br>▪ Members of scientific committees<br>▪ EMA involvement<br>▪ User-test patient leaflets and some risk management materials | ▪ Learn about treatments<br>▪ Contact developers about promising products for compassionate use<br>▪ Talk about treatments and goals with HCP<br>▪ Tell HCP / sponsor / regulator about side effects<br>▪ Engage conversations with developers following a safety signal once the product is on the market. This may be the first dialog between patients and drug developers. | ▪ Co-create / review non-promotional information<br>▪ Co-create / contribute (to) good information guidance |
| **Health care professionals** (HCP) | ▪ Give input on current treatment regimens | ▪ Learn about safe and appropriate use of product<br>▪ Report side effects promptly<br>▪ Engage with patients to establish treatment guidelines | ▪ Co-create / review / distribute non-promotional materials |
| **Sponsors** (academia, funders, pharma) | ▪ Include patient input in dossiers<br>▪ Propose patient-oriented labeling | ▪ Monitor safety and effectiveness of treatments in patient-friendly ways<br>▪ Involve patients in risk minimisation planning and activities; see also CIOMS IX | ▪ Co-create non-promotional information per guidance |
| **Regulators** | ▪ Include patient input in review of dossiers<br>▪ EUPATI regulatory<br>▪ EMA scientific committees review process<br>▪ Include user-testing for patient leaflets and relevant risk management materials | ▪ Monitor safety and effectiveness of treatments in patient-friendly ways<br>▪ EMA PV stakeholder forum<br>▪ FDA RWE Framework<br>▪ Hold public hearings for input | ▪ Co-create / provide guidance on including patients' input in non-promotional information<br>▪ EMA review of documents |



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## 4.1 Purpose of patient engagement in treatment development

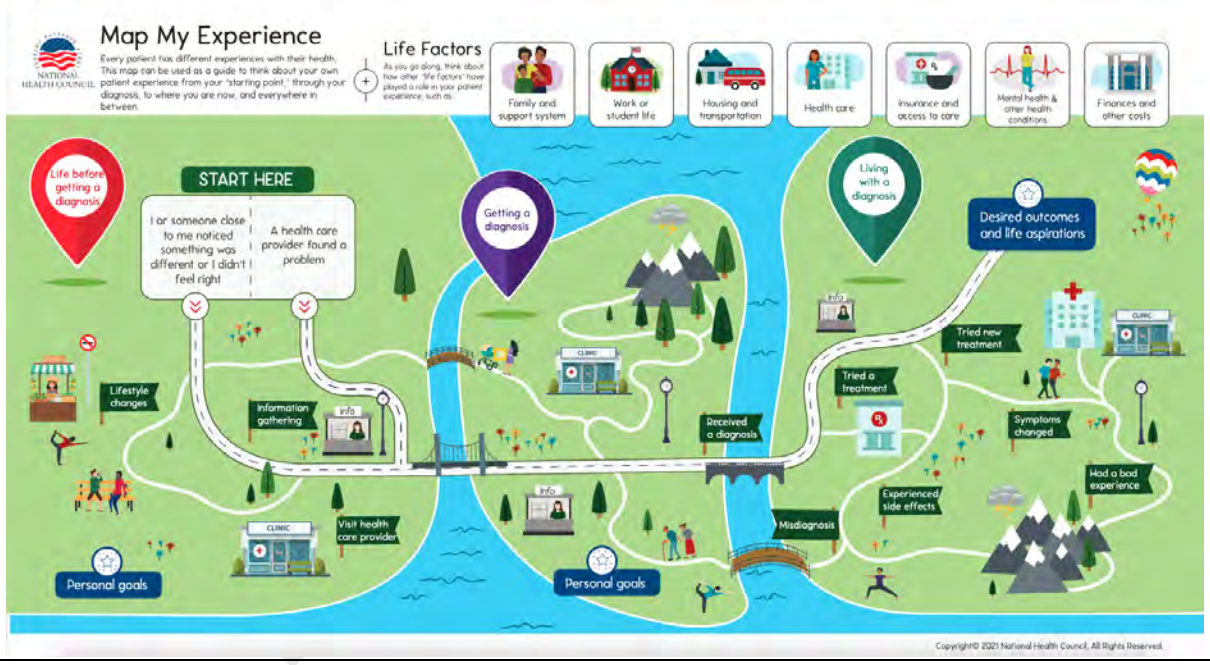
The involvement of patients, otherwise known as patient engagement (see also Glossary), is important for treatment development. When patients are recognised as experts who can advise on what a disease really means in a person's life, their importance becomes obvious in developing breakthrough medicines. Sponsors, clinicians, and regulators need to hear patients' priorities, concerns and suggestions.

Healthcare professionals need to explain treatment options clearly and ask for patients' views about how the risks weigh against the benefits for them. Shared understanding of patients' needs and desires from their treatment will support development, regulatory decision making, and communication to the benefit of patients.

Mapping patient journey or experience is a research method to gain insights about individuals' experiences, needs, and desires.

***Figure 3: 'Map My Experience' patient experience mapping tool***

From Oehrlein EM, Schoch S, *et al*. Patient Experience Mapping Toolbox. National Health Council; 2021. Available from: https://nationalhealthcouncil.org/resources/patient-experience-map[1] (used with permission)




Beyond advice on their diseases, patients also need to play a very important role in how medicines are made and tested. Their perspectives on the design of clinical studies – such as the selection of study endpoints or how they are measured, schedules of tests during clinical trials, how informed consents are written, the creation of educational materials, and support for managing medicine dosing and side effects – are crucial to designing a study that delivers the answers all stakeholders need. Well-designed trials will have better participation rates and clearer outcomes.

See also section 5.3.7 on the interaction between patients and researchers.

### Recommendations

- Involve patients as early as possible and throughout drug development.
- Ask for patients' views to fill any knowledge gaps. Many questions can be answered only by patients.

- Include patients as stakeholders: important co-creators, co-designers, and co-communicators.
- Engage patients through panels, focus groups, interviews, surveys and in other ways.

## 4.2 Patient engagement and unmet needs

Understanding unmet needs begins with assessing the gap between patients' experiences with current treatments and patients' and healthcare providers' expectations for health and improved outcomes. It is important to assess how best to measure these experiences and what makes a meaningful change from patients' and clinicians' perspectives. Patient organisations and individual patients often start this work and provide large amounts of data towards understanding diseases to support better health for themselves and for other patients.

A 2017 workshop illustrates collaboration between different parties to explore unmet needs. The European Medicines Agency (EMA), the US Food and Drug Administration (FDA), and Health Canada held a workshop to understand the unmet needs of a serious but rare condition, pulmonary arterial hypertension in children.[2] Specifically, the workshop sought to better understand problems with clinical trials in children for treating the condition. The 2017 workshop involved patient organisations, healthcare organisations, academic institutions, pharmaceutical industry and staff from regulatory agencies. Patients' and their families' views were collected ahead of the workshop and they were also presented during the workshop. One outcome of the exercise was the recommendation to:[3]

> involve all stakeholders, including patients, parents, and their organizations, as well as paediatric research networks in the conception, design, and conduct of research to improve the ethical, scientific, and clinical quality of paediatric studies.

This recommendation has been taken up by a European initiative, accelerating Clinical Trials in the EU described in section 4.4.

In this guidance, the term 'patients' broadly includes patients, caregivers, and patient (advocacy) organisations (see Glossary), but each may bring different perspectives and experiences about the disease. Young people may, for example, describe different needs and priorities from those of their parents. All these views help to inform considerations on treatment.

Patient organisations often play a role in linking patients with each other and other stakeholders and in constructing a patient registry (see Glossary). As part of this role, patient organisations need to include diverse populations in their membership and outreach (see section 3.1.2).

In considering which patient groups to include, and at which stages of the development process, the benefits of research must be weighed against the risks. The first human tests of a new treatment are often in healthy volunteers without the disease. Exceptions are made for some therapies, such as cancer treatments when patients with very advanced disease may be the first to be entered into a study to test if the treatment under investigation offers benefit over the usual care. Broader populations and larger trials usually follow in this manner, one group at a time, based on potential benefit versus potential risk, to gain experience before moving to more vulnerable populations such as pregnant women or women who could become pregnant, elderly or frail patients, or children ('special patient populations', see section 3.1.2).

The other side of this benefit-risk equation is the lack of data in vulnerable groups who need the treatment. Without clinical trial data, healthcare providers are left to use their own judgment to treat a patient who may be pregnant or who is older, younger, or has more than one disease. It is important to consider carefully how the treatment is likely to be used when it is approved and make every attempt to study all patient groups likely to be treated. Additional monitoring and clear guidance for reducing or stopping treatment during a clinical study, for example, may allow clinical testing in more vulnerable patients. It is important to discuss these issues with patient communities and include their input when designing clinical research.

Additional issues to consider in recruiting more diverse patients include location of clinical trial centres, costs of participation in a clinical trial, and cultural norms or expectations. Patients who live far away from clinical trial centres may find it difficult to travel for study visits. Study centres in areas that include many communities and broader ranges of patients will give more opportunities for diverse enrolment.

For treatments that can be given only in specialist centres, offering travel arrangements to patients (where travel is possible) can give wider groups of patients the chance to enrol. Patients may find that not all costs of a trial are covered either by the sponsors or their insurance. In addition to the expense of travel, they may not be able to take time away from work, or find childcare or eldercare, for example, and so sponsors may need to cover some expenses (see section 3.3.1), study sites may need to offer evening or weekend visit times, and patient organisations may need to step in with some benefits, depending on local ethical guidelines.

Remote options such as home nursing, telemedicine (doctor visits over smartphone or computer video communications), delivery of medicines to patients' homes, or devices that can be worn at home with data sent to clinical trial sites can help to include more patients. But suitable options must be provided to patients who do not own or use computers or smartphones or lack high-speed internet connections (see also section 4.5.3).

It is important for clinicians, medicine developers and regulators to create relationships with communities, community leaders, and community healthcare providers to understand diverse patients' needs. For example, some patient communities may have lost trust because of their experience of unethical research. Community leaders can help researchers and other healthcare stakeholders understand community history and help patients consider engaging in research. Some patients' religious beliefs may not allow certain medical procedures or ingredients in medicines. Early engagement to learn about the patients for whom a treatment is intended can inform the creation of appropriate treatments.[4]

Natural history studies (see Glossary) conducted by patient organisations and sometimes other stakeholders can play a critical role in learning about disease from diverse perspectives. This may be particularly true for rare diseases, enabling faster identification and enrolment of patients to clinical studies. Membership of rare disease patient organisations may include a large proportion of all patients with the disease and they may be especially active in treatment development. Patients are also increasingly involved in setting research priorities.[5–7]

Sponsors, healthcare providers, and regulators should strive to work with patient groups and through community outreach to include broad and diverse patient perspectives in the development of treatments and in communications about them.

### Recommendations

- Engage systematically and sustainably with patients and patient organisations to understand their views on disease and identify unmet medical needs.
- Enrol in clinical trials a range of patients appropriate to the disease or condition intended for treatment or prevention.
- Strive to include diverse viewpoints from patients, caregivers, and other representatives to gain broader understanding of patients' unmet needs.

## 4.3 Patient engagement in preclinical or early clinical development

Collaboration with patients during early development of a treatment is vital for understanding the symptoms and emotional impact of living with a disease as well as patients' perceptions of the disease and how it has affected them. How would they describe a good versus a bad day living with the disease? What impact does the disease have on their quality of life? Is the disease affecting work life, social life, and relationships? Is assistance required? What are the most troublesome symptoms? These questions provide context for understanding patients' experiences of their current therapies and identify any unmet needs.

Patients should be engaged in discussions of new treatment design, formulation and packaging as early as possible, *e.g.* through human factor validation testing.[8] Does the disease cause sensory impairment or mobility difficulty that affect patients' ability to use treatment independently and possibly require support from a carer? Could this issue be addressed by using a different formulation, dosing through a different device, or packaging that is easier to handle? Are there cultural or religious needs, *e.g.* does the medicine contain an animal product that could affect patients' acceptance of the treatment? Are the label and instructions on the packaging easy to understand? Which features of a treatment are most important to the patient?

Considerations for communication during early clinical development are important in at least two areas: around treatments and around the disease. What materials do patients need to make an informed choice to try a new treatment? And more broadly, how well do patients understand the disease, its long-term consequences and how treatable it is?

To engage with patients and to provide information they need, stakeholders should ask patients where they look for information and how they would like to access the information. Which information channels are the most used and trusted by patients? Where and how is it best to engage with patients in order to hear their views? Are patient organisations active in this disease area? Do patients prefer to work with their healthcare providers to answer their questions, or with patient organisations, or do they do research on their own? Healthcare providers and regulators can guide patients to objective, accurate information on diseases and treatments.

### Recommendations

- Engage patients early in the development of treatments better suited to their needs.
- Consider making the treatment fit the patient's lifestyle where possible, *e.g.* providing formulations, devices, or packaging that allows the patient independence in using their medicines rather than relying on a caregiver.
- Use communications platforms and methods that support information exchange with a wide variety of patients.

## 4.4 Patient engagement in clinical development

Engage patients in the clinical phases of treatment development for their input on study designs and endpoints. Patients can help define the research questions, identify appropriate patient groups, select the best comparator treatments, and identify clinical endpoints that matter to them. They can also define the trade-off between benefits and risks that they are willing to accept and help identify fair inclusion and exclusion criteria for broad and equitable participation. And patients can propose changes in study design to reduce the clinical burden on the patient participants (*e.g.* how site visits can be reduced) or lessen the operational burden (*e.g.* support for childcare to enable patients to participate in a study).

In addition, patients can provide insights on using digital technologies in the study and help with data privacy or ethical questions (see also section 5.2.1, Data from personal sensors and wearables). To test the effectiveness of these strategies, questionnaires during or after the trial can ask patients how difficult it was to take part in the study and why this was so.[9]

Clinical trials often also collect data directly from patient participants about their experiences the treatments during the trial. Creating or choosing such clinical outcome assessment tools including patient-reported outcomes (PROs) is another opportunity for collaboration among stakeholders, *e.g.* European Alliance of Associations for Rheumatology (EULAR) patient reported outcomes development in rheumatology.[10]

Some patient organisations develop quality-of-life indicators or recommend prioritisation of measures to include in studies.[11,12] Healthcare providers, sponsors, and regulators may favour tools to measure particular clinical features of a disease. It is important to consider all these stakeholder perspectives to decide what endpoints to measure and how to measure them. These data will be part of development decision-making, regulatory review, and they may provide information for the medicine labelling and understanding of the medicine's benefits and risks. Stakeholders' decisions should be built on the lessons learned around the unmet needs of patients.

An initiative was launched in January 2022 to improve clinical trials in Europe.[13] Called 'Accelerating Clinical Trials in the EU', an objective of the initiative is 'patient-oriented medicines development and delivery across populations'. It aims to achieve this by establishing 'a multi-stakeholder platform, including patients'.

Patients' perspectives also help to select study sites and their locations. Ask patients about the physical environment and processes at a study site. Working with all relevant stakeholders including patients and research site staff during this early preparatory phase of the clinical trial will help improve patients' and other stakeholders' experiences in clinical trials. These considerations can increase recruitment (patients enrolling to participate in clinical trials) and patient retention (patients remaining in trials rather than dropping out) as well as increasing the motivation of the site staff. Patients may also provide input on the feasibility of conducting trials in a country.

If new safety information emerges during the trial, patient organisations can participate in communicating the information according to ethical guidelines. They can review the communication to ensure that it is clear for patients, and they may also share information at pre-defined milestones during the trial.

Finally, at the end of the trial, patient organisations can help communicate the results of the clinical trials and increase understanding of the new medicinal product when it is placed on the market. Sponsors should understand from patients when and in what format communications to patients such as thank-you notes and clinical trial results should be sent. It is also strongly recommended that sponsors seek feedback about the clinical trial,

information materials, or the intended product. This can improve future clinical trials and increase trust and collaboration between partners

Sponsors are responsible for study quality, ensuring that the trial follows good clinical practices.[14] This requires personnel at the study sites to document the data, follow the study protocol, and respect the regulatory requirements.

Patient organisations have developed programmes to train patients on clinical development. Many patient organisations have patient experts who can act as consultants for drug development companies.[15] Patient organisations may also have preclinical or clinical research capabilities. They may work with researchers on developing tools such as quality-of-life measures. They may tell their members about research in which the members may want to participate. Or patient organisations may sponsor product development.

Healthcare providers (HCPs) play a key role in patient engagement as well, discussing with patients standard treatments as well as planned clinical trials with entry criteria. They educate patients about clinical trials and scientific research. Patients turn to HCPs to ask about clinical trials and best options for their care and are heavily influenced by them.

HCPs can be a critical and much-needed link to treatments under development, but information must be readily available and greater understanding must be built between the research community and the healthcare community, *e.g.* through education about clinical research during medical training.

Patients often become experts in some areas of their disease as well, and can educate HCPs about them. For these reasons, some patient organisations work closely with HCPs.

Putting patients at the centre of clinical development and more broadly throughout the medicine lifecycle is advantageous for all stakeholders. Patient-centric biopharmaceutical companies hold greater appeal for talented individuals who support a culture of putting patients at the centre of the decision-making process, build better trust among other stakeholders (HCPs, payers, government, and patients), increase revenues, and show improved patient outcomes. [16–18]

There are benefits and concerns about close ties between patient organisations, HCPs, and sponsors. There is some unease about patient organisation investment in product development due to conflicts of interest. The power balance between patients and other stakeholders is often unequal. Contracts and ethical governance of engagement among different stakeholders can provide protections and transparency for these relationships, as can public reporting of the financial relationships between parties. See also Chapter 3.

Regulatory authorities increasingly recognise the value of transparent and appropriate patient engagement in clinical development. They see the potential to improve the quality and relevance of clinical data for a submission dossier. Regulators engage with patients and patient groups themselves in a number of ways and ask for evidence of patient engagement by other stakeholders. See also section 4.8 on regulatory review.

### 4.4.1 Individual choices

Patients vary in their interest and understanding of clinical research and the medical aspects of their diseases as well as their preferences for how to approach care together with their healthcare providers.

Some patients wish full participation in decisions around their individual care. They need to expend a great deal of time and energy to learn about all their options for treatment. This is especially so if they want to try treatments that are still in development. Information

about clinical research or how to participate in trials is not provided in a consistent and coordinated manner. Patients may need help to find an appropriate study that is enrolling and is accessible for them. This is especially true of patients with co-morbidities that make them ineligible for many clinical trials. Ideally, information on treatment options should be accessible and understandable for patients so that patients can explore and discuss them with their healthcare providers.

Conversely, some patients do not wish to be involved in the decisions about their treatment and want HCPs to make decisions on their behalf, in their best interest. These patients' perspectives are important to capture so that their care is also supported, perhaps more through their HCPs and caregivers. Patients need partners in research and HCPs who respect their decisions and viewpoints.

#### Recommendations

- Involving patients early and often to plan a clinical trial creates a better experience for patients and improves the quality of the trial.
- Transparent communication between stakeholders enhances clinical trial recruitment and engenders trust through the relationships that develop as stakeholders work together towards patient-centred research.
- Stakeholders should engage with the broadest and most inclusive patient groups possible to ensure all patients have opportunities to participate in advancing treatments for themselves and others.

## 4.5 Challenges in clinical development

This section addresses challenges in clinical development and proposes recommendations. Chapter 3 should also be consulted for best practices in patient engagement.

### 4.5.1 Challenge 1: Communicating clearly

Use plain language to engage all stakeholders and particularly patients. Reading levels, experiences with health issues and technical literacy levels, and familiarity with medicine development processes vary among patients. Use plain language – supported by glossaries of technical terms if needed – for documents intended for patients such as contracts, clinical material or educational material. See also section 3.6, section 5.3.10, and section 6.5.

#### Recommendations

- Use patient-focused educational materials that are easily understood to introduce clinical trial concepts, patients' rights during the trial, and disease information.[19]
- Clearly explain benefits and risks. Discuss these with patients before getting their consent to participate in the clinical trial.
- Provide child-friendly, age-appropriate documentation and assent for paediatric trials (see section 3.1.2).[19]

### 4.5.2 Challenge 2: Including diverse and underserved patients

Include diverse patients' views in clinical development. This is achieved by working with advisors or collaborators and participants of the gender, age, geographical location, cultural background, or communities of the patients for whom the medicine is intended.

Seek the views of caregivers and legal guardians whenever needed, especially when patients are not able to speak for themselves (see also section 5.3.8).

**Recommendations**

- Seek a diverse array of patient insights at every stage of clinical development through community representatives and trusted leaders (see section 3.1.2). Create and sustain relationships with these partners.
- When relevant, include caregivers' priorities in the clinical development plan.

### 4.5.3 Challenge 3: Balancing digital technology with inclusiveness

Some clinical trial visits can occur outside the clinic with the support of digital technologies, like telemedicine, drone shipment of medicinal products to patients, sensors, or wearable devices to measure vital signs or functional abilities. On the one hand, these new approaches allow more patients to be included in studies by decreasing travel requirements but on the other, they exclude patients if the technologies require resources or capabilities that patients lack. It is important to seek patients' voices very early regarding the use of digital technology in clinical trials. Using devices not suited to patients' needs can lower patient participation, possibly leading to inconclusive data for the clinical trial and delayed treatment access for patients.

**Recommendations**

- Consult patients and their caregivers very early in the clinical development programme to evaluate the value, acceptability, and burden on patients of digital technologies or devices planned in the clinical trial.
- Based on the input, reduce the burden on patients and ensure access to digital clinical trials for diverse groups of patients.

### 4.5.4 Challenge 4: Patient engagement takes time

While engaging patients effectively takes time, this investment yields a sustained, productive and trusting relationship. In life-threatening diseases stakeholders often work to deliver therapies to patients rapidly. Seek to shorten the engagement period with patients without losing valuable patient input by creating efficient processes.

**Recommendations**

- Build and sustain relationships with inclusive patient populations. Building relationships takes time, but sustaining trusted relationships benefits all stakeholders and will lead to more efficiencies in the long term.
- Consult patient and community partners regularly on different aspects of clinical development, while respecting their independence and autonomy.

### 4.5.5 Challenge 5: Finding and engaging harder-to-reach patients

In rare or 'orphan' diseases, and in some acute diseases, it may be difficult to get patient's views due to the low number of patients in some regions or even globally. Consult sources such as the EUPATI guidance for help.[20] Patient organisations such as the European Organisation for Rare Diseases or the International Alliance of Patients' Organizations (IAPO) represent rare disease communities and global patient organisations.[21]

**Recommendations**

- For rare diseases, it is of utmost importance to seek patients' insights.

- International patient organisations with global reach are important in helping to include broader patient perspectives.

### 4.5.6 Challenge 6: Overburdening patient organisations

Coordinate with other stakeholders in approaching patients and patient organisations to avoid asking the same questions about their disease and treatments. Consider working with patient community advisory boards (CABs), which are organised and driven by patient advocates who decide on the agenda and the attendee list and create a professional space for stakeholders to come together.[22]

#### Recommendations to sponsors and drug developers

- Organise internally the collection and use of patient insights to avoid repeatedly asking patients or patient organisations the same questions at different stages of the development process.

### 4.5.7 Challenge 7: Providing clinical trial information to patients

Enable patients to get timely and understandable information on ongoing and future clinical trials. Although publicly accessible databases exist, most patients will be unaware of them.

#### Recommendations

- Facilitate access to the information on clinical trials from a patient perspective and communicate about clinical trials in patient-friendly language.
- Establish appropriate and easily searchable platforms to provide information.

### 4.5.8 Challenge 8: Engaging patients who cannot provide direct input

Some diseases affect patients who cannot provide direct input into the clinical development process or the clinical trials. Children not yet able to talk, adolescents or adults with cognitive disabilities or too sick to provide input on clinical questions, and others may pose challenges for patient engagement. These patients, when recruited in a clinical trial, may have difficulties understanding and giving informed consent. Provide accessible, clear and understandable information about clinical trials to these patients and their caregivers.

#### Recommendations

- Seek advice and input from variably abled or young patients by finding innovative ways to communicate with and informing them, or by involving caregivers or legal guardians.
- All stakeholders should follow the *International Ethical Guidelines for Health-related Research Involving Humans* (2016).[23] Guideline 16 refers to research involving adults incapable of giving informed consent. Guideline 17 refers to children and adolescents.

### 4.5.9 Challenge 9: Compensating patients for their engagement

Compensate patients for their time to prepare for an engagement and provide input, as well as any reasonable expenses. The guiding principle is set out in section 3.3. Ethical guidance for patient compensation differs by geographic region.

### Recommendations

- When planning to engage with patients, assess fair market value for reimbursing expenses and compensation for time and effort. Offer ethically compliant payment in line with fair market value as part of the agreement for the interaction.

## 4.6 How to engage

Sponsors may partner with patients in several ways, including requesting in-depth interviews, focus groups, participation on advisory boards, trial simulations, user testing of study devices, review of educational materials, or sponsors may attend community advisory boards sponsored by patient groups.[19,24]

Interactions with individual patients and group meetings may be conducted in person or through videoconferencing, phone calls, social media or online patient surveys.

User testing is used routinely in the EU to make sure information is fit for purpose (see also section 2.2.7, section 6.6 and section 8.3.4). This satisfies the requirement for patient leaflets to be 'legible, clear and easy to use.' User testing with 'real' patients – members of the public who are not necessarily skilled readers – highlights readability problems in a document.[25]

Some patient organisations help to identify patients who can review informed consents (with contracts in place to support these funded activities). PARADIGM, the multiple stakeholder Innovative Medicines Initiative (IMI) Project, aims to deliver 'an inventive and workable sustainability roadmap to optimise patient engagement in key decision-making points across medicines'.[26]

## 4.7 Patient engagement in patient preference studies

Patients' perspectives on their disease, disease management and treatment alternatives are increasingly recognised as important for decision-making throughout the medicine's life, not only to advance medicinal treatments but also for assessing the medicine's benefit and risks, reimbursement and health technology assessments (HTA).[27–32]

Patient preference information represents one type of patient perspective data. It is obtained by eliciting patients' preferences on the relative desirability or acceptability of specified attributes or characteristics of a medicine and choice of outcomes, compared to an alternative medicine or health intervention.[33]

Patient preference elicitation – typically through patient preference studies – is particularly valuable in 'preference-sensitive' situations[34] such as when:

1. the most important outcomes or attributes for a disease or medicine have not been definitively defined
2. numerous treatment options are available (*e.g.* standard of care) but no single option has a clear added value for all patients
3. clinical evidence in favour of one option over another is highly uncertain or variable, and patients' tolerance for such uncertainty may affect their decisions
4. there is considerable variability ('heterogeneity') in opinions among patients or between patients and other stakeholders (*e.g.* physicians) on the importance and value of different treatment attributes or options.[33]

Patient preference studies (PPS) can involve either qualitative or quantitative assessments. Typically, qualitative methods are used for insights into what matters most to patients (*e.g.* their primary needs are or clinical endpoints that are important to them). Quantitative

methods are used to determine how much patients value different alternatives (*e.g.* the relative importance of different clinical endpoints), what they view to be acceptable trade-offs (*e.g.* how benefits and risks are weighed) and how much uncertainty they can accept. Often the results of a qualitative study are used to inform the data collection instrument (*e.g.* questionnaire) for a quantitative study.

To date, focus group methodology has been widely employed for qualitative research while discrete choice experiments have been extensively used for quantitative assessments. However, the specific research approach should be dictated by the study purpose and objectives. A variety of qualitative and quantitative methods is available for patient preference research and each has its strengths and limitations. IMI-PREFER Final Recommendations give comprehensive guidance on choosing the type of method for various scenarios.

Involving patients in the design and conduct of a patient preference study is vital for ensuring the relevance, appropriateness, feasibility and acceptability of the study. As such, patient involvement in PPS is recommended as best practice.[33] Additional reasons to involve patients include ethical considerations (*i.e.* patients' right to be involved in shaping research that concerns them), and research validity (*i.e.* patients living with a disease can offer an important and unique perspective, distinct from that of clinicians, researchers or other experts).[33]

IMI-PREFER, a 5-year, multi-stakeholder initiative to provide evidence-based recommendations on how and when PPS should be performed to inform medical decision-making, has proposed the following principles for interacting with patients in the context of a patient preference study:[33]

1. Patient centricity: Systematic efforts should be made to assess whether, how, when and which ways patients can or should be involved.
2. Clear communication and transparency: Information should be provided in a manner that facilitates meaningful participation and builds trust.
3. Inclusiveness: The diversity (*e.g.* sex, race, ethnicity, ease of reach) of the specific patient group should be well represented.
4. Responsive and reciprocal: Exchanges should be meaningful for patient participants and partners as well as researchers.
5. Respectful and confidential: All contributions from patient participants or partners (*e.g.* medical knowledge, policy information, health outcomes) should be treated with respect and safeguards developed to protect individual rights, privacy and confidentiality.
6. Well-prepared: All engagement activities should have a clear, well-defined purpose so that it is clear at the start of each interaction how input will be used.
7. Objective: All activities and exchange of information must be done in a transparent manner that seeks to be free of conflicting interests.
8. Proportionate: All patient participant or partner interaction efforts (time burden, etc.) should be proportionate and specified as well as possible in advance of the interaction.
9. Non-interference with current health care: The relationship between the patient participant or partner and the healthcare provider should not be affected by the patient's involvement in the preference study.
10. Impactful and sustainable: Interactions should be as beneficial and as impactful as possible, *e.g.* for stakeholders and society as a whole.

The form of patient engagement in a PPS will depend on the intensity of involvement and level of partnership that an individual prefers. Patients can, for example, serve in an

advisory capacity for consultation by the research team on particular issues during the study (*e.g.* conceptualisation of research question; study design and execution; data analysis and interpretation; dissemination of study results to patients and other audiences). Such consultations can either be ad hoc (*i.e.* for a specific topic or issue arising during the study) or at planned points during the research. Alternatively, patients can be involved as members of the research team, which typically entails greater investment of time and deeper involvement in all facets of the study. In this capacity, patients are essentially partners in the co-creation of the research study. Not least, patient participants can play a role in developing plain language summaries of the PPS results, and in disseminating study findings to the patient community.

Strategies to empower patients effectively include:[33]

- presenting study documents and information clearly and accessibly, see section 4.5.1;
- providing clear, concise descriptions of the patients' or patient partners' roles (see also section 3.6.3);
- offering flexibility around meeting times and assistance with transportation;
- providing opportunities to participate remotely (*e.g.* by video conferencing);
- reimbursing patients for time and expenses, see section 3.3.2;
- providing training for patient partners, see section 3.4.2; and
- educating researchers on engaging with patients, see section 3.4.1.

Given the growing emphasis on patient-centred healthcare in increasing regions in the world, PPS are expected to become an important type of evidence for advancing treatments, evidence that complements clinical trial data. Patients can make a critical contribution to raising the quality of these studies.

## 4.8 Patient engagement in regulatory review

### 4.8.1 Purpose of involving patients in regulatory processes

If a developer has evidence from laboratory and clinical research that a medicine is effective and safe for its intended use, the company can apply to regulators to market the medicine. Increasingly, regulators are involving patients in their work. They may hold public forums to discuss the burden of disease and available treatments and facilitate input from patients during the development and evaluation phases of products.

Patients' participation in regulatory activities can be categorised as follows:

- Patients representing 'patient community' interest *e.g.* through nomination to a regulatory authority management board or a scientific committee.
- Patients, representing their own organisations, who participate in public consultation on specific guidelines or act as advocates on a specific disease condition.
- Patients providing individual expertise on their own disease, for example during the evaluation of a marketing authorisation application.
- Patients commenting as a member of the general public, for example, on an issue posted for public consultation.

### 4.8.2 Patient involvement at key milestones during medicine regulation

Patients can get involved in every aspect of the regulatory procedure of a medicine from pre-submission and evaluation through to post-authorisation use. Some regulators have standing advisory committees that include patients. There are challenges with involving diverse patients, such as young people, special populations, or surrogates, but regulators

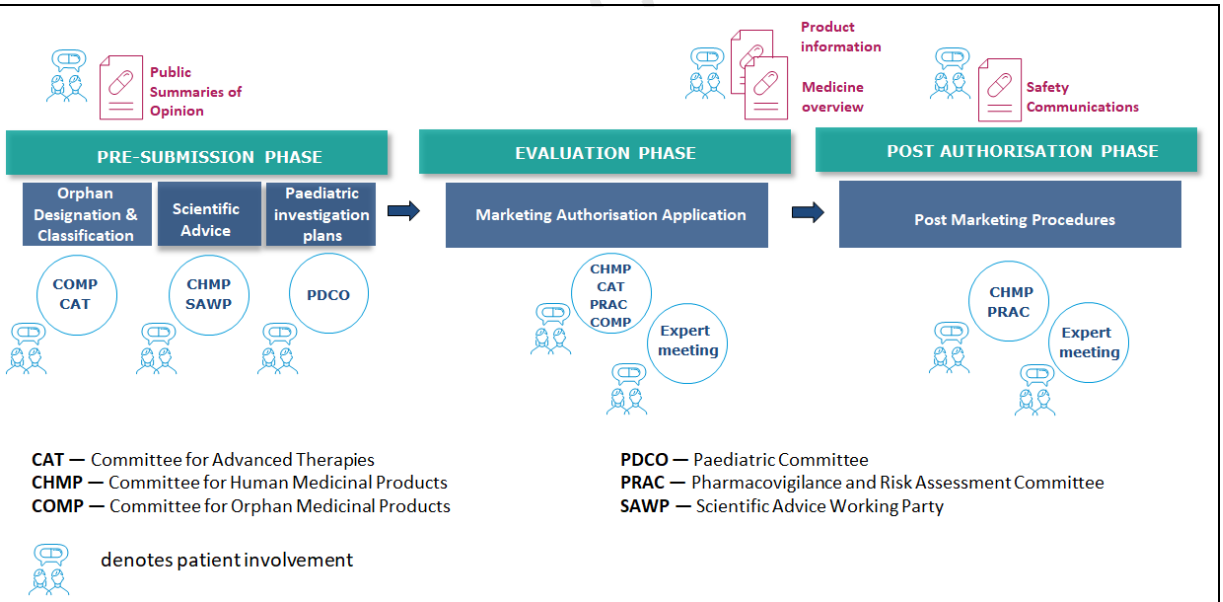
are seeking more patient input to increase inclusiveness. US Food and Drug Administration (FDA) Devices Patient Engagement Advisory Committee, European Medicines Agency (EMA) Scientific Committees, and the Pharmaceutical Affairs and Food Sanitation Council (PAFSC) of Ministry of Health, Labour and Welfare in Japan have members representing consumers and patients.

Recent FDA draft guidance[35] highlights the importance of patient involvement in the benefit-risk assessment throughout a product's life, for example, how patient-experience data can inform critical aspects of a medicine development programme, as well as pre-authorisation and post-authorisation benefit-risk assessment more broadly. The patient voice is considered critical during a product development programme to provide input on assessing the clinical relevance of the study endpoints, effectiveness and safety.

Figure 4 illustrates the touch points for patient engagement at EMA during a medicine's lifecycle. Patient engagement takes many forms in EMA's regulation of medicines. Patient organisations are represented in the membership of scientific committees (CAT, COMP, PDCO and PRAC) and they are nominated as experts in scientific meetings as needed. Patients are also involved in contributing to and reviewing EMA's public-facing information (shown in red in the figure). In addition to the scientific committees and scientific meetings, patients are represented as full members of EMA's Management Board, and patients and consumers' perspectives are also conveyed through EMA's Patients' and Consumers' Working Party (PCWP). The PCWP is a forum for dialogue and exchange between regulators, patients and consumers on issues related to medicines.

***Figure 4: Patient involvement in the medicines lifecycle at European Medicines Agency***

Source: Kindly provided by the European Medicines Agency

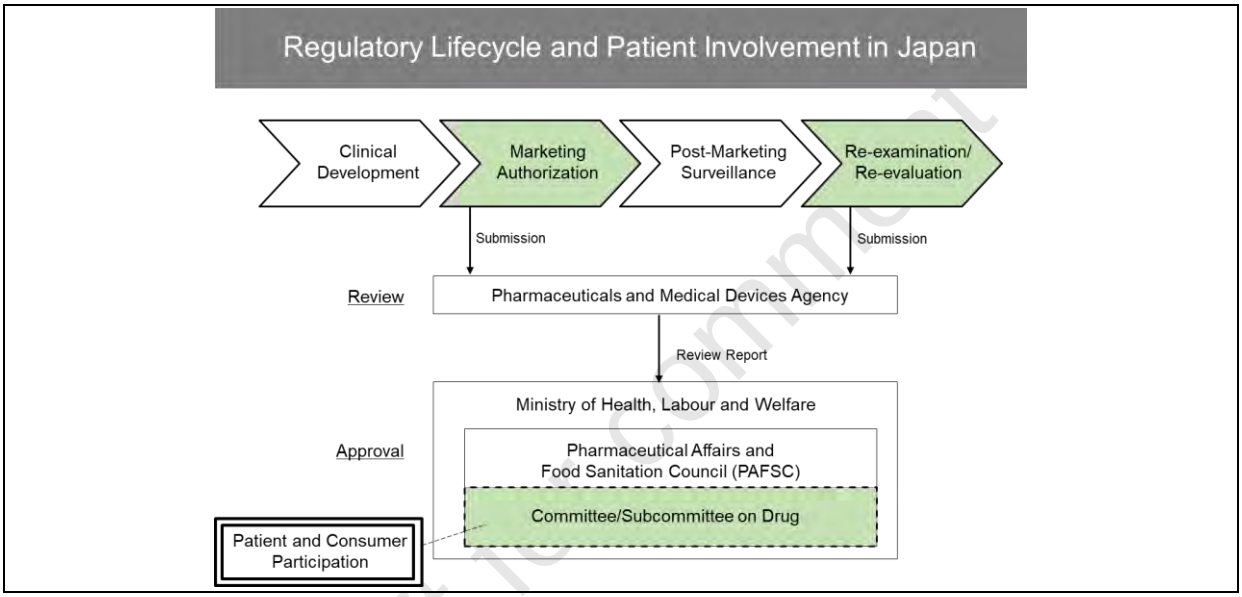



Note: For examples of 'Product Information', see Table 11 on page 138.

In Japan, patients and consumers participate in the approval of medicines ('pharmaceuticals') and medical devices (Figure 5). They are involved when the Pharmaceuticals and Medical Devices Agency (PMDA) sends its review report to the Pharmaceutical Affairs and Food Sanitation Council (PAFSC), the body within the Ministry of Health, Labour and Welfare (MHLW) in Japan that approves medicines for marketing. MHLW sends the request of recommendations to the PAFSC, and the PAFSC submits the approvable opinions to MHLW before final drug approval decisions in the regulatory process in Japan.

***Figure 5: Patient involvement in the medicines lifecycle at the Pharmaceuticals and Medical Devices Agency, Japan***

Source: Modified by Pharmaceuticals and Medical Devices Agency (PMDA), Japan, from chart entitled "Flow of Examination for the Approval of a New Pharmaceutical", Health and Medical Services, p. 93. (PDF accessed 17 February 2022)[36]




Regulatory scientific committees ask patients specific questions about treatments under review and take into account the feedback for the final conclusions. In addition to increasing transparency and trust in regulatory processes, patients' participation engenders mutual respect between regulators and the community of patients. Patients' contributions enrich the quality of the scientific committees' opinion.

Patients often contribute scientifically into the evaluation discussion, but the purpose for including them in scientific committees is to bring unique and critical input based on their lived experience of a disease and its treatment. Scientific experts on the committee cannot provide this perspective, and patient engagement has proven necessary to achieve the best possible regulatory outcome. See Annex 1 to this chapter for information on EMA scientific committees that include patients as full voting members.

Having a patient as a member of the scientific committee does not guarantee the most relevant input of experience and expertise into every therapeutic area or condition being discussed. Experience indicates that the best results are obtained by, in addition to the member, as-needed involvement of experts or representatives from the most relevant patient organisation.

Patients are also invited to scientific committees where their involvement can bring value to the discussion on benefits and risks; for example, patients can be involved:

- for a new medicine in an area with an unmet medical need and when the committee wishes to assess the impact of its recommendation on the relevant patient group;
- when the committee wishes to assess the impact on the relevant patient group of a committee recommendation to maintain, suspend, or revoke a marketing authorisation, or to restrict the indication of an authorised medicine.

### 4.8.3 Contributions on disease and product-specific questions

Public hearings are an additional engagement method which gives voice to citizens in the evaluation of the safety of medicines and the management of risks. They provide regulatory safety committees input and insights from the public and around a specific concern or risk with a treatment or group of treatments.

By working directly with people affected by treatment along with those who treat and advise patients, regulators can increase their understanding of how the treatment is used and make sure that regulatory actions to manage risks are appropriate and practical.

Some regulators broadcast public hearings live and record them, enabling the general public to learn how the regulators work and particularly how they aim to improve a medicine's benefits by minimising risks. Contributions from the public at hearings inform committee decisions. Committee assessment reports show how information from the hearings contributed to the overall evaluation of the medicine under consideration.

### 4.8.4 Ad hoc advisory committees and panels

Health Canada's ad hoc advisory panels, EMA scientific advisory groups and scientific advice working parties involve patients in discussion of medicines under evaluation or still in development. For example, EMA provides early advice to pharmaceutical companies during the development of new medicines. They have seen the benefit of consulting patients and considering their views during the preparation of such advice, particularly for the groups included in the study; patients provide their perspectives around quality of life, feasibility of proposed protocols, relevance of endpoints, standard of care, and potential clinical and life-affecting benefit of 'orphan' medicines (medicines developed for very rare but serious diseases).

Patients and patient representatives' unique perspective may confirm the committee's position or sometimes alter the committee's advice which was based only on scientific assessment. These discussions, as well as those during the evaluation of marketing authorisation applications, are confidential and take place in closed meetings.

### 4.8.5 Communication

An area that has greatly benefited from the involvement of patients is communication. Patients help to prepare information directed at patients such as package leaflets, patient support materials, summaries of assessments of new medicines (evidence for why they were approved), communication about minimising risk, new safety information, or supply shortages. Some regulators provide drafts for patients to comment on the clarity of the text and whether it is comprehensible to an average patient. Regulatory authorities are responsible for approving information on authorised medicines, including information for patients and the public. During the preparation of this information, the involvement of patients ensures that it is well written and comprehensible to the intended audience.

### 4.8.6 Ongoing patient engagement forums

Regulators are structuring ongoing engagement forums with patients, consumers and their organisations through regular interaction. They aim to better understand lived experiences of diseases and their management and how information on the use of medicines is obtained. They also want to understand patients' views on the value of the scientific evidence for decisions on the medicine's benefits and risks. And they would like more efficient and targeted communication to patients and consumers to support safe and appropriate use of medicines. Finally, they hope to enhance patient and consumer organisations' understanding of the role of the regulatory network.

By working with balanced representation of the different types of patients and consumers, regulators can identify gaps and priorities in the overall interaction. Such representation can comprise organisations representing patients, consumers or civil society, organisations representing those with specific diseases, and organisations representing special populations.

In many countries patients can contribute to broad public consultations on new policies, regulations, and legislation. People may comment on issues such as safety monitoring, ethical aspects of clinical trials conducted in other countries, or the development of a clinical trial register.

### 4.8.7 Training-capacity building

For their contribution to be meaningful, patients must have an understanding of the regulatory environment and more particularly the mandate of the regulatory body as well as their expected role in the evaluation process.

Opportunities are needed for both regulatory authorities and patient groups to build capacity for the engagement activities described in this chapter. Some regulatory authorities run training programmes. They can be tailored to the type of participation needed and can be complemented by personalised or one-to-one support.

Some patient groups and collaborative projects have also developed training to empower patients to play an advocacy role in regulatory authorities. See Chapters 3 and 5 for further information on training and capacity building before and after treatment approval.

#### Recommendations

- Regulators should continue to enhance their interactions with panels of patients and broader groups of patients and the public.
- Patient groups are encouraged to help their membership and other patients and members of the public to take up training opportunities and build capacity to participate in interactions with regulatory authorities.
- Patients and the broader public should be facilitated to provide valuable insights to improve communication and enhance the safe and appropriate use of treatments.

## Chapter 4 – Annex 1: EMA scientific committees

At EMA, Patients have been included as full voting members of EMA scientific committees since 2000. The Committees that include patients are listed below as well as the year of their creation. Activities covered by these committees include orphan designation of medicines, assessment of paediatric investigation plans, classification of advanced therapies and assessment and monitoring of safety issues of medicines.

- COMP – Committee for Orphan Medicinal Products (since 2000)
- PDCO – Paediatric Committee (since 2007)
- CAT – Committee for Advanced Therapies (since 2009)
- PRAC – Pharmacovigilance Risk Assessment Committee (since 2012)

Community legislation (Regulation (EC) Nº 726/2004,[37] Regulation (EC) Nº 141/2000,[38] Regulation (EC) Nº 1901/2006,[39] Regulation (EC) Nº 1394/2007,[40] and Regulation (EU) Nº 1235/2010[41] amending Regulation (EC) Nº 726/2004 and Directive 2004/27/EC) provides the basis for the participation and membership of patients in some EMA scientific committees while the *Framework on the Interaction between the EMA and Patients' and Consumers' Organisations* (EMA/637573/2014)[42] outlines EMA's interaction with patients and consumers.

- Members participate in accordance with the committee's rules of procedure and defined tasks. They must maintain confidentiality, declare any conflict of interest and abide by the EMA code of conduct.
- Members take part in committee decisions and have equal voting capacity. Members are expected to actively contribute to the discussions and to the work of the committee and where necessary, build awareness of therapeutic progress in specific areas.
- Their expected contribution includes:
- Reflecting on real-life implications of regulatory decisions.
- Helping and assisting in decision making.
- Increasing transparency and building confidence and trust in the regulatory process.
- Ensuring credibility by guarantying that scientific regulatory bodies act for the benefit of society.
- Continuously contributing and asking for any changes in the system that improve reliability.
- Representing patients' interests and providing a patient perspective, on behalf of those directly affected by regulatory decisions.
- Bringing experience of the disease and identifying patients with experience of the disease that can be consulted when necessary.
- Reflecting on the risk that patients are prepared to take. Ensuring appropriate representation among the range of patients who would be affected. Repeating consultations as risks are better identified and defined.
- Identifying potential topics which require or benefit from additional patient consultation.
- Actively contributing to patient information and communication related to medicines. Ensuring that patients and patient's organisations can access useful and understandable information.
- Disseminating committees' outcomes when they become public; passing on information to other patients and patient organisations.
- Bringing specific expertise from a patient communication perspective (*e.g.* to put safety issues into context), including contribution to the decision on when to communicate.
- Ensuring that information in any document prepared by the committee for patients and the general public is clear and understandable and that it fulfils patients' needs for information content (*e.g.* wording of package leaflet, Q&As, etc).

- Advising and supporting regulators on the feasibility of planned investigations (*e.g.* for paediatric investigation plans, orphan designation, risk management plan, etc).
- Guaranteeing that scientific opinions address patient needs and that there is a rational and adequate use of incentives (*e.g.* in orphan designation) for the benefit of patients.
- Advising and supporting regulators in their dialogue with industry and other stakeholders when identifying areas of medical need for target research.
- Contributing, in a general capacity, to public health (raising awareness, where appropriate, of the impact of regulatory decisions) in the context of their organisation.
- Independently of patients' participation in scientific committees (*i.e.* members, experts, observers or representatives), they can contribute the following:
- **Expertise**: Convey a combination of specific education, training or professional experience
- **Experience**: Convey practical disease knowledge obtained from direct contact with the disease (affected person or close contact with affected person, *e.g.* family, carer)
- **Advocacy**: Act on behalf of the affected patients in defence of their rights; provide patient-oriented public health / healthcare policy perspective
- **Empowerment**: Participate in decision-making process within the committee; having access to information and process on behalf of patients

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# Chapter 5: Use of real-world data

This chapter looks at the guiding principles for patient engagement related to information sources available after a medicine has been approved.

**Key points**

1. Collecting 'real-world data' – information collected from routine use of medicines in the community – is essential for making sure that medicines continue to be used to their best effect.
2. Strong collaboration between patient communities, regulators and the pharmaceutical industry leads to better collecting of real-world data – meaning data on the effectiveness and safety of medicines.
3. Patients should be seen as partners in deciding what information is collected, how it is collected, and how it is used. Care is needed to involve diverse patient views.
4. Patient-engagement frameworks for real-world data have been developed - but there is scope to improve them and for implementing them more fully.
5. Patients' involvement in generating real-world data – often using emerging technologies – should continue to be expanded.

## 5.1 Patient involvement in generating real world data on medicines

By definition, real world data (RWD) refers to information on patient health status and healthcare service use collected from a variety of data sources including electronic health records (EHRs), administrative healthcare claims and billing records, product and disease registries, patient-generated data including in home-use settings, and wearable devices that collect personal health information (*e.g.* 'smart watches').

Real-world evidence (RWE) is the clinical evidence on the usage and potential benefits and risks of a medicine derived from analysis of RWD.[1] RWE can be generated using different study designs, including certain types of randomised trials (such as large simple trials, pragmatic trials [2]), and observational studies (prospective and retrospective) – see section 5.2.1.

The rules of data acceptability for development and regulatory review of medicines are evolving. The shift away from the exclusive reliance on data from randomised clinical trials (RCTs) to inform product development and regulatory review is most notably exemplified by the increasing use of RWD, pragmatic and low-intervention studies and patient-reported outcomes (PROs). Use of neither RWD nor PROs is possible without active participation of key non-medical, non-regulatory stakeholders – specifically patients and patient organisations.

### 5.1.1 Patients and regulators

New rules are required on patient voices to formalise and facilitate communication between patients and regulatory authorities. Both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) now routinely consider the patient voice during their regulatory considerations.

One way that patients have had a voice with national regulatory authorities has been to share the experience of living with the disease. This has largely meant sharing personal anecdotes; these highly individual patient stories are important in informing regulatory decision making.

### 5.1.2 Patients and industry

Sponsors of medicines are increasingly turning to patients for input on their diseases and treatments to improve the evaluation of their medicines. Patients have been providing data to medicine sponsors for many years, but usually as consumers and not as partners.

In the past, patients provided their personal data to drug developers exclusively in their capacity as clinical trial subjects and as consumers in market research studies. They did not participate in the generation and utilisation of these data.

The Patients Focused Medicines Development (PFMD) initiative was established in 2015 as an independent global initiative. It is an open, non-profit partnership based on expertise and commitment to improve patient engagement. PFMD seeks to include diverse stakeholders to ensure transparency, inclusiveness, diversity and credibility.

### 5.1.3 Patients and healthcare professionals

Healthcare professionals (doctors, nurses, pharmacists, etc.) address patient needs and concerns as part of their daily practice. Engaging patients in generating data including effectiveness and safety data can be facilitated by using a proven model. One such model is shared decision making (SDM): 'an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences'.[3] SDM places patients at the centre of different types of decision making, including decisions on diagnosis, treatment and follow-up. SDM is based on the ethical principles of transparency, accountability and integrity.[4,5]

### 5.1.4 Patients and patient organisations

The role of patient organisations (see section 2.1.1) is most developed in representing patient communities' views on specific issues; they have experience of navigating the research and regulatory environments, However, they also have opportunities to support greater engagement in medicines research, development and use. Some of the most important of these roles are briefly described below.

#### Capacity-building and networking

Many patient organisations train people in their communities and beyond to be patient advocates in regulatory affairs, pharmacovigilance, clinical research and other scientific topics, and more generally on medicine research and development and self-advocacy skills. These capacity-building activities can be undertaken at international, regional or more local levels. For details on training and education of patients for patient engagement activity, see section 3.4.2.

#### Peer support

Many patient organisations provide peer support to their communities, in the form of knowledge, shared experience, emotional, social, legal and practical help. Peer support is closely linked to capacity-building and educational initiatives.

#### Education and information

Several patient organisations – and individual patient advocates – disseminate up-to-date information to their members, for example by providing research results in a public-friendly, relevant and accessible way to their community. They also share information about opportunities to participate in research. Many engage in peer-to-peer education, for

example on self-management and coping with disease and treatments. Patient organisations can also be an important source of information to the general public on health-related issues.

## 5.2 Patient data and their use in post-authorisation environment

FDA and EMA have published guidance on how to use RWD for regulatory decision making.[1, 6–8] This section describes examples where patients' data is used in the post-authorisation environment.

### 5.2.1 Collecting patient data

There is not necessarily one single 'patient perspective' on questions relating to the collection and use of patients' data on the effectiveness and safety of medicines; views may differ depending on the patient group or between patient organisations representing disease groups, and consumer organisations (that also represent healthcare users). Patient organisations' perspectives on sharing and use of data have usually been developed in the context of research on diseases and the development of new therapies. The broad principles advanced by patient groups may be applied specifically to the use of data to improve safe and appropriate use of medicines, but there may be some questions that need further exploration. 'Ownership' of data and the compensation of patients for their contribution, for example, continue to be discussed.

At the same time, for patients the question of potentially sharing their routinely collected health data cannot be divorced from them being able to access their own data in the first place and contributing to it, which is still far from routine. Patient groups and advocates consulted by the European Patients' Forum have called for routine free access to an EHR and the development of interactive health records that enable patients to add information – including the effects of medicines or suspected adverse reactions.[9] Thus, supporting greater patient empowerment and collecting high-quality information on the real-life impacts of medicines go hand in hand.

#### Primary data collection and secondary use of patients' data

'Data' describes facts that can be used to make conclusions or decisions.[10] While it usually refers to numbers, data can also take the form of words, sounds, and images.

Patient data can be primary or secondary, structured or unstructured.

Primary data from patients is generated or obtained by asking questions either where they receive healthcare or in a setting not connected to medical treatment (*e.g.* online). Secondary data, on the other hand, is generated from patients as a consequence of their healthcare, for example, aggregated data from healthcare providers or insurers. It is called secondary data because the reason for collecting the data was the treatment of the patient, and therefore its use for research is secondary to that main purpose.

Both primary and secondary data can be structured or unstructured. Structured data use a pre-defined and expected format, usually referred to as rows, fields, cells, and tables.[11] The use of a predetermined data model makes entry, storage, and analysis more efficient. With unstructured data, there are no predefined fields or format.

Unstructured data are typically open field texts captured in some type of a form. Social media posts are a good example of unstructured data, and researchers must usually organise these data into a structure before analysing them.

### Post-authorisation safety studies

Post-authorisation safety studies (PASS) are conducted for approved medicines during their routine use in clinical practice. They aim to identify, characterise, or quantify a hazard associated with the medicine. PASS are often required by regulatory authorities, such as the FDA, who refer to them as post-authorisation requirements and the EMA, as a condition for the approval or continued marketing of medicines.[12] The number of these studies has been rising in recent years. EMA reported an increase of PASS protocol discussions from 46 in 2013 to 162 in 2017.[12]

Post-authorisation safety studies may collect data directly from patients (primary data collection) or use existing healthcare data recorded in a database (secondary data collection). The level and nature of patient participation differs between these approaches. Robust and sustained engagement with patients is essential for the success of a PASS involving primary data collection. However, it is typically very challenging to recruit and retain participants in these studies. One reason is that they do not offer a clinical incentive to patients to participate, such as access to medicines in development or additional clinical care.[13] Approaches to motivate patients need to be specific and different from those used in clinical trials.[13]

In a primary data collection PASS, the points of interaction between patients and study investigators offers opportunities for patient engagement and retention. For instance, patients are recruited to join the study, asked to give informed consent, provide data on themselves through direct questions and access to their medical data, and are requested to participate in the ongoing study possibly for several years.

### Post-authorisation efficacy studies

A post-authorisation efficacy study (PAES) is performed after marketing authorisation to address concerns about the efficacy of the medicine or when an efficacy evaluation might have to be modified significantly because of better understanding of the disease or improved clinical methodology.

In the EU, a PAES may be initiated and financed voluntarily by a sponsor. However, EMA guideline on good pharmacovigilance practice states that the regulator can require a PAES. The PAES can complement efficacy data available at the time of the initial authorisation and may be imposed during evaluation of the marketing authorisation application. It may also be imposed after approval in response to concerns about a medicine's real-world effectiveness.[14]

### Health economics and outcomes research

Health economics and outcomes research (HEOR) aims to help healthcare decision makers – such as clinicians, governments, payers, and patients – to compare treatment options and decide which are preferable. Treatments are evaluated on economic and clinical cost and benefits.[15]

Best practice calls for meaningful engagement of patients in the design and use of HEOR. Studies into which treatments lead to the best outcomes for patients can inform robust shared decision-making between patients and their healthcare providers. Recent consensus methods recommendations describe how patients' insights can be leveraged by researchers developing real-world evidence.[13]

Patients can provide their data to HEOR studies in similar ways to other real-world research, such as granting access to their healthcare records and participating in surveys. However, pathways unique to HEOR also exist, one of which is patient-reported outcomes

(PROs), which are the patient's direct reports of health and treatment outcomes. PROs must be free of a clinician's (or anyone else's) interpretation of the patient's response and typically pertain to patient's health, quality of life, or functional status.[16]

PROs systematically capture the patient perspective and provide a more holistic assessment of treatment effects. PROs can be used as either a primary or a secondary endpoint in a randomised clinical trial. They complement traditional outcomes, such as survival rates and biomarkers by reflecting aspects important to the patient regarding symptoms and quality of life. The consensus in this field is that active and sustained involvement of patients is fundamental to high quality and relevant research, which puts PROs at the forefront of patient-centric research.

A policy favouring patient engagement in HEOR is exemplified by the framework of patient and public involvement (PPI) in the United Kingdom's National Health Service (NHS). This initiative identified the benefits and barriers to patient involvement in research and the associated research governance activities, such as human research ethics committees.[17] The PPI report included a policy directive to involve patients and the public in the NHS research and development process, thereby promoting PROs and HEOR studies overall.

### Reporting adverse events

Reporting suspected adverse drug reactions (ADRs) is key for detecting harms of medicines. Some countries have allowed patients to report to the national spontaneous reporting systems for many years but it was in the early 2000s that countries started to actively include patients as reporters to spontaneous reporting systems.[18,19] With the change in the European pharmacovigilance legislation in 2012, patient reporting became mandatory throughout the EU. Elsewhere, the value of patients as reporters is recognised and more countries have opened their systems to patients; for instance, Japan introduced it in 2019.[20–22] Despite many countries allowing patient reporting, and in many instances encouraging it, the reporting rate and awareness are still low.[23,24]

Patient reporting has the advantages of bringing novel information, from the patients' perspective, on suspected ADRs. It provides more details of adverse events, and reports about different medicines and system-organ classes compared to reporting by healthcare providers. Patients describe the severity and impact of adverse events on daily living, complementing information from healthcare providers.[25,26]

There were doubts about the quality of the reports from patients.[27] A study of adverse events reported by patients and healthcare providers found that patients report clinical information at a similar level as their healthcare providers.[28] Studies have also shown that patient reports contribute to signal detection.[29,30] Signal detection is the identification of an association between a medicine and an unwanted event (but this may not necessarily mean that the medicine causes the event).

Signal detection's current focus on serious and rare spontaneous adverse event reports needs to shift to also include severe and frequent events which affect the patient's quality of life and daily functioning. To make the most of information from patients, the systems for collecting, coding and recording patient-reported information and the methods for signal detection and assessment warrant further development.[31]

The top priority for improvement is data collection from patients. It is important to optimise reporting forms so that they capture fully all the relevant information that patients can provide. To know what to include in a patient-specific form, one can draw on experience (what type of information have patients reported in free text in the old reporting form?) and consultation with one or more patient organisations.

Patients should be involved in drafting the questions and in the selection of the answer options (for closed questions) to ensure that the questions are unambiguous and easy to understand and answer.[31] Strides have been made to include online adverse-event reporting portals developed by manufacturers, use of artificial intelligence to assist with adverse event reporting case intake, as well as regulator-developed reporting websites such as the FDA Medwatch and the MHRA Yellow Card Scheme websites. However, there is still need for further improvement and innovation on how patients report suspected ADRs.

Reports of suspected ADRs are divided into serious and non-serious categories, using the CIOMS (Council for International Organizations of Medical Sciences) definition of seriousness. Serious reports are prioritised for investigation since they have the highest potential to harm the patient. However, with the introduction of patient reports, the division of reports based on seriousness may require re-thinking. The concept of 'seriousness' of an adverse drug reaction was introduced when primarily doctors were reporting. For patients, an adverse event might be of importance not only because of medical seriousness but also because of severity and the impact on quality of life. Healthcare providers may regard many adverse events as non-serious even though the effects may be intolerable and cause severe problems or have major impact on a patient's life: there might be a difference in the perceived importance of an adverse event between the medical community and patients.[32–34]

Patients can provide a rich narrative in their reports. These narratives are coded (using controlled vocabulary) by trained and experienced assessors supported by quality management systems and audit. However, such coding of patient narrative risks loss of information and misinterpretation.

### Risk management programmes

Additional risk minimisation activities or programmes might be required for selected medicines to ensure that their benefits outweigh their risks. Patients are not routinely or consistently involved in decisions on the most appropriate activities or in programme design and measurement of its effectiveness. However, patient input into programme design and checking its effectiveness is encouraged and can increase a programme's success. Support for this has been demonstrated by the EMA's Pharmacovigilance Risk Assessment Committee consulting patients during evaluation of safety concerns and at two public hearings (on valproate and fluoroquinolone medicines). The FDA has also committed to incorporating patient input into risk evaluation and mitigation strategies (REMS) programmes whenever possible (see section 8.4.2). The FDA has used patient feedback to support modifying REMS programmes.

Section 7.7 outlines approaches for obtaining this input. This information becomes a rich data source that can inform not only the structure of the program, but also details of how it is optimally implemented so as to increase uptake of the risk minimisation programme and adherence to it. This information can be re-visited, or further data obtained, if a programme requires modification or evaluation of the medicine's benefit-risk profile.

Having developed these programmes and activities, their effectiveness must be measured. Regulators in the US and Europe regularly call for more rigorous standards for assessing risk minimisation programmes,[35] and patient input should be used for evaluating the design when feasible. Storage of this data, and long-term data utilisation and of trending should be considered during initial phase of implementation.

This information represents a unique dataset of real-world evidence including patient-focused drug development data and patient-reported or patient-relevant outcomes, with a specific focus on risk minimisation activities. However, at this time there are no agreed

standards for its use.[36] Care should be given to planning how use of this data may assist in multiple activities (*i.e.* programmatic design and evaluation design), the long-term necessity of obtaining this data, and interactions with regulators on how to best include this data into regulatory submissions in support of these activities.

### Data from personal sensors and wearables

Wearable technologies – in the form of watches, bracelets, patches and garments – and software applications (apps) on mobile devices can measure movement and position, assessing physiological function such as heart rate and its electrical activity or other physiological properties such as body temperature and oxygen carriage in the blood. Moreover, wearable technologies can collect data as people go through their daily routines at home and work. Data from such continuous monitoring can be communicated instantaneously or intermittently to healthcare providers.

Use of wearable technologies can also provide objective measures of traditionally subjectively reported outcomes such as pain and fatigue, complementing or even replacing self-reporting.

Patients benefit from the convenience of avoiding interruption to their daily lives and fewer clinic visits; healthcare providers benefit from receiving the data reliably and in a planned way. The use of wearable technologies can therefore reduce costs to both parties.

There are also ethical and legal challenges with the use of data from wearable sensors. This category of challenges includes data ownership and sharing, consent requirements, privacy and security.[37]

Another challenge to the increased use of sensors for data collection from patients is the lack of regulatory guidance specifically on the implementation of wearables in clinical trial protocols and post-marketing surveillance. Uncertainty regarding the regulatory acceptability of data collected in this way – specifically in understanding what evidence should be available and considered when selecting a device for use in a clinical trial to ensure adequate precision, accuracy, and reliability of data collected and the nature of evidence required to demonstrate appropriateness and clinical relevance of endpoints derived from the data.[37, 38]

## 5.3 Challenges and opportunities for patient engagement in the development and use of real-world data

This section describes a few challenges and opportunities for patient engagement in development and use of RWD. Methods and processes of RWD collection and use are described in this chapter and in clinical and scientific literature.

Decision-makers (*e.g.* regulators and researchers) used to prefer engaging with 'naïve' or 'real' patients and were suspicious of the 'professional patient'. But it is now increasingly recognised that patient representation can take different forms and roles, depending on the objective. Various good practice guidelines have been developed, but they need to be embedded into practice.

Increasing demand for patient input can lead to a scarcity of patient advocates to take on various roles. This may be due to a lack of capacity (especially in roles that require in-depth scientific knowledge), inadequate compensation (as too many requesters still assume that patients will volunteer their time and expertise), or simply a lack of time since better known patient advocates and organisations can find themselves overwhelmed with requests.

The international patient community has diversified in recent years, with 'traditional' membership-based patient organisations being complemented, and occasionally challenged, by the emergence of new communities, often virtual. Patient advocates network with each other, often through online platforms, but are not necessarily formally affiliated with traditional patient organisations.

Communication technology and social media have played a major role in patient networking; thanks to them, patients can access more information more quickly than ever, and communicate rapidly with each other and with health professionals across borders. The 'e-patient' phenomenon is gradually spreading, advocating for a participatory model where patients are responsible drivers of their health, and full partners in care.

Patient organisations collaborate among themselves, but in many cases they do so on a multi-stakeholder basis. In fact, the strength of patient organisations is that the engage with all stakeholders in the medicines research and development and lifecycle: academia, industry, regulators, policy makers, and decision makers. However, such wide collaboration is sometimes seen as a drawback because it can lead to conflicts arising from mismatched goals and ambitions of the different organisations..

### 5.3.1 Informed consent

Informed consent is a fundamental patient's right and an ethical imperative in medicine. It is not simply about providing information: meaningful informed consent enables a person to make an 'enlightened decision'[37] about whether or not to participate in research. Given the increasing importance of secondary use of health data, informed consent in a research context should involve a full and frank discussion on data sharing, data protection and privacy, including to what extent it is possible to make the patient unidentifiable from the data, and what future-proof protection can be offered given the rapid increase in the capacity to store, link and analyse health data from different sources. Advance directives for secondary use of data should also be explored.[37,39]

Generally, the European Patients' Forum has called for mechanisms for clear and understandable informed consent for individuals to share control of their data so as to facilitate effective and ethical data use for research that also reassures patients that their rights are respected; for example, this can be achieved by developing dynamic consent models in compliance with the EU General Data Protection Regulation (GDPR).[38,40]

A summary of EMA's consultation on data protection noted that the European Patients' Forum called for a reflection on 'broad consent': [37]

> Patients may be happy to grant blanket permission for use of their data in specific types of research or they may wish to opt out of specific types of research. The parameters of broad consent should therefore be flexible to consider individual patients' preferences and values.

### 5.3.2 Patient privacy

Health systems across the world are expanding their services and technology to deliver healthcare reliably. Maintaining privacy of patient information is fundamental in the era of health information technology. A comprehensive understanding of the factors that influence privacy is an ongoing necessity; this means overcoming the challenges at all levels including legislation, technology, patients' and healthcare providers' needs, and the capacity of health institutions.

Privacy is defined as 'the ability of an individual or group to stop information about themselves from becoming known to people other than those they choose to give the

information to'.[41] Major concerns with data privacy are how data is collected, shared and used; data security is the protection of data from external and internal fraud and theft to guard privacy. Balancing privacy and security on the one hand and data utilisation on the other is challenging. Ensuring privacy at all levels while collecting, entering, storing, processing, and sharing and using data is also a challenge. Data privacy is a growing concern for regulators, researchers, health service providers, pharmaceutical companies, IT programmers, payers, consumers and patients themselves.

Threats and attacks at any step in data handling can compromise data privacy. In fact, patients may have concerns that breach of their private health data can affect their employment and social status. However, patients may disclose their own health information when there is an advantage like, for example disclosure of information to insurance companies.[42]

Data privacy legislation has been in place in many countries to control and organise privacy-related issues. In the EU, the General Data Protection Regulation (GDPR) aims to safeguard personal data by giving European individuals the right to request and delete their data. In the US, the Health Insurance Portability and Accountability Act (HIPAA) is the data protection and privacy law that gives individuals the right to access their health records and control how their information is used and disclosed. However, companies have the challenge of responding to individual access requests and specifically to locating, providing and deleting personal data on the individual's request.

The use of emerging technologies to recruit patients for clinical trials without healthcare professionals' intervention poses a challenge to ethical committees about the requirements of informed consent; respecting the patient's interest on data protection and medicine safety monitoring when sharing clinical trials data with third party researchers is another challenge.[43,44]

Increasingly, healthcare providers and patients are shifting to mobile devices to easily and effectively communicate varied health information including photographs and images. However, this can endanger patient privacy and increase healthcare providers' risk;[45] preserving healthcare providers' privacy is as important as maintaining patient privacy. While the need to protect privacy is receiving increasing attention, there is a long lag in deploying necessary measures when using digital technology to deliver healthcare.[46]

Additionally, technology advances offer new applications like e-health, m-health, and telemedicine. These applications, which use 'internet of things' connect many people, devices and services; consequently, security is pivotal and should cover all aspects of their operation.[47,48]

Finally, it is more efficient to combine all social, technology and legal efforts together to reduce the privacy threats.[49]

### 5.3.3 Data ownership or control

While patients are largely in favour of sharing their data, they still wish to keep control of the data-sharing process. Respondents to the EURORDIS survey were overwhelmingly in favour of having the strictest control on their data.

The European Patients' Forum, too, has expressed this view. It states in its 2020 response to the European Commission's data strategy:

> Patients must be in control of their data. They should be able to freely access it, decide who to share it with, and on what conditions … It should be possible for those individuals who wish to do so, to give wider access to the data held about them (*e.g.* through so-called data altruism or

data donation), as long as the implications of doing so are fully transparent and clear. Patients want to know and have some control over what purposes their data is used for and track its use when possible, and they often want to know about the results of research using their data.

The European Patients' Forum also asks for more clarity and harmonisation on data ownership at European level.

Patient organisations have often referred to patients 'owning' their data. This has not always been intended in a legal sense; the legal implications of terminology are still being discussed (for example in relation to GDPR). The intention is to ensure that patients are considered owners of their data in a moral sense, regardless of the legal framework. They should thus have a right to participate in decisions about what happens with their data, including governance and policy making.

### 5.3.4 Patient engagement

Understanding what patients want from research and the benefits they expect from sharing their data is important to ensure meaningful patient engagement. Researchers should integrate patients' perspectives in the design of the research and align research questions with the needs and priorities of patients. Governance frameworks for health data sharing and other related activities, such as ethical review, should include patient representatives.

Engaging patients in the development and use of effectiveness and safety data is complex. It involves ensuring that patients possess the relevant knowledge, have the opportunity to engage, are allowed to engage (*i.e.* have a seat at the table), know how to engage, and have the confidence to do so.[50] Factors that influence patient engagement include personal capacity, experiential knowledge, beliefs and behaviours, relationships and meaning of safety.[51] The latter factor is specifically important, when engaging in patient safety. The impact of health consumers' literacy on their engagement in shared decision making (SDM) was studied in Australia by using a literacy training programme that includes introduction to decision making, engaging, and self-efficacy to participate in it. The study concluded that participants improved their skills of health literacy and recall of SDM questions after taking specific training.[52]

See also section 8.2.2 on collecting patient experience data in the context of minimising risks from medicines.

The SHARE and MAGIC (making good decisions in collaboration) are two approaches developed to increase patients' capacity for SDM in medical decisions. SHARE, developed by US Agency for Healthcare Research and Quality, helps clinicians work with patients to make the best possible healthcare decisions; while MAGIC, a programme from the Health Foundation in the UK helped to embed best practice in SDM.[53]

Implementing these approaches could facilitate and promote patient engagement in generating and using effectiveness and safety data. However, the approaches require teaching SDM skills and attitudes to both healthcare professionals and patients. The development of specific tools and decision-making support at the health facility level is also a prerequisite. Other factors that affect patient involvement are clarity on the rationale for patient engagement, identifying the correct model to achieve the desired outcomes, clear roles and responsibilities for patients, and a meaningful engagement.[54] These approaches have been slowly implemented by some countries like Canada, the UK, and the US. Other countries need to take these approaches forward.

### 5.3.5 Patient voice in regulatory advances

Patients' enthusiasm for involvement is important but it must be combined with dispassionate, scientific understanding of regulatory paradigms. The patient voice can and must evolve to increase impact on regulatory decision making. See section 4.8.2 for patient involvement at key milestones during medicine regulation.

From the patient's perspective, the information revolution needs to shift from generating data to figuring out the meaning and purpose of the data. Nowhere is this more pertinent than for the patient voice and its impact on real world evidence (patient-relevant outcomes data and quality of life data), personalised medicine and the role of clinical trial design and subject recruitment.

Individuals and groups may not be trained in data analysis. Transparency policies at the US National Institutes of Health, FDA, and other agencies may guarantee access to data and analyses, but do not necessarily equip all stakeholders to review studies in a meaningful way.

As with any ecosystem, the component parts of drug development and review are not necessarily equal to each other, but they are all requirements for success. The patient voice must fight for equal respect and a recognition of mutual value to both parties: the developer and the patient. It is not a question of 'equal' but of 'integral'.

#### The patient voice at the intersection of a US regulatory revolution

It is predicted that the information revolution will shift from the generation of data to figuring out the meaning and purpose of the data with the patient's perspective in mind. Nowhere is this more pertinent than in the discussion of the future of the patient voice and its impact on real world evidence [patient outcomes data, quality-of-life (QoL) data (specifically in the development of patient-referenced clinical endpoints), personalised medicine and the role of clinical trial design and subject recruitment.

According to a recent white paper from the Network for Excellence in Health Innovation (NEHI), individuals and groups who are not trained in data analysis face a different challenge. Transparency policies at the NIH, FDA, and other agencies may guarantee access to data and analyses, but do not necessarily equip all stakeholders to review studies in a meaningful way.

The advancement of healthcare technologies and the tools and techniques of modern regulatory science depends on willingness and ability to implement new approaches based on infrastructure, capabilities, and trust between stakeholders. The end goal is the same for all: ensuring optimal use of resources for healthcare systems; improving access to value-adding medicines for patients; and appropriate reward for innovation.

A recent draft guidance for industry, *Benefit-risk assessment for new drug and biological products*, states that 'patient experience data can help inform critical aspects of a drug development program, and benefit-risk assessment more broadly'.[55]

*Identifying the benefits and risks of emerging treatments for idiopathic pulmonary fibrosis: a qualitative study*,[56] identifies multiple issues spanning the impact of emerging therapies, including the need to document the patient experience with treatment, and factors associated with disease progression and the value of qualitative research both in understanding the benefits and risks of emerging therapies and in promoting patient-centred drug development.

When combined with data and a more dispassionate understanding of regulatory paradigms, a patient-driven pathway can, and must, evolve into a tool used to impact both drug development and regulatory decision-making.

### 5.3.6 Patient engagement with healthcare providers

In China, the views of cancer patients, doctors and nurses on patient involvement in symptom management was studied in two oncology medical units. They found that despite concerns that patients had limited knowledge and ability to negotiate their treatment options, all parties recognised that information exchange is key to patient involvement; it can enhance care through different activities namely: information exchange, negotiated decision making, and self-management.[57]

Reducing the number of medicines or their doses especially if more than five medicines are used regularly (polypharmacy) is another area of patient engagement. Shared decision making, particularly in older patients, could be fruitful when taking into account patients' willingness and preferences. This is a systematic process that includes the following steps:[58]

- creating awareness that options exist,
- discussing the options and their benefits and harms,
- exploring patient preferences for the different options, and
- making the decision, bearing in mind this should be a continuous process.

Managing medicines problems, including errors, is another aspect were patients could participate with a very positive outcome; patients were able to develop their own strategies to reduce the risk of medicines errors even when care was transferred from one health organisation to another.[59] Patients can also play a major role in preventing medication errors and preventable adverse events; a review found that cancer patients were vigilant in detecting errors relating to the giving of chemotherapy and strategies were identified to increase patient involvement in medication safety.[60]

### 5.3.7 Patients and researchers

Patient engagement in academic and governmental research can take place on different levels. The first level is in setting the research agenda. Traditionally, researchers and funding agencies set research agendas, but patients are increasingly involved in this process. There are different methods to engage patients.[61] In the UK, the James Lind Alliance has proposed methods to engage patients, carers and clinicians in dialogue about uncertainties in medical treatment and in the Netherlands the Dialogue Model has been extensively used.[61]

The second level of patient involvement – the design of the study – is crucial for identifying the questions to ask and the outcomes to assess; therefore, it is increasingly common to involve patients or patient advocacy groups on study design.[62]

In the execution of the study, patients can be involved either in the organisational phase, where they contribute to the development of materials and tools suitable for the target group, or in the recruitment of study participants. In this phase, patients are also involved as study subjects, being the ones providing data to the study.

Several studies reported that engaging patients in research improves patient enrolment and decrease attrition.

See section 4.4 for further information on patient engagement in clinical development.

### 5.3.8 Vulnerable populations

Vulnerable populations are groups or communities at a higher risk for poor health because of the barriers they experience to social, economic, political and environmental resources, as well as limitations due to illness or disability (see also section 3.1.2). Typically, these

groups include racial and ethnic minorities, the economically disadvantaged, and those with chronic health conditions. Vulnerability poses a major challenge in scientific research especially to clinical researchers, regulators, ethics committees and other parties interested in trying to better accommodate the needs of this population.

To increase patient engagement, it is important to think about how vulnerable people can be included since their possibility to engage might be different.

### 5.3.9 Social media

The ability of patients, caregivers and patient organisations to influence the development and regulatory review of medicines has increased exponentially. Nothing more than the rise of social media has helped to alter and augment patient participation in generating and utilising data on effectiveness and safety. But the benefit of healthcare technologies must be weighed against the realities of risk.

In any discussion of social media and healthcare, the sharing of scientific information should be distinguished from opinion and commercial communications. What is the intent of the interaction? Is it to advance the standard of care? Offer solace to desperately ill patients? Create a broader and more immediate sense of community across towns, nations and continents? Or assist in sales and marketing programmes? To further complicate matters, none of these opportunities are mutually exclusive. Just because a social media platform is facilitated by a commercial enterprise (such as a pharmaceutical company) does not mean it is without value to patient health or scientific advancement.

Social media presents the opportunity for collecting as well as sharing important real-world insights and data on post-authorisation surveillance. While the sheer vastness of the digital universe threatens to create a tsunami of adverse event reports (and make it difficult to identify a signal among the noise), it is also an important new tool to help advance pharmacovigilance.

Another crucial issue is the reliability of information (irrespective of intent or origin) on social media platforms. Mark Twain's warning is apt: 'Be careful about reading health books. You may die of a misprint'.

While social media often lends itself to false promises, hyperbole and errors, perhaps its most dangerous consequences are driven by purposeful manipulation; unsubstantiated claims of cancer cures, sales of counterfeit medicines, unproven uses of existing medicines, etc. abound. To help identify and mitigate against such malevolent uses of social media output, patients, patient organisations, healthcare providers, responsible commercial entities, regulatory authorities and the social media platforms themselves must be vigilant in their oversight of both content and context.

Social media facilitates the rapid sharing of healthcare communications. So, while we must embrace the potential for social media to advance and amplify the patient voice, we must also be wary of irrational exuberance. This is and will continue to be an evolutionary undertaking as social media expands and increases its influence within the healthcare ecosystem.

### 5.3.10 Health literacy and user-friendly interfaces

In an increasingly digital world, health literacy – including digital and data literacy – is important for health inclusivity, equity and avoiding exacerbations of the digital divide. Health literacy builds on clear, understandable information – in the context of data sharing, on why data is collected and how it is to be used – especially in secondary use involving

third-party organisations. In turn, transparency is the cornerstone of accountability to and trust from patients and citizens.

The development of easy-to-use and understandable data applications and products is important to enable meaningful engagement. Simple and usable interfaces and data collection platforms can bridge health literacy gaps, increase trust levels, and enable people with low health literacy to participate. This requires an inclusive process for developing solutions for health data that are co-designed with patients. Patients have expressed wishes, for example, for interactive tools that enable them to receive updates on their medicines in real time but also to be able to give feedback themselves, for example on symptoms or suspected ADRs (see section 5.3.1).[63]

## 5.4 Conclusion

This chapter has attempted to explain and discuss some of the most important aspects required to advance the impact of patient engagement in the development and use of medicines effectiveness and safety data.

As with any ecosystem, the component parts of global healthcare systems are not necessarily equal, but they are all requirements for success. The patient voice must be recognised as integral to the advancement of new cures and treatments. This requires that all ethical, patient consent, scientific and public health processes involve patients and adhere to robust methodologies and responsible peer review in order to avoid decisions that could bring about dangerous public health consequences.

Patients' experiences and perspectives regarding their disease and treatment options are important to assess and understand. When combined with other data sources (*e.g.* clinical trial results), a patient-driven pathway can effectively impact regulatory decision-making.

Communication that is jointly developed with patient partners, and which is timely, reliable and factual, must be disseminated in plain language. Patients are already organising in such a way as to exchange experiences regarding their own disease situations. Enhancing the value of the patient voice is an opportunity for researchers (who are also patients!) to apply methodologies to the exchange of information. There is important information and context to be communicated through the experiences and perspectives of both patients and caregivers.

According to the FDA: [64]

> Creating knowledge requires the application of proven analytical methods and techniques to biomedical data in order to produce reliable conclusions (…) There must be a common approach to how data is presented, reported and analysed and strict methods for ensuring patient privacy and data security(…) Rules of engagement must be transparent and developed through a process that builds consensus across the relevant ecosystem and its stakeholders (…) To ensure support across a diverse ecosystem that often includes competing priorities and incentives, the system's output must be intended for the public good and be readily accessible to all stakeholders.

There is considerable potential in patient-patient networking driving forward issues that matter to the patient community. Patient organisations are seen as legitimate stakeholders and representing the patient perspective; sometimes they are challenged by emerging individual advocates and networks. Challenges remain in terms of establishing new ways of working in partnership between all stakeholders, changing cultural norms, and ultimately embedding patient involvement as 'the normal' way of doing things.

# Chapter 5 – Annex 1: Real-world data uses

## A. Expanded access programmes and compassionate use programmes

Not all patients have access to clinical trials for clinical, logistic, practical, or other reasons. For seriously ill patients who cannot participate in a clinical study and who have no other satisfactory treatment option, access to an investigational product outside a clinical trial may be considered. Expanded access (alternatively termed 'compassionate use', 'preapproval access', 'early access' or 'special access') programmes have been developed to provide access to investigational or unlicensed medicines to such patients.[65] These programmes are a source of real-world data.

National legislation governs the expanded access process in each country.[66] Expanded access can be at the initiative of the company, the patient's doctor or both. For example, the European Medicines Agency has described how programmes may be created in the European Union (EU).[67] However, each EU country is responsible for regulating, co-ordinating and implementing its own expanded access programme including those for individual patients on a named basis; access is arranged through the patient's doctor, the product manufacturer and the regulatory authority.[68]

In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for the early access to medicine scheme (EAMS), a three-step process (MHRA, 2014) (MHRA 2018).[69]

In the US, the FDA has defined three variations of the expanded access programme: one each for widespread treatment, for 'intermediate-size' patient group, and for the individual patient (21 C.F.R. §312 Subpart I), including those for emergency use, designed to address doctor requests on behalf of their individual patients.[70,71]

Japan has its own system for clinical trials conducted from a compassionate viewpoint (expanded access trial) which has been in place since January 2016 under the Enforcement of Ministerial Ordinance to Partially Revise the Ministerial Ordinance on Good Clinical Practice for Drugs (GCP Ordinance) (PHSEB Notification No. 0122-2 by the Director of Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated January 22, 2016).

In India, according to the Drugs and Cosmetic Act 1940 and Rules 1945, the Drug Controller General of India (DCGI) provides oversight of use of an unapproved drug by a patient (Rule 36) or by a hospital or institution (Rule 34).[72]

Codified guidance for expanded access in certain countries such as China does not appear to be readily available. It is very important to consult the relevant national regulatory authority before proceeding with expanded access in order to understand specific requirements and regulations. The regulatory requirements can vary greatly for the generation, interpretation, and application of effectiveness and safety data. Also, not all national regulatory authorities use data from preapproval access programmes in the same way to make their marketing authorisation decisions.

## B. National and international health surveys

Many countries monitor the health of their populations through national surveys at regular intervals. Treatment of disease is a common topic in these surveys, which therefore, give patients an opportunity to provide information on drug treatments, including in some cases, their effectiveness and safety.

In the US, the National Health and Nutrition Examination Survey (NHANES) has been conducted since 1960, with the most recent in 2019–2020.[73] NHANES is unique in that it collects data from patients using three distinct approaches: by direct interview; from in-person clinical tests, measurements and physical examinations; and from places where persons received medical care, such as hospitals, clinics, and doctors' offices. The findings from NHANES are used by government agencies, state and

community organisations, private researchers, consumer groups, companies, and healthcare providers. NHANES data were used to identify trends in the use of selected medicines.[74]

The National Health and Wellness Survey (NHWS) is an annual population-based survey of patients dating back to 1998 in the US, 2000 in Europe and 2008 in Asia.[75] Countries included in the NHWS are Brazil, China, France, Germany, Italy, Japan, Russia, Spain, UK, and US. The NHWS contains patient-reported information which provides insights on more than 200 conditions on patients formally diagnosed but also on those, undiagnosed yet symptomatic, on patients untreated, and on those who use prescription and over-the-counter medicines.

### C. Online patient-centred initiatives

Patient-centred initiatives (PCIs) are relatively new; they create opportunities for patients to provide data on themselves for research purposes.[76] PCIs usually establish an online community through social media, which then becomes the foundation of a long-term, interactive, research relationship. Two well-known examples of PCIs are PatientsLikeMe[77] and 23andWe.[78]

PatientsLikeMe enables individuals to share health information and create online communities, while 23andWe is the research arm of 23andMe, an online, direct-to-consumer, genetic testing service. Both platforms give their customers the opportunity to contribute their data to research studies on an ongoing basis. PCIs vary in the services they provide and in their approach to patient research, but they share several common features shown below.[76]

- Placing participants in control
  - Participants in Genomes Unzipped have set up their own website, making their genome sequence publicly available.
- Using social media technology
  - In the EnCoRe 'Dynamic Consent' prototype, individuals can express and change their choices, track and audit changes, and choose when and how they are contacted for secondary research purposes. The use of 'sticky policies', or machine-readable disclosure policies that attach to data, means that these preferences can travel with their samples.
  - The Indivo[79] interface was developed by the Boston Children's Hospital Informatics Program to give participants control over access through a web-based medical record.
  - In the case of PrivateAccess, which facilitates clinical trial recruitment, a web interface allows registered users to grant access individually to their personal information by specific people or groups and under specific circumstances or conditions.
- Promoting active participation
  - As a part of a reciprocal partnership, individuals who contribute clinical information or take part in surveys receive information on their own health status. This approach is taken by the following: CuraRata, CHRIS, 23andMe, Indivo and PatientsLikeMe.
  - The CuraRata model for personalized medicine facilitates patient-tailored, prevention-orientated treatment by integrating individual care in a research setting. Therefore, in exchange for the storage of anonymous medical data and the collection of biomaterials, an infrastructure is created for each patient, who receives regular feedback on data outcomes and analysis.
  - This is also the basis for 23andWe, which encourages participation in a research project that is open-ended, using online surveys and then feeding this knowledge back to customers.
  - In the EnCoRe Dynamic Consent model, participants are informed as to how their samples and information are used in research, and they can also monitor this use.

- Facilitating communication
  - In the TuAnalyze partnership, information sharing and self-management of disease is encouraged through enhanced conversations via online forums, blogposts and members' profile pages.
  - During the signing up process for PrivateAccess, it is possible for aspiring members to choose a more experienced patient advocate to guide them in the setting up of their privacy preferences. The website also includes videos to facilitate registration and membership uptake.
  - In the EnCoRe Dynamic Consent model, plans are underway to integrate video clips about biobanking users' own stories.
- Appealing to public goods
  - Genomes Unzipped seeks to promote open-access science to encourage constructive public discussion on the benefits of genetic technologies and to dispel fears about potential risks.
  - The philosophy underpinning TuAnalyze is to encourage individuals to share their clinical results with the aim of improving clinical outcomes.
  - Private Access is aimed at accelerating research findings by improving recruitment to clinical trials, thereby reducing costs.

Nearly all PCIs included above collect information on medicine use and have published research studies on medicine effects.[80,81]

### D. Patient preference studies

A type of patient surveys is patient preference studies (PPS), which assess the patient's view on the benefit-risk balance of medical treatments (see also section 4.7). Patients are recruited and asked about the 'relative desirability or acceptability of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions'.[82] Insights from PPS include: what attributes are important to patients, how important they are, and what trade-offs patients are willing to make between attributes. Patient preference studies have also been referred to as health preference assessment, stated-preference health survey, health preference research, and broadly described as patient-centred research in other sources of scientific literature.[82]

PPS are increasingly being used by regulatory authorities in their benefit-risk assessment of new medicines submitted for approval. PPS provide regulatory decision makers a measure of patients' willingness to accept identified risks associated with medicines. PPS can also be used for product development decisions by industry, reimbursement decisions by health technology assessment bodies, and shared medical decision making by doctors and patients. They can be used throughout the medicine's life, from early development decisions through pharmacovigilance activities and post-marketing decisions.[83]

Well-designed PPS are the natural evolution of patient testimony to decision-makers. The science of survey design can be leveraged to represent the broad range of preferences across a patient population. Thus, the patient voice is 'translated' into scientific data, so bringing patient input into the decision-making process.

### E. Qualitative studies

Public and private health systems and their stakeholders are increasingly accountable for the value of their decisions, products and services to individual patients and society at large. But the emergence of value-based health care is hindered by a lack of transparent and standardised outcome data. We are beginning to see a shift from the generation of data to figuring out the meaning and purpose of the data from the patient's perspective. Over the years, health economists

have developed sophisticated tools and techniques to measure costs. However, the numerator — patient outcomes — remains ill-defined and unevenly measured.

Measurement of the actual therapeutic outcomes of treatment was first proposed over a century ago by Dr Ernest Amory Codman, known for advocating the 'end result idea'.[84] The 'idea' was simply that hospital staff would follow every patient long enough to determine whether or not their treatment was successful, then learn from any failures and how to avoid those in the future.

More recently, the US Department of Health and Human Services (HHS) has created an online portal that discloses, for each hospital, indicators such as readmissions rates, complications and mortality, payment and value of care. HHS inpatient prospective payment system rule contains proposals to advance a healthcare system that pays for value, as well as a request for information on future value-based reforms. This rule is designed to 'disrupt our existing system and deliver real value for health care consumers. … We are going to move toward a system that provides better care for Americans at a lower cost'.[85]

Measuring patient-reported outcome measures (PROMs) requires complex case mix adjustments. It is much easier to measure traditional items such as volume of care, average length of stay, compliance to administrative procedures – and ignore patient outcomes. With the myriad of unvalidated proxy indicators that health systems use to define quality, we lose the ability to accurately define 'success'.

Patient-reported experience measures (PREMs), for example, assess a patient's satisfaction during hospitalisation. Indicators often measure the quality of food, cleanliness of the room, procedures for discharge, communication with the medical team and various waiting times during hospitalisation.

Are higher PREM scores valid predictors of better PROMs? While there is certainly a link between hospitalisation and hospitality, hospitals are not hotels. While a guest may choose to return to a good hotel, a good hospital is largely indicated by not having to come back. PREMs measure outputs that matter to hospital administrators. PROMs measure healthcare outcomes that matter to patients and healthcare providers. Not surprisingly, patient response rates to PREM surveys are on average less than 20% compared to 90% for PROM questionnaires.

The goal of value-based healthcare is to facilitate making 'outcomes' the defining variable in the multifaceted decision-making process, superseding both cost and quality. In that respect, value-based healthcare becomes '21st-century tendering' for both payers and patients, and when evaluated with quality, it allows assessment of '3D quality'. It advances 'quality' from a 'soft' to a 'hard' measurement tool.

PROM registries are complex to design and execute but represent a transformative investment that can change medical behaviours, enable patients to orient themselves to the most appropriate practitioner and sites of care, and generate savings for public and private payers. Patients and payers will prefer providers who disclose their outcomes. Those who do not subscribe to outcome-based measurements will be viewed with suspicion or derision – or both.

It is also important to consider the role of quality-of-life (QoL) data. QoL measures have become a vital part of health outcomes appraisal. For people with chronic disease, measuring QoL provides a meaningful way to determine the impact of healthcare when cure is not possible. Over the past 20 years, hundreds of instruments have been developed that purport to measure QoL. With few exceptions, these instruments measure causal indicators of QoL rather than QoL itself. QoL implies value based on subjective functioning in comparison with personal expectations and is defined by subjective experiences, states and perceptions.

The future is becoming increasingly clear. Value-based health care turns concepts such as 'value' and 'quality' into hard data. It is time to adopt the same language to measure success in healthcare with indicators that truly matter to patients. Value-based healthcare isn't about harmonising decision

making; it's about harmonising design and process. 'Value' should be a constant, and policy makers should make decisions based on constants — but decisions can be different based on different national needs, priorities and biases.

### F. Industry medical information systems

Nearly all sponsors of medicines maintain systems for patients seeking information on the company's product. Companies respond to patients' medical information requests by using telephone systems, internet sites, and face-to-face interactions. Patients often seek information for reassurance that they are receiving the best treatment, to improve their compliance or recognise potential adverse or other reportable events.

In many regions, industry is mandated to provide accurate and balanced information on their products in accordance with the product label. The flow of information to patients must enable the safe and appropriate use of medicines. The flow of information from patients is also very valuable for the industry to understand patients' concerns in an aggregate manner. Insights into patient enquiry trends give medicine developers a better understanding of their medicines and can identify gaps that can be acted upon to improve patient outcomes. It is likely that patients underuse this communication channel and do not fully appreciate how their queries can lead to medicine improvements and better guidance on their use.

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# Chapter 6: Product labelling

In this chapter we discuss product labelling, which includes information given to patients with medicines.

**Key points**

1. Most regulatory authorities require some form of information for patients ('patient labelling') – the most common type is a patient information leaflet (PIL).
2. There have been many attempts to improve the quality of information for patients.
3. We propose criteria for guiding the development of high-quality patient labelling.
4. We also propose principles for engaging patients in developing and evaluating patient labelling.
5. All regulatory authorities should aim for a requirement to provide patient labelling – and they should involve patients effectively in designing and evaluating this information.

## 6.1 Summary

Product labelling for patients ('patient labelling') is a comparatively recent phenomenon globally. Although there are many different ways for patients to obtain information on medicines, the accuracy of such sources varies widely. Patient labelling materials are not only accurate and reliable, but comprehensive, accessible and are kept updated in response to new information regarding the medicine's benefit-risk profile.

Many regulatory authorities stipulate some form of patient labelling. Of those that require it, the most common type is the patient information leaflet (PIL). Over the past two decades, a range of initiatives have been launched worldwide to improve the quality of patient labelling.

This chapter puts forward criteria for high-quality patient-centred patient labelling, and principles for engaging patients in the development of such labelling. The chapter concludes with a discussion of future directions for developing patient labelling including recognition for the need for patient labelling globally, electronic patient labelling, and the importance of establishing regulatory standards for patient involvement in the development of such labelling. Lastly, guidelines are needed regarding the design of patient labelling materials that involve multi-media tools, and metrics to assess the quality of patient labelling.

## 6.2 Introduction

This chapter focusses on patient engagement in the development of patient product labelling ('patient labelling'). Product labelling is intended for healthcare professionals. It represents the official 'source of truth' concerning all clinically relevant medicine information (*e.g.* indication, posology, benefits, warnings, contraindications and side effects) regarding a medicinal product. Patient product labelling is based on the product label and, as its name suggests, is intended for patients, informal caregivers, and other consumers. Marketing authorisation holders ('sponsors') are required to develop product labelling (including patient labelling) and submit it to the regulatory authority for review and approval as part of the marketing authorisation application. They are also required to ensure that both the content of the product labelling and the patient product labelling are

kept updated and consistent with each other as long as the product is on the market and as relevant new information emerges regarding the product.

Patient product labelling is a relatively recent phenomenon. Until patient labelling was introduced, patients relied heavily, if not exclusively, on counselling mainly from doctors, nurses and pharmacists about the uses and risks of their medicines. The 1938 US Federal Food, Drug and Cosmetic Act stipulated that medicine labelling information should 'appear only in such medical terms as are not likely to be understood by the ordinary individual'.[1] It was not until 1970, in light of the risk of venous thrombosis associated with hormonal contraceptives, that the FDA mandated the development of a Patient Package Insert (PPI), a safety communication for patients.[2]

In western Europe requirements for product labelling, including Package leaflets (PLs), date back to the thalidomide birth defects tragedy in the 1960s.[3] However, it was not until 1992 that further legislation led to the development of patient labelling with an implementation deadline of 1999 for all medicinal products in the EU.[4] In 2005, an additional requirement, that of readability testing for the patient label, was added.[5] The latest standards are legally defined [5,6] and underpinned by revised guidance.[7]

Health Canada's 1989 Product Monograph (PM) Guidance Document first introduced a section on 'Information for the Consumer' to encourage manufacturers to prepare medicine information reviewed by Health Canada (based on data provided for safety, efficacy and quality) so that it could be supplied to healthcare professionals (HCPs) and patients with their prescription medicines. This requirement was updated in 2004 as the PM Consumer Information and again as part of the 2014/2016/2020 PM as the 'Patient Medication Information' (PMI) section.[8–10] The revamping of the PM Guidance Document for 2004/2014 involved extensive consultation, including with patient advocacy groups, and in a number of workshops.

As these developments unfolded, a larger shift was occurring in the broader healthcare environment, one that emphasised a more patient-centred approach to medical care. This changing perspective was evident in such developments as the emergence of the 'medical home' care delivery model, the adoption of plain language principles in developing patient-facing written materials, and the growing ascendency of informed choice and shared decision-making between patients and their doctors, including the acceptance of patients' right to choose a therapeutic option other than that recommended by their physicians.[11,12]

Collectively, these trends have helped to transform patient's role in healthcare from that of a passive recipient to a more active partnership. Within the pharmaceutical sector, patient involvement is now recognised as important in informing regulatory decision -making as well as in many aspects of product design and lifecycle management, including the development of patient labelling and other patient-targeted medicinal benefit-risk communication.[13–17]

### Communicating to patients on risks of medicines and safe and appropriate use

What is the purpose of communicating information on the risks, and the safe and appropriate use of medicines to patients? Communication scientists identify the following main goals:[18]

1. to share information to aid informed decision making;
2. to provide instructions on how to use a medicinal product safely and effectively;
3. to influence beliefs about the importance of using a product safely and appropriately; and
4. to encourage behaviour that promotes safe and appropriate use of the medicine.

Providing such information does not necessarily mean that patients will understand it and act on it.[18] In order to change knowledge and influence beliefs and actions on medicine risks, and their safe and appropriate use, the patient must first understand the information.[18] Educating patients is a necessary pre-condition for engaging in informed decision-making about treatment options. It is also a precursor for action, the third goal of risk communication.[19]

Risk communication aimed at getting patients to take specific actions is relevant when the evidence clearly supports the value of a particular course of action.[18] For example, the medication guide for an osteoporosis medicine tells patients to take calcium and vitamin D to minimise the risk of developing hypocalcaemia, a possible side effect of the medicine.[20] Another example concerns the use of a malaria prophylaxis drug, doxycycline, which increases skin sensitivity to sunlight. Patients taking doxycycline must apply sunblock daily and avoid direct sunlight between 10 am and 3 pm.[21]

## 6.3 Sources of medicinal product risk and safe use information for patients

### 6.3.1 Product labelling

The main and, arguably, the most accurate source of medicine risk communication to patients is the regulator-approved product labelling. Product labelling includes the packaging (*e.g.* messaging on outside and inside of the carton) as well as printed information on the medicine's uses and risks, distributed with the medicine at the time of dispensing. Warnings, in the form of graphical and textual messages, are used in the label to highlight specific risks or contraindications associated with product use.

The FDA requires severe, life-threatening risks associated with a medicine to be shown as a boxed warning, which is prominently displayed at the top of the label. For example, isotretinoin medicines carry a black-box warning on the risk of birth defects due to the product's teratogenic effects.

In Australia and Europe, the 'black-triangle' scheme identifies new drugs.[22,23] Under this programme, a black triangle symbol, along with explanatory text, is included in the product information and consumer medicine information to encourage healthcare professionals and patients to report adverse events and thus build up knowledge on the medicine's safety profile. The black triangle symbol is also included in the Australian public assessment reports for prescription medicines (AusPARs), and efforts are underway to include the symbol in other sources of medicine information.

Marketing authorisation holders (MAHs) are responsible for developing product labelling, including patient labelling. Companies develop product labelling as part of the application submission for marketing authorisation. The product labelling is reviewed and approved by the regulatory agency.

Jurisdictional limitations in some countries and regions can influence the communication of labelling information. For example, in Canada there are divisions of regulatory authority between the federal, provincial and territorial governments. The federal government has a role of reviewing and approving accurate Patient Medication Information whereas Canada's provinces/territories have the authority to specify whether there is need for patient counselling and how labelling approved by Health Canada should be disseminated by pharmacists and other healthcare professionals. This division of powers can pose challenges for timely dissemination of approved labelling to consumers, patients or end-users, particularly if pharmacy systems are not synchronised with the Drug Product

Database (where the approved labels are stored), as third-party information cannot be shared unless it reflects the approved labelling. To address this concern, the Plain Language Labeling regulations in Canada were passed in 2014.[24]

Patient labelling consists of product information deemed essential for patients and informal caregivers to use a medicine safely and appropriately. As shown in Annex 1 to this chapter, development and provision of patient labelling is a condition of marketing authorisation approval for medicines in many countries worldwide, and sponsors must also ensure that such information is updated to reflect the medicine's uses and latest knowledge about risks of the product.

In the EU, the regulated patient leaflet is called package leaflet (PL); the term patient leaflet is used informally in the EU as well as in other regions of the world. For centrally authorised and national authorised medicines (through mutual recognition and decentralised procedures), the PLs are agreed at the EU level and legally binding on all member states. There are also national PLs for products that are available only in a single country (typically very old products or those which are authorised in only one EU country). In the US, there are two types of patient labelling: the Patient Package Insert (PPI), and the Medication Guide (MG). While the EMA requires all prescription medicines to have a PL, not all medicines in the US are required to have either a PPI or MG.

The Pharmaceuticals and Medical Devices Agency (PMDA) in Japan also requires the development of patient labelling (called Drug Guides for Patients) under certain circumstances, including when the medicine has a package insert that:

- includes a warning section (some medicines are excluded);
- contains wording on the necessity to inform patients of a specific risk in order to avoid serious adverse reactions or other undesirable outcomes.

The decision regarding whether a guide is necessary for a medicine is made by the Ministry of Health, Labour and Welfare (MHLW) in Japan based on the criteria at the time of marketing authorisation or at the point of revisions of the medicine's package insert after authorisation.

In Australia, consumer medicines information (CMI) is required to be produced by the manufacturer for new prescription medicines and specified over-the-counter (OTC) medicines. Specified OTC medicines consist of Schedule 3 or what is known as 'Pharmacist-only Medicines'. It is the responsibility of the medicine's manufacturer or sponsor (as not all products are manufactured in Australia) to develop the CMI. The Therapeutic Goods Administration (TGA) reviews and approves CMI, but only reviews compliance with the legislation about content and matching the Product Information. The TGA does not require user test nor does it ask for user testing data for CMI.

Health Canada reviews and approves the Patient Information within the Product Monograph. This Patient Information is primarily prepared by the manufacturers; however, Health Canada reviews these documents (which includes the CMI) and ensures that the safety, efficacy and quality information aligns with the pre-marketing and post-marketing data that were assessed. This review occurs before authorisation and in the post-marketing period when any labelling is updated. The review covers the content as well as readability according to plain language labelling requirements to ensure that the information is understandable at a 6th–8th grade reading level. A similar approach is taken for medicine package labels and package inserts, with the sponsor proposing the contents and design, and Health Canada assessing the content and label design according to the relevant Health Canada guidances, including plain language requirements.[24]

Many components of the patient label across other regions are similar in content. For example, a PL developed for the EU and a PPI developed in for the US would both contain information on the medicine's name, what it is used for, side-effects, how to take the medicine, warnings and precautions (*e.g.* for an extended-release tablet, not to split or crush it), how to store the medicine, and what to do if a dose is missed. In some instances, both EU and US patient labelling might include links to additional, more detailed information in the product label.

However, one of the challenges a patient faces in reading the PL (as well as the PPI and Medication Guide) lies in understanding that the medicine's unintended effects (also known as adverse drug reactions or ADRs) vary in the degree of established causality, with some having well-established causal relationship and others having only a reasonable possibility of such a relationship.[7,25] In addition, the patient label lacks information about the medicine's specific benefits, thereby limiting patients' ability to make an informed benefit-risk decision about whether to take the medicine or not.

In several countries, both the elements and format of the patient label are set out in an official template. Examples include those specified by the EMA and FDA and the TGA in Australia.[26,27] The patient label is typically printed on paper, either as part of the product label (*e.g.* Medication Guide) or as a standalone document (package leaflet). Distribution methods may range from inclusion in the drug packaging or delivery to the patient by a healthcare professional. While EMA and FDA mandates inclusion of the standard elements, in some instances sponsors may include additional formatting elements beyond the template requirements.[28] The content requirements for these patient labelling materials is presented in Annex 2 to this chapter.

In addition to patient labelling, patients can access information about their medicines from diverse sources. The accuracy of the information from these sources is highly variable, and consumers may not be aware of this. Some common sources are outlined below. Such materials can also be developed specifically for healthcare professionals.

### 6.3.2 Additional risk minimisation materials

In many countries, sponsors are required to develop risk management plans which set out the company's position on the medicine's safety profile and proposed pharmacovigilance actions to monitor, further characterise, and minimise or prevent specific risks.

As part of the risk management plan, sponsors may be requested to develop 'additional risk minimisation measures' (in addition to the labelling materials), to manage, minimise or prevent specific serious risks (see Chapter 8). Such materials may be addressed to healthcare professionals and to patients where relevant. The patient-targeted materials can take the form of tools intended, for example, to inform patients about specific risks (*e.g.* alert cards, reminder cards, and information brochures), and measures intended to affect habits (*e.g.* patient-provider contracts for opioid medicines). These tools are for patients and informal caregivers to raise their awareness of medicine-related risks and any safe-use practices. As with labelling, these materials require regulatory authority review and approval. In the EU, the EMA approves the proposed messaging for additional risk minimisation materials (materials that are developed based on the approved label) and the national competent authorities retain the authority to approve the final national risk minimisation materials (not only the content but the format and distribution of the materials as well), adapted to the local language, healthcare systems and circumstances.

### 6.3.3 Promotional materials from pharmaceutical companies

In contrast to risk minimisation materials, which must be non-promotional, medicine safety information may be developed as part of promotional materials in certain jurisdictions. For example, in the US, sponsors must include safety information about the medicine in any promotional materials, including direct-to-consumer television and print advertisements, and patient informational materials on the medicine's promotional websites. In contrast, for European Economic Area (EEA) countries, safety material is not allowed to also carry promotional statements or be part of a package that also includes promotional material. However, advertisements in EEA countries must include a statement acknowledging that risks may occur and advising patients to consult a physician or pharmacist in that regard.

Jurisdictions vary in how much they permit sponsors to directly advertise to either patients or healthcare professionals. For example, in EEA countries, companies are not permitted direct-to-patient communications of any type for prescription medicines. In Canada, unlike in the US, marketing authorisation holders cannot advertise a prescription medicine direct to consumers or patients with the exception of the medicine's name, price and quantity.

Typically, however, in countries where direct promotion is allowed, the materials have to undergo regulatory review before distribution. Whether such marketing materials correctly convey safety information has been called into question. In an FDA-sponsored study of the impact of direct-to-consumer (DTC) medicine marketing advertisements, 70% of primary care physicians said that DTC advertising confuses their patients either 'a great deal' (28%) or 'somewhat' (42%) about the relative risks and benefits of prescription medicines, while about 60% of specialists rated the confusion as either 'a great deal' (24%) or 'somewhat' (36%). Of the physicians in both categories, 75% indicated that DTC advertising causes patients to believe either 'a great deal' (32%) or 'somewhat' (43%) that medicines work better than they actually do.[29]

Although regulatory authorities administer their rules and regulations (*e.g.* Food and Drugs Act in Canada), it is the pharmaceutical companies' responsibility to comply with the national advertising rules.

### 6.3.4 Other sources of patient-targeted medicinal product benefit-risk information

Scientifically trusted sources about a medicine's benefits and risks include published, peer-reviewed literature, as well as regulatory agency websites. Increasingly, sponsors of clinical trials supply trial results directly to study participants as recommended by international guidelines or as required by regulators.[30] For example, since 2020 in the EU, sponsors have to provide clinical trial participants with plain-language versions of the trial results, and to post those results publicly.[31] In other regions, external consortia are moving to provide individual results to patients in a clinical trial.[30] In addition, some countries host health websites separate from regulatory websites for patients.

Other types of benefit-risk information from regulators include public summaries of product information. For example, the EMA releases a European public assessment report (EPAR) for each approved medicine along with key data, an 'effects table', a tabular summary of the key benefits and risks of the product.[32] The EPAR is accompanied by a plain language summary ('medicine overview') which is available in the local languages of each EEA country. The EMA also publishes the summary of product characteristics (SmPC) and the PLs in 25 EEA languages for every medicine authorised through the EMA.

Within the EEA, the national regulatory bodies maintain their own websites, often with links to the EMA website. For example, the Dutch regulatory authority (Medicines Evaluation Board) maintains a patient portal on its website to provide access to

information about medicines licensed for use in the Netherlands. In the United Kingdom (UK), the electronic medicines compendium (emc) includes authorised labelling information for healthcare professionals and for patients as well as supplementary information such as risk minimisation materials and letters to healthcare professionals. Health Canada has developed a 'summary basis of decision and regulatory decision summary' for new drugs that is published on the Health Canada's Drug and Health Product Register site.[26]

Patient advocacy groups, and patient networks, including both non-profit and for-profit organisations, are additional sources of information for drug benefits and risks for particular diseases and health conditions. The last two decades have witnessed a proliferation of virtual patient communities, blogs, and patient forums that host discussions on the benefits and risks of treatment options for a given disease. Currently, however, there is no central clearinghouse that vets information from these different sources for accuracy and relevance. As a result, patients may be exposed to differing, even contradictory messages regarding a product's benefits, risks and safe-use practices, some of which may not be accurate, up-to-date or scientifically valid.

Determining which product information sources are credible and which are not can be a challenge for patients. Information from trusted sources (*e.g.* regulatory authority sources such as official websites) will be accurate, but is not necessarily comprehensive (*e.g.* EMA's medicine overviews), nor public-friendly (*e.g.* EPARs and effects tables) and have not been evaluated for accessibility, understandability and actionability. Notably, as one of the regulatory authority sources, patient labelling alone is not only accurate and reliable, but comprehensive, accessible and continuously updated.[33]

The sheer wealth of available information can lead to 'alert fatigue' in response to risk warnings or dilute or undercut the effectiveness of the messages in the product labelling. For example, patients can access amateur videos on YouTube demonstrating medicine self-injection techniques that are incompatible with information in the medicine's approved instructions for use. In addition, no single communication vehicle, including patient product labelling, may suffice in communicating product benefit-risk information to patients.[34]

## 6.4 Initiatives to improve the quality of patient labelling

Over the past two decades there have been numerous initiatives to improve patient labelling (see Annex 3 to this chapter). Most of them have focused on improving the quality of patient labelling design and formatting.

Examples such initiatives include the UK MHRA's *Always read the leaflet*[35] and subsequent *Practice guidance on patient information leaflets*[36] initiatives. Landmark initiatives in the EU included legislation requiring readability and user-testing of the leaflet,[5] which specified that all leaflets in the EU must be tested for readability to ensure they are clear and easy to use (see section 4.6). The European Commission's Summary Study Report[37] has recommended improvements to the summary of product characteristics (SmPC) and the package leaflet.

Other examples include the FDA's release of *Communicating risks and benefits: an evidence-based user's guide*, a guidebook with principles and practical strategies for designing high-quality risk communication materials, and the TGA's Medical Device Consumer Workshop which focused on developing patient cards for patients with medical device implants.[38] A related Australian initiative was the *Investigating consumer medicines information* study by Aslani and colleagues.[39]

Health Canada developed a medicinal product risk communication statement in 2011 that described why and how the agency developed risk communications.[40] Health Canada also convened an Expert Panel on the Effectiveness of Health Product Risk Communication that resulted in a comprehensive guidance in 2015 featuring recommendations on designing and evaluating patient leaflets and other forms of patient-targeted labelling.[41]

In the US, a series of workshops was hosted jointly by the Brookings Institution and the FDA between 2012 and 2014 to improve CMI. This effort was prompted by evidence that patients were confused by the different medicinal product information sources in the US, and by the fact that many of those sources contained information that was 'overly lengthy, poorly organized and weakly summarized'.[1] The workshops explored options for developing a concise, standardised one-page summary of information for patients. A leading example of such a format included the Drug Facts Box, which leveraged research from nutritional product labelling.[42] The Drug Facts Box features the following elements: what the medicine is intended for, who can take it, recommended monitoring (*e.g.* blood tests, symptoms to watch for), other things to consider (*e.g.* warnings about driving or operating machinery), and a summary of clinical trial results for the medicine. The Drug Facts Box has strong empirical support based on extensive testing in the US.[42–44]

Subsequent research resulted in the development of a *Patient-centered Medication Guide*.[45] Similar to the *OTC Drug Facts Label*, this version of the *Medication Guide* was a one-page synopsis of the key product risk information and applied plain-language principles to guide the *Medication Guide* design, including use of simple language, headings, grouping of text by topic and white space between paragraphs.

Some initiatives have focused on practical ways to encourage patient involvement in the development and review of patient labelling. Examples include the Innovative Medicines Initiative (IMI)'s GRAVITATE Health project[46] (2020), and the EMA's young persons advisory groups (YPAGs),[47] which offer access to groups of children and adolescents with different disease conditions for reviewing proposed patient labelling materials.

Other initiatives have focused on leveraging new technologies to enhance the presentation and distribution of patient labelling. Examples include the EMA and European Commissions' collaborative project on electronic product information (ePI), which explored the use of structured product information, and the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) initiative. SCOPE was initiated in November 2013 by a group of European regulators to assess prevailing practices in pharmacovigilance and to develop tools to improve the skills and capability in the pharmacovigilance network. The project was divided into eight work streams, one of which focused on communicating risk and assessing risk minimisation measures and provided guidance, training in key aspects of pharmacovigilance, and tools and templates to support best practice in this area of risk communication.[48]

## 6.5 High-quality patient-centred patient labelling

Annex 4 to this chapter summarises empirically determined best-practices for developing printed patient labelling that is accurate, understandable, actionable and 'low demand' (*i.e.* minimises cognitive burden).[8,13,49,50] Highlights of these recommendations include:[49]

- Use of plain language principles to guide content development and design lay-out;
- Statement of purpose
- Content focuses on what the reader needs to know and actions to take
- Making content as concise as possible;
- Grouping or 'chunking' of similar content together with appropriate headings;

- Liberal use of white space;
- Providing explicit dosing instructions (*e.g.* according to the Universal Medication Schedule, a methodology to simplify medicine use instructions for the patient or their caregiver or both), to improve patient understanding of medicine instructions and adherence to them;[14]
- Avoiding need for calculations or interpretation of graphs or charts;
- Involving patients in the design and testing of the materials.

Several systematic reviews of the published literature have recommended use of colour, graphics and symbols (*e.g.* pictographs) to improve understandability of information materials. Consensus is lacking, however, regarding whether or not the inclusion of these is critical for improving comprehension.[13,49]

Readability assessments are often used to measure the quality of health information. Numerous readability assessment tools exist, including the Lexile, the Fry Formula, and the Simple Measure of Gobbledygook (SMOG).[51–54] While the exact method differs from tool to tool, all are based on counts of word, number of syllables in words, sentence length, and most give the final score in terms of a reading grade level. For example, the recommended target for patient materials is a readability assessment score of between fifth- and sixth-grade reading level (US). Due to differences in these formulas, experts recommend that readability assessments include multiple tests (*e.g.* SMOG, Lexile, Fry).[18]

Readability assessments are considered blunt instruments and, on their own, are not adequate for assessing the quality of patient labelling information as their formulas focus on assessing word and sentence structure and length. Their value as quality assessment tools is put into perspective by the fact that a piece of text written either correctly or backwards can have the same readability score as the words and sentence lengths are the same in either direction.

In addition, readability formulas fail to address the main factors that facilitate ease of reading and comprehension.[55] Such factors include whether the material:[55]

- is attractive to the reader
- can hold the reader's attention
- makes the reader feel respected and understood
- facilitates understanding of the key messages (understanding), and
- helps the reader take appropriate action (actionability).

One widely used tool in this regard is the Suitability Assessment of Materials,[52] which proposes 21 design criteria for developing easy-to-read patient information. Another instrument, the Patient Education Materials Assessment Tool (PEMAT), has been developed to assess the understandability and actionability of written as well as audiovisual materials.[56] PEMAT has been validated, requires no special training to use, and is publicly available.[56] Chan and colleagues used the PEMAT to assess FDA-approved patient-targeted risk communication materials. They found that while most materials were understandable, far fewer met standards for actionability.[57]

## 6.6 Principles for patient engagement in the development of patient labelling

Below, we propose patient-centred principles for developing patient labelling. Patient involvement is fundamental to the development, implementation and evaluation of patient labelling to ensure that it is of high quality and impactful. Not only can patient involvement improve the relevance and comprehensibility of patient labelling materials,

but it can enhance their reach, uptake and sustained use. Moreover, as underscored by lessons from the COVID-19 pandemic, patient involvement is instrumental in improving trust in the information, thus increasing the likelihood that patients will read and retain the materials, and ultimately use the prescribed medicine safely and as intended.[58]

### Principle 1: Involve patients in the design of the patient label

Patient input should be sought for developing the content as well as for layout (*e.g.* use and positioning of headers, amount of white space, inclusion of illustrations).[14] Involvement should start at the point of inception and continue through to finalisation of the patient labelling material. There should be a clear rationale for patient selection, and include target groups in the design of patient information, to ensure that content and presentation are relevant and appealing to patients.[59,60]

Participatory design should encompass not only initial development of the labelling but subsequent updates as well. Patient involvement could include: co-creation sessions; in-person or virtual individual interviews; dyadic or triadic group interviews; focus groups; and crowd-sourcing techniques. Establishing a standing patient advisory board, such as is offered by the YPAGs programme in the EU, is another option for patient input.

A variation on participatory design is to employ a mental models approach. This entails several phases of research, beginning with an expert mental model review (*e.g.* via a review of published literature, or consultation with experts or both); a lay mental model phase in which a small sample of patients is interviewed to determine their beliefs and knowledge about a risk or set of risks; and lastly, a follow-up survey in a larger sample of patients to compare the expert and lay models, results of which can be used to inform the design of the information materials.[61]

### Principle 2: Include patients in the iterative testing of patient labelling materials

The purpose of testing patient labelling materials is to obtain input on the acceptability and feasibility of the patient labelling materials, and ways to improve or enhance it. Pilot-testing can include interviews with individual patients; completion of scenario-based, structured or semi-structured questionnaires; or usability studies in which patients are asked to read the materials, and then instructed to 'think out loud' as they perform a label-specified task.[16,60] Based on initial pilot testing results, the patient materials should be revised to reflect patient input, with specific aims and patient needs in mind.[62]

### Principle 3: Engage patients to evaluate the effectiveness of patient labelling after authorisation

The purpose of involving patients in assessing the effectiveness of patient labelling information is to understand whether patients have actually received the information, whether they have read it (in part or in whole), whether it is understandable, and whether they are able to act on the information.[13,18,63] Patient evaluation studies can take the form of surveys (on-line or in person), or ethnographic studies in which patients are observed using their medicine and labelling materials in a real-world context, such as in their home.

Some important caveats apply to implementing Principles 1 and 2 in the real-world context of drug approvals. In some countries (*e.g.* Canada), regulatory reviews are conducted on timelines established by legislation. As a result, due to the lack of mechanisms that allow operational flexibility (*e.g.* 'stop the clock' rules), patient engagement is best undertaken before filing the application for marketing authorisation.

## 6.7 Evaluating the effectiveness of patient labelling

Patient labelling material should be evaluated for effectiveness after distribution to ensure that it is working effectively in the real world. Several reviews have been published on the effectiveness of written information for individual medicines in real-world settings.[64–67] These reviews cover studies that evaluated leaflets accompanying medicines, printed information provided by healthcare practitioners and information on the internet. The authors tried to evaluate the effects of written information about individual medicines on knowledge of medicine information, attitudes and behaviour related to medicine intake and health outcomes.

The most rigorous of these reviews found improvement in patient knowledge, attitudes towards safe use of the medicine, and adherence as a result of receiving written medicine information.[68] None of the studies, however, examined the effect of written information about medicines on patient health outcomes. The review acknowledged that even when written patient information about individual medicines (*e.g.* a package leaflet) is developed in a state-of-the-art manner, one cannot assume that it will be effective in daily practice.

Intended improvements of written package leaflets for patients should follow the recommendations presented in section 6.6. Furthermore, they should be tested in patients in the context of real-world healthcare delivery settings. Such studies should be randomised, have an adequate concealment of the allocation process, an adequate method for blinding the outcome assessment and an adequate follow up duration. Furthermore, validated measures should be used to assess outcomes.

## 6.8 Future directions for patient labelling

An aspirational goal would be for all regulatory agencies worldwide to provide patient-targeted labelling materials, such as in the form of a patient leaflet (PL). In addition, technological advances underway will enable an electronic version of the PL (an 'e-label') to complement or replace traditional paper-based PL. A digital version of the PL would also permit the development of a 'personalised patient leaflet', one that can be customised to key individual patient characteristics such co-morbidities, concomitant medication use, and specific physical conditions. Such an approach would complement the accelerating trend towards developing personalised medicines.

Second, regulators should adopt practical guidance for involving patients (and informal caregivers) in the development of patient labelling. Experience from the involvement of patients in drug development, including the design of clinical trials, and the development of lay summaries for clinical trials, [33,69,70] can provide valuable insights and potential models for engagement. Relatedly, work is underway to explore how patients can and should be involved in authoring reports of their own medical data, such as per the International Committee of Medical Journal Editors (ICMJE) guidelines, and plain-language summaries of clinical trial studies published in medical journals. These new directions may provide pertinent lessons.

Third, there is a need for developing regulatory standards for patient involvement in patient labelling. Such standards would establish greater methodological consistency, and scientific rigour. For transparency, at a minimum, it may be valuable to have mandatory reporting of practices for engaging patients in the design of the patient labelling materials and standard methods for such reporting. To promote adoption of these standards more widely, outcomes beyond understandability and actionability, should be assessed. Such outcomes include impact on medicine-taking behaviours, and clinical and safety endpoints.[71,72]

Guidelines are also needed for designing multi-media patient labelling materials (*e.g.* interactive computer programmes, web-based applications; audio booklets; avatars and other forms of simulation; and gamification programmes), as well as those involving new distribution modes (*e.g.* through social media forums, including on-line patient communities on platforms such as Twitter and Facebook). Again, lessons from research and experience of the development of plain-language summaries for clinical trials may be valuable.[73,74] For example, Health Canada has approved a handful of e-videos linked to the package labels and 'gated' for only patients who are prescribed the drug to access. These were for products that have safety risks associated with product use, including medication errors associated with self-administration (*e.g.* inhalers)[*].

Metrics should be established to enable internal and external benchmarking of degree to which pharmaceutical companies meet standards of excellence in patient-centric labelling.

In the longer term, social media may be leveraged to distribute accurate medicinal product risk information, including how such information can be personalised to the needs and preferences of the targeted recipients.[63]

Lastly, work is needed to develop communication tools that are demonstrably effective not only in informing patients but in in changing their beliefs and actions so as to increase the likelihood that they will use the medicine safely and appropriately.



[*] [Personal communication] Lacroix, Talia. (Office of Paediatrics and Patient Involvement, Centre for Regulatory Excellence, Statistics, and Trials (CREST), Health Products and Food Branch, Health Canada). Email to: Meredith Smith (Risk Management, Global Drug Safety, Research & Development, Alexion Pharmaceuticals). 2020 October 28.

# Chapter 6 – Annex 1: Product labelling for patients – requirements worldwide

***Table 3: Patient labelling requirements worldwide***

| Region | Required or not (Y or N) | Voluntary | Comment |
|---|---|---|---|
| Africa | Y | | Most countries have this requirement. Some countries only require the paper version of the patient information leaflet; the electronic version is voluntary. |
| Asia/Pacific | Y | | Japan and most other countries require some form of patient labelling except for Bangladesh, China, India, Republic of Korea and Nepal (see rows below). In some countries this requirement only applies to pharmacy medicines and over-the-counter medicines. |
| Asia/Pacific | | Y | Specifically: Republic of Korea |
| Asia/Pacific | N | | Specifically: Bangladesh, China, India, Nepal |
| Europe EU | Y | | All 27 EU Member States plus UK |
| Europe non-EU | Y | | Specifically: Iceland, Moldova, Norway, Switzerland |
| Eastern Europe | Y | | |
| Middle East | Y | | Requirement in all countries except Iran (where it is unclear) |
| Central and south America | Y | | Most of the countries (see next row for exceptions) |
| Central and south America | | Y | Specifically: Bolivia, Colombia, Ecuador, Paraguay, Uraguay, Venezuela |
| Canada | Y* | | Applies to pharmaceutical, biological, and radiopharmaceutical medicines as per Canadian requirements. |
| US | Y* | | Medication guides, patient product information, and instructions for use as per FDA requirements. |

*=Special requirements apply.

Note: The table was adapted by the CIOMS Working Group from the contributions by Carolyn Sperl and Deborah Bebbington, Bayer AG.

# Chapter 6 – Annex 2: Comparison of content requirements

***Table 4: Comparison of content requirements: Package Leaflet, Medication Guide, Patient Package Insert and Consumer Medicines Information***

Source: CIOMS Working Group XI

| Type of patient labelling | Country/region | Content |
|---|---|---|
| Package Leaflet | European Economic Area (EEA) and United Kingdom (UK) | 1. What [PRODUCT NAME] is and what it is used for<br>2. What you need to know before you take [PRODUCT NAME]<br>3. How to use [PRODUCT NAME]<br>4. Possible side effects<br>5. How to store [PRODUCT NAME]<br>6. Contents of the pack and other information |
| Medication Guide (per 21 CFR 208, Subpart B, Sec 208.20) | United States of America (US) | 1. Name of medicine<br>2. Most important information for patients to know<br>3. Who should not take medicine<br>4. How the medicine should be taken<br>5. Importance of adherence, and use only for prescribed condition<br>6. Risks and precautions<br>7. Likely side effects<br>Adverse reactions |
| Patient Package Insert (per 21 CFR 310.501 and 21 CFR 310.515) | US | A patient package insert for an estrogen (oestrogen) medicine is required to contain the following information:<br>1. The name of the medicine<br>2. The name and place of business of the manufacturer, packer, or distributor<br>3. A statement regarding the benefits and proper uses of estrogens<br>4. The contraindications to use, *i.e.* when estrogens should not be used<br>5. A description of the most serious risks associated with the use of estrogens<br>6. A brief summary of other side effects of estrogens<br>7. Instructions on how a patient may reduce the risks of estrogen use<br>8. The date, identified as such, of the most recent revision of the patient package insert |

(continued)

| Type of patient labelling | Country/region | Content |
|---|---|---|
| (Table 4, continued)<br><br>Consumer medicines information (TGA, https://www.tga.gov.au/consumer-medicines-information-cmi) | Australia | Name of the medicine<br>Names of the active and inactive ingredients<br>Dosage of the medicine<br>What the medicine is used for and how it works<br>Warnings and precautions, such as when the medicine should not be taken<br>Interactions the medicine might have with food or other medicines<br>How to use the medicine properly<br>Side effects<br>What to do in the case of an overdose<br>How to store the medicine properly<br>Name and address of the sponsor<br>Date the CMI was last updated |
| Health Canada, Patient Medication Information (Health Canada, https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/product-monograph/master-template.html#a18) | Canada | Read this leaflet to understand the safe and effective use of your medicine<br>Brand Name of drug product<br>Proper Name of drug product in final dosage form<br>Serious Warnings and Precautions<br>What is [BRAND NAME] used for?<br>What is Notice of Compliance with Conditions?<br>How does [BRAND NAME] work?<br>What are the ingredients of [BRAND NAME]?<br>What are the dosage forms for [BRAND NAME]?<br>Do not use [BRAND NAME] if:<br>To help avoid side effects, talk to your healthcare professional (HCP) before you take [BRAND NAME]<br>Other Warnings you should know<br>Tell your HCP about all the medicines you take<br>The following may interact with [BRAND NAME]:<br>How to take [BRAND NAME]:<br>Usual Dose of [BRAND NAME]:<br>Over does<br>Missed Dose<br>Possible Side Effects<br>Serious Side Effects and What You Should Do About Them<br>Reporting Side Effects<br>Storage<br>If you want more information:<br>The leaflet was prepared by [SPONSOR NAME]<br>Last revised on: |

# Chapter 6 – Annex 3: Initiatives to improve patient labelling

***Table 5: Initiatives to improve patient labelling: 2003–2018***

Source: CIOMS Working Group XI

| Initiative (Start date) | Description | Goals | Key outputs/deliverables |
|---|---|---|---|
| MHRA's *Always read the leaflet*: Getting the best information with every medicine (2005) | Committee report on providing quality medical information to patients | To improve quality of medical information to meet patient needs and propose criteria to assess patient information leaflet (PIL) quality | Formal report with 10 recommendations regarding good practices to use when developing a PIL |
| EU Directive 2004/27/EC included new requirements for the 'package leaflet' (2005) | The package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use. | The package leaflet must be written and designed to be clear and understandable, enabling the user to act appropriately. | Operationalised by pharma companies with the 'user testing' process. |
| FDA Guidance for Industry on the Use of Structured Product Labeling (2005) | Guidance for industry for preparing regulatory submissions using electronic format for content of product labelling | To improve efficiency of submission of product labelling via use of electronic format. | Guidance for industry. |
| Ministry of Health, Labour and Welfare (MHLW)'s Pharmaceuticals and Medical Devices Safety Information (PMDSI) Report (2006) | MHLW PMDSI report #222, outlining plans for PIL enhancement and revisions | To provide an overview of current plans for PIL changes: use of IT for med history management, standardisation of symptom and adverse event terminology, enrichment of pharmaceutical information for public consumption | Formal report published in Feb 2006 |
| Investigating Consumer Medicines Information study (2007) | Study funded through a TGA agreement with Pharmacy Guild of Australia. | (a) To consolidate evidence related to CMI effectiveness | Investigating Consumer Medicines Information study (2007) |
| PMIs: FDA's Safe Use Initiative (2009) | FDA report on current efforts in reducing preventable harm from medicines | To provide recommendations on reducing medicine risks | Formal report published in 2009 and recommendation to begin FDA's Safe Use Initiative and subsequent medication risk reduction projects |
| Joint Brookings & FDA Workshop (2010-2014) | Collaborative effort between FDA and Engel-berg Center for Health Care Reform to provide a PMI education series | To optimize, implement, and evaluate adoption of 1 standard PMI document | 4 workshops |

(continued)

| Initiative (Start date) | Description | Goals | Key outputs/deliverables |
|---|---|---|---|
| (Table 5, continued) | | | |
| MHRA Best Practice Guidance on PILs (2012) | PIL best practice guidance published by MHRA to supplement info presented in *Always read the leaflet* | To ensure use of best practices before submitting PILs to MHRA | Publication of Best Practice Guidance on PILs, published in 2012, to be used in supplement to current legislative requirements |
| Formation by the EMA of Pharmacovigilance Risk Assessment Committee (PRAC) (2012) | Responsible for assessing all aspects of risk management of human medicines | Formally established in line with pharmacovigilance legislation to help strengthen the safety monitoring of medicines across Europe. | PRAC issues recommended wordings for additional safety text in PILs. In addition public hearings are held on specific topics. |
| PMIs: National Health Council's Patient Information Tool & Implementation Guide (2012) | To provide a tool for guiding patient communication to understand risk/benefit, in response to FDA's PDUFA reauthorisation | To provide comprehensive risk/benefit information to patients | Patient Information Tool & Implementation Guide |
| FDA establishment of a Risk Communication Advisory Board (2009-present) | | | Publication of Fischhoff Brewer & Downs (Editors) (2011). *Communicating Risks and Benefits: An evidence-based user's guide* (FDA, 2011). |
| PILs: European Commission Summary of PIL and SmPC Study Report (2015) | Summary of views on 2 external study reports on PILs and SmPC from the Universities of Utrecht & Leeds. | To document committee comments and recommendations | PIL Improvement Recommendations on design, layout, and format, such as:<br>• Considering alternative formats (*e.g.* booklets)<br>• Remove information that is irrelevant to patient (*e.g.* available pack sizes and doses)<br>• Reduce visual length by changing format to landscape vs. portrait<br>• Adequate font size and line spacing for readability |
| IMI-PARADIGM PIL Opportunity (2016) | Open call for patients to review 21-page PIL for study from Novo Nordisk Ltd, investigating a new fatty liver disease treatment | To involve patients in reviewing PILs | Improvements in the clarity, and understandability of the PIL |
| EMA Electronic Labelling Initiative (2017) | Proposal for assessing and optimising electronic SmPCs and PLs | To develop key principles for use of electronic SmPC/PL formats | EC/EMA multi-stakeholder workshop, mapping of current initiatives |

(continued)

| Initiative (Start date) | Description | Goals | Key outputs/deliverables |
|---|---|---|---|
| (Table 5, continued) | | | |
| CIOMS EU: Mapping of ePI (2018) | Re-assessing current and new content of information on medicines | To enhance the formatting and content of the PIL | Watchyourmeds support programme on better use of medicines, information aid for HCPs and patients (ex: Spain's structured product information) |
| Therapeutic Goods Administration (TGA) Medical Device Consumer Workshop on Patient Implant Card and PIL (2018) | Patient cards and consumer information for implantable medical devices at TGA's Health Consumers Workshop | To provide updates on medical device regulation reform | Implementation of MDRR: PIL to be supplied from Dec 2018, staggered roll-out of patient implant cards |
| EMA's Plain Language Summaries (2018) | EMA regulation for life science and pharma firms to include 'plain language summaries' for Phase I to IV trials. | To increase clinical trial transparency, improve external engagement, improve public trust, improve efficiency and progress in clinical research | Publication of study results and recommendations: *Summaries of Clinical Trial Results for Laypersons*, published in 2017. Results focused on health literacy, writing style, readability, plain language, numeracy, visuals, and language. |
| Enpr-EMA's young persons advisory groups (YPAGs) | The European Young Person's Advisory Group Network (eYPAGnet) is a member of the Enpr-EMA and acts as a single point of contact for all YPAGs in Europe. | To improve collaboration with diverse stakeholders who participate in the research and development process of health and social care interventions for children and young adults | Establishment of YPAGs among several Enpr-EMA networks<br>Developing YPAG database as resource for EMA and Pharma |
| SCOPE Joint Initiative | The Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action focused on coordinating European pharmacovigilance operations and ran from 2013–2017. | To support regulatory authorities and industry in interpreting the implications of the 2012 Good Pharmacovigilance Legislation for impact on risk communication practices. | Final reports on risk communication initiatives and results:<br>*Risk communication – proposals for improvement*<br>*Good practice guide – web-based safety information*<br>*Patient and consumer consultation report*<br>*Risk communication on medicines: report from the workshop*<br>*The national strategy for implementation of recommendations on risk communication: key actions* |

(continued)

| Initiative (Start date) | Description | Goals | Key outputs/deliverables |
|---|---|---|---|
| (Table 5, continued) | | | |
| phactMI (PhRMA) | Collaboration of pharmaceutical company Medical Information (MI) departments | To support healthcare professionals in providing quality patient care | 2017 – Launch of phactMI.org, for easy access to accurate medical information<br>2017 – Publication of *The medical information code of practice*<br>2018 – *Benchmark study of globalization in medical information* published |
| Institute of Medicine's Workshop Standardizing Medication Labels: Confusing Patients Less | 2007 IOM workshop | To examine known and unknown factors on how medication labelling affects patient safety and how to best approach identified problems | Publication of a workshop summary, *Standardizing medication labels: confusing patients less* – released in 2008 |
| Japan's E-Labeling Initiative (Ongoing as of 2020 – to be finalised in 2021) | | To replace paper labelling with electronic labelling | A code (*e.g.* QR code) will be printed on the outside of the medicine's commercial package to allow the healthcare professional and patient access to the latest version of the product label and Patient Information Leaflet. |

(continued)

| Initiative (Start date) | Description | Goals | Key outputs/deliverables |
|---|---|---|---|
| (Table 5, continued) | | | |
| The Electronic Patient Leaflet Pilot Project in Belgium and Luxembourg (Ongoing as of 2020) | The e-PIL pilot is a collaboration between the pharmaceutical industry and the regulatory authorities in Belgium and Luxembourg. It is supported by the European Commission. In this 24-month pilot, the leaflet of selected medicines restricted to hospital use and marketed in Belgium and Luxembourg is no longer included in printed version but can be consulted online via trusted websites. Interim results have shown that for 98% of pharmacists, absence of the paper leaflet from the packaging has not generated inconvenience in their daily practice, nor has it affected requests from other healthcare professionals in the hospital. Based on these positive results, the authorities in Belgium and Luxembourg have asked the European Commission to allow the expansion of the pilot to further consolidate the results. | To demonstrate that the electronic format provides sufficient, adequate, and tailored information on the use of medicines to healthcare professionals and patients in a hospital setting. | The key deliverable is a final evaluation report containing results and recommendations to the European Commission. |

(continued)

| Initiative (Start date) | Description | Goals | Key outputs/deliverables |
|---|---|---|---|
| (Table 5, continued) | | | |
| IMI-GRAVITATE Health | IMI-GRAVITATE Health was initiated in 2020 as a 60-month long public-private partnership. The partnership consists of 39 members from Europe and the US and is co-led by University of Oslo (coordinator) and Pfizer (industry lead). It is funded by the Innovative Medicines Initiative (IMI) – a joint undertaking of the European Commission, the European Federation of Pharmaceutical Industries and Associations (EFPIA), IMI2 Associated Partners.<br>Its mission is to equip and empower citizens with digital information tools that make them confident, active, and responsive in their patient journey, specifically encouraging safe use of medicines for better health outcomes and quality of life.<br>To that end, IMI-GRAVITATE Health will develop the Gravitate Lens (G-Lens), which focuses on (but does not conceal or filter) approved electronic product information (ePI) content, and offers a route for patients to access trustworthy, up-to-date information that better meets their individual needs. | To demonstrate how the use of an integrated, digital, user-centric health information solution could enable a tangible improvement in citizens' ability to access and understand reliable, relevant health information from different sources;<br>To measure how improved access to and understanding of health information translates into better treatment adherence, safer use of medicines and consequently better health outcomes, with new insights into how health information can be optimised to act as an effective risk minimisation measure. | To build a federated, open-source technology platform that will enable integration of common services;<br>To develop a digital solution application layer and end user services with educational materials;<br>To establish inter-operability, accessibility and regulatory support for the platform; and,<br>To conduct proof-of-concept pilot studies with a multi-faceted evaluation. |

# Chapter 6 – Annex 4: Best practice recommendations for patient labelling information

***Table 6: Best practice recommendations for patient labelling information***

Source: Recommendations included in this table are derived from the Suitability of Assessment Materials tool;[52] and from: Bailey S. 2015;[49] Shoemaker S *et al*., 2014;[56] Mullen R. *et al.*, 2018.[13]

| Number | Recommendation |
|---|---|
| I | Content |
| 1. | Purpose of patient labelling is evident and clearly stated up front |
| 2. | Content emphasises actions |
| 3. | Scope is limited. Information is kept as concise and short as possible: essential content is presented; extraneous or auxiliary information is omitted |
| 4. | Content is accurate and reflects what patients need and want to know |
| 5. | Information in the patient label is organised in terms of importance to patient safety and appropriate use, with most important information listed first, followed by less important information |
| 6. | Headline section or key information section (or both) |
| II | Literacy Demand |
| 1. | Health literacy and plain language principles are used to select vocabulary and formatting to optimise understandability |
| 2. | Reading grade level is between 6$^{th}$ and 8$^{th}$ grade |
| 3. | The writing is in the active voice |
| 4. | Context given first |
| 5. | Learning aids provided in the text (*e.g.* use of appropriately worded headings in each section) |
| III | Layout and Typography |
| 1. | Evidence-based design is used in formatting materials (*e.g.* sufficient white space, use of bullet points, inclusion of headings and subheadings, 'chunking' of text by specific topic) |
| 2. | Layout is easy to follow |
| 3. | Typography is appropriate (*e.g.* font size of 12 (or 14–16 for groups with visual impairment; avoidance of italics and of text in all capital letters) |
| IV | Graphics* |
| 1. | Use graphics, symbols, pictographs and other visualisations to enhance understanding |
| 2. | Include relevant illustrations |
| 3.2 | Use graphics to show fractions |
| 4. | Use colour |
| 5. | Avoid need for calculations or interpretation of graphs and charts |
| 6. | Involve patients in the design and testing of the labelling materials. |
| V. | Learning Stimulation and Motivation |
| 1. | Use interaction (*e.g.* use questions and frequently asked questions; provide links for patients to access additional information) |
| 2. | Desired behaviours are modelled and specific |
| 3. | Support self-efficacy; enhance motivation |
| VI | Cultural Appropriateness |
| 1. | Match in logic, language, experience: at very least label information should be available in the language that the patient is proficient in (*e.g.* match with the literacy, and educational levels of target patient audience) |
| 2. | Provide cultural image and examples (the material is designed with consideration of the culture of the end users, *e.g.* older patients; patients with certain physical impairments |

*Note: the inclusion of graphics, colours and symbols is not universally endorsed as being necessary for aiding comprehension, see Raynor and Dickinson, 2009.[75]

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# Chapter 7: Rapid safety communication

This chapter describes how patients can contribute to urgent patient safety information which needs to be passed on quickly.

**Key points**

Patients can contribute to urgent safety communication in different ways:

1. Taking part in decisions about which new safety issues patients need to be quickly alerted about.
2. Providing guidance on which information needs to be communicated from the patient's perspective.
3. Using the different communication channels available to patient organisations to send out urgent safety communication.
4. Responding to questions or moderating discussions among patient organisation members about the urgent safety information.
5. Providing input from an early stage through pre-set processes.
6. Providing input on the appropriate information and terminology (lay language) in the information to be sent out.
7. Providing input into the translation of the information into plain language and helping to create a glossary of terms specific to a disease and set of treatments.

## 7.1 Summary

People who use or are likely to need medicinal products – patients – should be routinely involved in constructing safety communication. Time-bound communication issued to avert or minimise an emerging risk is of particular importance and, because of the need for rapid dissemination, involvement of patients can be challenging (sections 7.2 and 7.3). But in section 7.7 we describe why patient involvement is important and how it could be achieved.

Safety communication can affect a range of people from those participating in clinical trials to those using well-established and widely used medicinal products (section 7.5).

Reactive communication, mostly directed at healthcare professionals (section 7.3), is obviously of relevance to those who use the affected medicinal product: users need to be aware of the concerns and they may need to act to reduce or prevent the emerging risk.

Using pre-tested templates and preparing in advance to involve patients speeds up the drafting of a clear message, having it reviewed by interested parties, and disseminating it (section 7.4). Planning can also take the particular needs of patients into account by drafting plain language text, issuing supplementary patient-oriented communication, or setting up infrastructure to deal with patients' concerns. All communications must include full details of the medicinal product and the emerging concern; above all, actions that healthcare professionals and users should take must be clear.

The involvement of patients and patient organisations is valuable for disseminating safety communication (section 7.6). Traditional means of communication (paper, website, emails) should be combined with newer methods (social media, mobile digital technology, interactive apps); however, there are attendant risks of modernising the means of

communication. For specific conditions, patient organisations can enhance dissemination of safety messages through their experience of communicating with their members.

So, patient input should ideally be incorporated in all the different stages of preparing and distributing safety messages (section 7.7). Planning such involvement can make patient review of the communication and its dissemination smoother and more efficient.

Every safety communication should be evaluated for its impact, ultimately to measure its beneficial effect on health outcomes (section 7.8).

## 7.2 Introduction

Safety communication is a broad term covering different types of information on medicines. Safety communication on an important emerging risk with a medicine or a class of medicines aims to raise awareness, provide information about the risk, and, ideally, set out actions to mitigate the risk. These safety communications include background and important details on the safety concern as well as recommended actions in a clear, concise, understandable and actionable way whilst avoiding unnecessary alarm among people affected by the risk. Safety communication should be tailored to the target audience by using appropriate terminology, language, and the audience's level of knowledge and understanding.

Scenarios for which safety communication might be needed include recommendation to watch out for an unwanted effect, changing to how a medicine is used to immediately stopping the use of a medicine and switching to an alternative intervention.

Depending on the nature of the safety communication and the stage of the medicinal product's development and whether it is authorised, the safety communication may be issued by a regulatory authority, clinical trial sponsor, market authorisation holder or manufacturer.

**Time-bound safety communication** is issued in response to a safety risk that needs:

1. to be addressed promptly (within hours or days) to avoid the risk of serious potential harm
2. to inform the target audience to become aware of information
3. to alert the target audience to take immediate action or change current practice in relation to a medicinal product .

In general, the primary target audiences for safety communication are healthcare professionals who then act on this information. The development of time-bound safety communications rarely involves people affected by a safety concern due to time sensitivity and potential harm caused by delays in safety communication. Given this, the safety communication may not fully address the concerns of individuals using the medicinal product or properly cover how the safety issue affects them. However, there are good practices such as those in the European Union where the European Medicines Agency (EMA) consults the patient working party and patient representatives also in time-sensitive situations.

Often, general communication (non-time-bound safety communications) in mainstream and social media could alarm people or give inappropriate or incomplete information which can affect treatment if people do not have complete and authoritative information to act on in a timely manner. An example of such a communication concerns the use of certain blood pressure and heart medicines – angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs) – during the COVID-19 pandemic. These medicines were alleged to increase the risk of more severe consequences of the viral

infection. Such a situation may call for a reactive time-bound safety communication from regulatory authorities, marketing authorisation holders or manufacturer to clarify the issues and provide the necessary context. In this case, regulators advised that patients should not interrupt their treatment with these medicines as the risk mentioned in sections of the media was based on a hypothesis only, not supported by clinical studies (European Medicines Agency, March 2020[1] and June 2020).[2]

The nature of regulated safety communication (and its urgency) is understood by industry, regulators and to a lesser extent by healthcare professionals. This chapter makes recommendations to enhance patient involvement in the development of safety communications.

## 7.3 Type of safety communication

Any safety communication must be clear, concise, understandable and actionable and consider the knowledge and understanding of the target audience. Importantly, the healthcare professional prescribing the medicine and the individual using it must know what to do as a result of this safety communication.

Safety communications on medicinal products can be categorised as:

- **reactive** – issued as a result of reports of an important unwanted effect, product complaints, and concerns arising from clinical trial or observational study observations
- **proactive** – issued before any unwanted effect occurs, for example when a medicinal product is launched. Examples of proactive communication include advice on preventing serious harm from medication error, detailing the requirements of a pregnancy prevention programme; or, in a clinical trial, addressing changing environmental situation like the requirement to test for SARS-CoV-2 and sharing experiences of COVID-19 participants.

In general, time-bound safety communications are directed to healthcare professionals who play an essential role in ensuring that medicinal products are used as effectively and safely as possible. An effective time-bound safety communication enables them to act to minimise risks and to give clear and practical information to those using the affected medicinal product.

Additional communication material in plain language can also be prepared to help those using the affected medicinal product. When possible and appropriate, individuals using the medicinal product should be involved in the preparation of such additional communication to ensure that it is useful and adapted to the target audience. Over the medicinal product's life the primary target audience may change as its use broadens and a safety communication directed at patients may become more appropriate.

In most instances the emerging concern should also be reflected by amendments to the labelling and product information, in accordance with local legislation. The regulatory authority has to authorise the safety communication as well as the amendments to the labelling and product information.

In some cases, a follow-up safety communication may need to be issued *e.g.* on the resolution of a safety concern or updated recommendations to minimise risk.

## 7.4 Constructing the content of safety communication

The information in a time-bound safety communication should not mislead and should be presented objectively and not include any material or statement which might constitute

any kind of advertising. The content needs to be tailored to the issue to be communicated and the target audience (*e.g.* patients and healthcare professionals). Nevertheless, it is useful to have the communication as uniform as possible and use a template.

Most time-bound safety communication is written for target audiences like healthcare professionals. The public may have access to such time-bound safety communications because they are posted on regulatory authorities' websites and elsewhere. Therefore, it is recommended that safety communications to audiences other than patients should be written in public-friendly language as far as possible so that the public can easily understand the information without the risk of misinterpretation. A preferred option is to create additional communication in public-friendly language to accompany the time-bound safety communication for healthcare professionals.

An outline of the principles of safety communication should contain as a minimum, guidance on information to be included. Template wording for rapid drafting (section 7.4.1), review and dissemination might be very useful for time-bound communication; the template can guide layout (*e.g.* use of bullets and more prominent type face for key information). The use of standard format allows those constructing the communication to focus on the content, purpose of the message, and the actions that might be needed. Such a template may also be considered for a communication plan like that from EMA or other regulatory authorities.

Ideally, patients (or those eligible to use the medicinal product) and healthcare professionals should pre-test safety communication early in preparation, particularly on complex safety concerns. They may also help to identify the target audience. However, for time-bound safety communications, this may not always be feasible in the time available. See section 7.7 for further information on how such engagement can be achieved in a time-sensitive context.

Establishing and using a template can facilitate rapid development of the content, its review and promote consistency in editing, thereby expediting finalisation and dissemination. Additionally, marketing authorisation holders or manufacturers and regulators could prepare for rapid review of time-bound safety communication when the need arises. This involves identifying in advance healthcare professionals, patient groups and subject matter experts in specific therapeutic areas who can be sent a time-bound safety communication to support fast review and quick turnaround.

Where multiple languages are spoken, translation into the relevant languages should be taken into account in the preparation of the safety communication. However, translation needs to be accurate and provide the same level of understanding in each language for the target audience.

The review process needs to take into account the target audience. This of course is easier for proactive safety communication and more challenging if it is reactive and time-bound. Due to time sensitivity, in parallel to the review process, a communication plan could be established and appropriate communication channels identified. If needed, call centres could be established or questions and answers documents prepared to explain and manage enquiries arising from the communication, or follow up communications prepared.

### 7.4.1 Safety communication for healthcare professionals

Guidance and templates exist for time-bound safety communications directed to healthcare professionals in many parts of the world. Such guidance may also include a template for a communication plan. In the European Union patients were consulted during

the development of the template. Where such guidance and templates are available, they must follow applicable legislation. Examples of guidance and templates include:

- European Union
  - Guideline on good pharmacovigilance practices (GVP) Module XV – Safety communication, Oct 2017 (EMA/118465/2012 Rev 1)
  - Template: direct healthcare professional communication (DHPC)
  - Template: Communication Plan for Direct Healthcare Professional Communication
- League of Arab States
  - Template and guidance for GVP for Arab Countries V3, Dec 2015.

In countries that have not developed guidance or templates, existing templates developed in other regions or countries should be consulted.

Many regulatory authorities have developed templates for direct healthcare professional communication ('Dear Healthcare Professional' communication, DHPC) (EMA/36988/2013 Rev1). The safety communication should cover all relevant information in accordance with the template or guidance from regulatory authorities such as the following:

- important new information on any authorised medicinal product which has an impact on the medicine's risk-benefit balance under any conditions of use;
- the reason for initiating safety communication clearly explained to the target audience;
- any recommendations to healthcare professionals and patients on how to deal with a safety concern;
- when applicable, a statement on the agreement between the marketing authorisation holder and the regulatory authority on the safety information provided;
- information on any proposed change to the product information (*e.g.* the summary of product characteristics (SmPC) or package leaflet (PL));
- any additional information about use of the medicine or other data that may be relevant for tailoring the message to the targeted audience;
- a list of literature references when relevant or a reference to where more detailed information can be found, and any other relevant background information;
- where relevant, a reminder of the need to report suspected adverse reactions in accordance with national reporting systems.

At present regulatory authorities' templates for time-bound safety communications do not always receive input from consultation and review by market authorisation holders or manufacturers, industry bodies, representative healthcare professional associations, relevant patient subject matter experts, patient representatives or patient organisations.

In the European Union, people who might use a medicinal product were consulted on the template for a DHPC. We recommend that organisations that are updating or developing templates or guidance seek input from patient organisations or patients. This ensures that the templates or guidance include information that is more relevant and helpful to individuals using the medicinal product and that the communication plan template or guidance reflects how they prefer to receive time-bound safety communications that directly impacts them. In this way, time-bound safety communications targeted at healthcare professionals will also support healthcare professionals pass on information verbally to those using the medicinal product and caregivers because the communication already reflects their potential needs.

### 7.4.2 Safety communication for individuals using a medicinal product

Plain language communication (*e.g.* using a question-and-answer format) helps those using the affected medicinal product and the general public to understand the actions to take on the safety issue as well as the background evidence. Healthcare professionals can also use this approach in communicating with individuals. Such a plain language document should include:

- what medicinal product the communication is about;
- the nature of the safety concern and which individuals are affected;
- recommendations for action and advice to the individual using the medicinal product on minimising risk;
- who to consult in connection with any action that the individual should take or has taken.

The communication should also include background information on why the safety communication has been initiated. Additional information on how to contact the clinical trial sponsor, marketing authorisation holder, manufacturer and regulatory authority with questions about the specific safety communication is helpful. In addition, consider patient organisation as an additional source of independent information for time-bound safety communication.

Alternatively, the information can be summarised as shown in Table 7, below.

***Table 7: Safety information that should be communicated to individuals***

Source: CIOMS Working Group XI

| | |
|---|---|
| Names of the medicine | brand names and names of active substances |
| Safety issue | describe the relevant risk |
| Action for the individual to take | *e.g.* 'contact your healthcare professional as soon as possible' |
| Which healthcare professional can the patient consult? | specify prescriber, family doctor, investigator, emergency hotline (as for public health emergency such as a pandemic), pharmacy, etc. |
| What the individual should do while waiting for a healthcare professional's advice (if applicable) | recommendations and advice to minimise risk *e.g.* 'do not stop taking your medicines until you have spoken with your doctor or pharmacist' |
| Additional source of information for the individual (if applicable)? | include, as appropriate, emergency hotline number (as for public health emergency such as a pandemic), name and contact details (email, telephone) of marketing authorisation holder, clinical trial sponsor, regulatory authority or patient organisation |

The safety communication should also consider that patients' knowledge about the disease and the treatments may vary; those suffering from a rare disease tend to be better informed about their disease than others.

Further information may be needed depending on the specific safety concern such as whether there are ongoing consequences, the need for clinical examination, recommended steps for follow up or for further sources of information.

## 7.5 Safety communication for different public audiences

### 7.5.1 Safety communication for clinical trial participants

Communication with clinical trial participants is normally through their investigator and the clinical unit that the participants interact with. There are, however, situations where a

media alert or some other public information could cause participants to require rapid and informative communication to ensure they act in line with the advice of their investigator at the participating unit. The ICH Guideline for Good Clinical Practice E6 and applicable local legislation and the channels for informing and keeping in contact with participants in clinical trials should be followed rather than broad non-targeted communications. Contacting ethic committees and any relevant patient organisations is still recommended for their input and insights into understanding of the emerging concern.

### 7.5.2 Safety communication for individuals using proprietary products

Communications on marketed products need to have the greatest input; they have the broadest implications and potentially affect many more people than those in clinical trials. The communication needs to take into account all the people affected by the safety concern and their varying ability to understand and act on the information; the communication should be prepared with an understanding of the implications of the actions on the people affected. Appropriate and rapid input from all stakeholders involved will help to provide wording in relevant languages, develop actionable guidance, and ensure information is understandable and provided in an accessible format. Guidance for further details and follow up by those using the medicinal product, their caregivers and healthcare professionals must be clear and relevant (section 7.4).

### 7.5.3 Safety communication for individuals using generic medicines

The requirements for safety communication for individuals using generic medicines are similar to those for the marketed proprietary products. Multiple brand names of generic medicinal products need to be specified and the approved name, such as the International Nonproprietary Name (INN), of each of the active substances must be clearly shown.

Rapid and early coordination and cooperation is encouraged between the developers of the communication and the multiple marketing authorisation holders or manufacturers, using industry bodies. This ensures that communication and a common timetable for publishing the information are aligned between the originator, generic manufacturers, regulatory authorities and patient organisations. In this way healthcare professionals receive a single time-bound safety communication covering all the marketed products affected.

The marketing authorisation holder or manufacturer of the originator product is generally the lead contact point and coordinator. If no originator product is marketed in the country, one of the generic manufacturers is encouraged to act as the contact point. The contact point coordinating the communication should be provided to the regulatory authority to facilitate rapid development of the communication.

Also, patient organisations may be included as an additional source for information.

## 7.6 Dissemination

Multiple channels and formats can be used for safety communications including postal mail, press communication, bulletins, newsletters and publications in scientific journals or through professional bodies. For time-bound safety communication, dissemination is most likely to be digital (*e.g.* emails, website post and social media), using multiple channels that give the broadest, most user-tailored and audience-sensitive medium for appropriate coverage.

For successfully communicating safety information, the best method should be chosen for disseminating it to the relevant target audience, and the content should be well understood and lead to the desired action. Involving carers and others can help to deliver and explain time-bound safety communication and support any necessary action.

Currently, time-bound safety communications are mostly targeted to healthcare professionals. The healthcare professionals then have to pass on the message orally to those using the medicinal product and caregivers based on their needs. Individuals with an interest in the subject but who do not have a scientific or regulatory background may search the internet for specific information accessing, for example, websites that publish time-bound safety communication targeted at healthcare professionals.

However, not all information that the individual using the affected medicinal product requires may be included in the safety communication and it is for the healthcare professional to pass on appropriate information to affected individuals, based on the individual's medical circumstances. But the only opportunity for the healthcare professional to pass on the information may be when the individual contacts the health professional. This may be during a routine visit or when the individual contacts the healthcare professional after learning about the safety concern (*e.g.* through news or social media or online browsing). Reliance on the individual contacting the healthcare professional can delay passing on of important information to the individual; this needs to be considered in the light of the nature and urgency of the safety communication.

For certain illnesses the content and the medium for dissemination need to be adapted to the age groups that the illness affects. Patient organisations and specialists in communications should be consulted in advance to identify the most appropriate tools and content appropriate to the people affected. Depending on the breadth of communication required, it may be appropriate to use the regulatory authority to engage public media and news channels. The best means of reaching the individual using the medicinal product requires preparation and research of the channels that the target audience uses.

If individuals using the affected medicinal products are children or babies, the safety communications should be targeted at healthcare professionals and the child's parent or caregiver; this target audience may be considered digitally competent. Elderly patients on the other hand may not be digitally competent and alternative media in parallel with digital media must be planned such as audio, video with subtitles and audio prompts.

Mobile communications and the use of apps on mobile devices are ideal for rapid and timely dissemination where this is suitable for the target audience. The devices can also be set up for alert notification, two-way communication, monitoring of impact or adverse effects of medicinal products. Follow-up information, questions and further details are well suited to mobile and digital communications.

Many patient organisations are experienced in communicating with their audience, including choice of wording, medium and channels to ensure understanding of the message.

Engagement between market authorisation holder and regulatory authority in developing rapid communication will ensure regulatory oversight and responsibility of the communication and so protect public health.

In future, increasing use of digital tools in healthcare, and regulatory authority digital engagement on urgent issues, will speed up the dissemination of time-bound safety communications. However, speedy dissemination cannot substitute early engagement with patients on the content, understandability and access to coherent, timely and relevant information, which ensure that patients and healthcare professionals are better able to

make well-informed treatment decisions. Technology may also enhance communicating with patients with disabilities, such as those with visual and hearing impairment and conditions such as dementia, where caregivers may be required to act on their behalf.

Advances in mobile and cellular phones and networks should be considered for distributing time-bound safety communications in some jurisdictions. In the US, 8 in 10 Internet users search for health information online, and 74% of them use social media.[3] Patients can get the information they need about the risk of a medicinal product by sharing information, communication of risk or regulatory messages, sharing images and other content, and, in some cases, by collaborating with other users in real time.[4,5] Marketing authorisation holders have at their disposal a range of digital and social media platforms such as YouTube, Flickr, Facebook, MySpace, Google Plus, Instagram, Twitter, Snapchat, Tumblr and Newsletters. Companies could potentially use them to reach users of medicinal products and share time-bound safety communication or provide a link to the communication.

Media-sharing sites can also serve as important resources for time-bound safety communication. As the world's largest video hosting website,[6] YouTube, has had impact in many fields and it's about time that market authorisation holders or manufacturers and regulatory authorities consider these transformative technologies to distribute time-bound safety communications. For example, a proactive time-bound safety communication targeted at parents or caregivers to prevent serious medication error by explaining through video how and when to use an asthma inhaler for an 8-year-old child is much more impactful than a 3-page user manual with instructions and diagrams.

Evidence indicates that digital communication with patients can improve their care and health outcomes.[7,8] Studies have shown that by using online applications physicians and patients become more connected and physician's advice is followed, which resulted in improved adherence among patients with chronic diseases.[9] It may also improve patient satisfaction by increasing the time spent communicating with and having questions answered by their healthcare professionals.[9]

Although healthcare professionals have been reluctant to use social media for direct patient care, this practice is slowly being accepted.[8,10] Some physicians are using social media, including Twitter and Facebook, to enhance communication with patients.[8] The study also found that about 60% of physicians favoured interacting with patients through social media to provide patient education and health monitoring and to influence attitudes towards medicines and encourage adherence. These efforts could lead to better education, increased compliance, and better outcomes.[7] Healthcare professionals can also use such social networking platforms to transfer a time-bound safety communication to their patients.

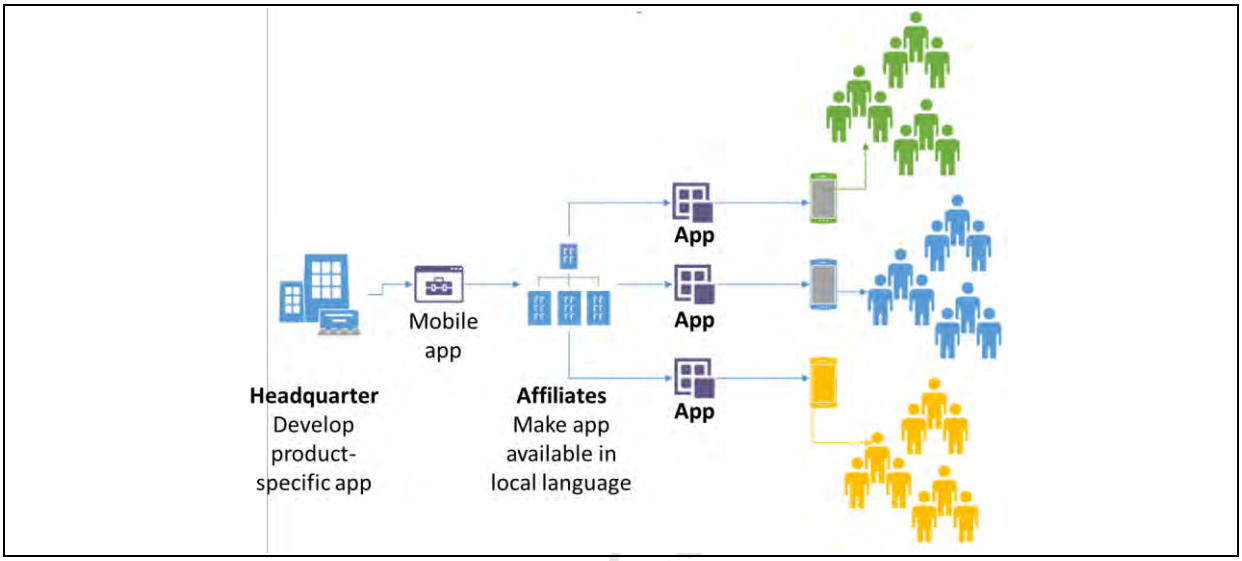
Pharmaceutical supply chain and multilayer regulatory requirements which vary for different jurisdictions contribute to the complexity of time-bound safety communication. Establishing controlled communication pathways using digital medium and technologies can be complex but are critical and can be paradigm shifting in how time-bound safety information is delivered and communicated to users of medicinal products, caregivers and healthcare professionals.

Figure 6 shows the pathway that can help establish control over a safety communication structure using web technologies and mobile platforms to support safety communications. A market authorisation holder or manufacturer can take ownership of developing a mobile app or platform for the content of safety information and communication controlled centrally. Versions of the app or platform in local languages, unique requirements or elements specific to the territories can be integrated by local affiliate organisations or

partner companies in individual territories before providing them to individuals or caregivers in those territories. Establishing such a framework in advance, as part of distribution of medicinal products, is the key in ensuring proper impact and effectiveness of time-bound safety communication. People using a medicinal product or their caregivers need to be encouraged to download such apps and platforms and to understand how to navigate and act on time-bound safety information, when such communication is issued from pharmacovigilance teams working at a central level.

***Figure 6: Cascading centrally generated safety information through product-specific Apps***

Source: CIOMS Working Group XI




Social networking platforms, apps or media-sharing sites should be chosen beside the current traditional channels to communicate time-bound safety communication effectively to the target audience. This also allows information to be passed on in a uniform way through other channels by ensuring consistent messaging and broad distribution.

However, transforming safety communication introduces risks such as:

- quality content breaches
- damage to professional image
- breaches of privacy
- violation of the patient-healthcare professional boundaries
- licensing and patent protection issues and other legal ramifications.

These risks need to be carefully considered when enhancing safety communication.

## 7.7 Patient involvement

The involvement of patients through patient organisations has many advantages for developing time-bound safety communications. It helps to ensure that information is transferred in an effective and impactful manner to patients.

Patient involvement is possible at several steps in the development of time-bound safety communications. They can contribution to the decision on whether the identified concern constitutes an important health risk and should therefore be considered for safety communication. And if it is deemed urgent then it is time-bound. At the moment, this decision is mainly made by the regulatory authority, clinical trial sponsor and the marketing authorisation holders or manufacturer.

Time-bound safety communication often concerns important new safety information like new serious unwanted effects or important quality deficiencies (*e.g.* contamination). However, for an individual who uses the medicinal product, many more safety issues would be potentially eligible for communication. An example of safety communication that users (or their caregivers) might expect is how to use a child's asthma inhaler safely and correctly to prevent serious medication error. Another example of communication relevant to patients is information on contraceptive measures and frequent pregnancy tests according to the medicine's pregnancy prevention programme for medicinal products that can cause serious harm to the fetus.

For a person using the medicinal product, safety communication that uses understandable language and terminology is more valuable, especially if a large number of people – with potentially more variable level of understanding – is affected. Clear and comprehensible communication of recommended action to people using the affected medicinal products can increase the communication's impact. In general, if patients are the target audience then they should already be involved in the development of the communication (see section 7.4).

Ideally, time-bound safety communication should be developed either jointly involving all stakeholders or by asking members of the patient organisations for input on drafts prepared by other stakeholders. However, in situation which requires urgent safety communication, this may not be feasible because of the challenges of identifying and contacting patients who can provide prompt input so that the communication is not unduly delayed. The chances of obtaining prompt patient input can be increased by making preparations in advance: using predetermined processes for patient involvement, assessing the need of patient involvement, and considering the timetable for preparing the communication (and when patient involvement should be sought).

Advance preparation for dealing with urgent situations could include involving patients in setting up criteria to identify a safety issue which require their prompt input. This would ensure that the right safety issues are communicated to patients in an appropriate and timely manner when the need arises. It would therefore be beneficial to liaise with patients or with patient organisations or patient advocacy groups whose members are using the medicinal product. A patient organisation can describe what questions and concerns their members have about the medicinal product.

Patient organisations use varying means to communicate with their members such as magazines, newsletters, bulletin boards and social media. Therefore, they can use these means to support the dissemination of time-bound safety communication to their community (see also Box 2 in section 2.2.7). A patient organisation can also support effective communication after dissemination of a safety communication by responding to questions from their members and moderating their social media accounts. This may require regulatory authorities, marketing authorisation holders or manufacturer to provide additional information and training to the staff or volunteers in patient organisations (see section 3.4.2).

To understand their expectations, we recommend discussing in advance with patients the fair compensation for time spent in developing a safety communication (see section 3.3.2).

In conclusion, patients can contribute to time-bound safety communication by:

- **selecting issues for communication** – setting criteria for identifying safety issues for time-bound communication to patients (patient group unspecific);

- **selecting what needs urgent communication** – providing information on urgent matters to be communicated from patient perspective and information required (patient group specific);
- **disseminating safety communication –** using patient organisations' communication channels to disseminate time-bound safety communication (patient group specific);
- **answering questions** – responding to questions and moderating discussions about the safety communication among their members (patient group specific);
- **early involvement** – providing input from an early stage through predetermined processes;
- **improving access** – providing input on the information and language used to improve understanding; and
- **increasing reach** – providing input into plain language translation. In addition, patients could help to create a glossary of terms specific to a disease and treatments (patient group specific).

## 7.8 Measuring the effectiveness of safety communication

A safety communication is considered effective when it is received and understood by the target audience in the way it was intended, and leads to appropriate action. The effectiveness should be evaluated where appropriate and in general quantitative or qualitative methods can be used to measure:

- **Dissemination.** How successful was the dissemination of the communication to the target audience? How many mailings failed to reach their destination? How many times was the safety communication downloaded from websites? How many of the planned recipients receive the communication?
- **Awareness and knowledge.** How many of the target audience understood the communication? How many had already learnt of the communicated safety issue through other routes? Which routes did the target audience use? Did the individual using the affected medicinal product understand the communication, whether received indirectly or directly?
- **Practical change.** Did the actions of the target audience change as intended by the safety communication?
- **Health outcome.** To what degree did the safety communication prevent harm from the safety concern? Has harm from the safety issue decreased?

Robust methods should be used to measure how well the safety communications has achieved its aim. Surrogate measures and outcomes, including actions, attitudes, and knowledge can be used separately or in combination.

Any shortcomings in disseminating the safety communication (*e.g.* problems with the list of recipients or the timing and mechanism of dissemination) as well as individuals misinterpreting recommended actions should be identified. If the safety communication has not achieved its aim, a root cause analysis should drive interventions to correct any failings. Experiences of past safety communications should be considered to prevent recurrence of any failings and also to apply lessons from successes. This requires flexible systems that can be adapted to improve practices and approaches.

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# Chapter 8: Additional risk minimisation

Every medicine is associated with some risk of harm to the patient. Risk minimisation is about preventing or reducing these risks to protect patients from harm. Usual measures to minimise risks include classifying some medicines as prescription only, providing detailed prescribing information to healthcare professionals (HCPs), as well as including plain language information for patients in the packaging (product labelling, see Chapter 6). Because these measures apply to most medicines, they are called 'routine risk minimisation'.

Routine risk minimisation measures may not be sufficient to manage the risks of some medicines, so additional risk minimisation measures (aRMMs) are sometimes needed. These aRMMs are usually aimed at a particular risk or group of risks and may be directed at particular groups *e.g.* physicians, pharmacists or patients.

In this chapter we describe ways in which patients can be involved in the design, development and implementation of aRMMs – those which go beyond the usual methods to minimise risks.

**Key points**

1. Every authorised medicine has potential benefits and potential risks; the balance of its benefits must outweigh its risks for it to be licensed.
2. Some medicines have risks which need more than the usual risk minimisation measures.
3. Additional risk minimisation measures may place an additional burden on patients and on the healthcare system. This means that the measures need to be proportionate to the relevant risk.
4. Additional risk minimisation measures should be designed to fit easily into the healthcare system.
5. Patients can provide invaluable insights into the best way to minimise risks. This means they should be involved at all stages when considering additional risk minimisation measures.

## 8.1 Risk minimisation

Medicinal products – which include medicines, biological medicines, vaccines and medicine-device combinations – are developed to benefit patients. This may be by treating, preventing or diagnosing a medical condition, slowing disease progression, reducing its signs and/or symptoms or restoring or altering some function of the body. These products also have risks (unfavourable or harmful effects). Risks vary in severity (*e.g.* from mild and temporary side effects such as a slight stomach upset or headache, to serious ones such as heart conditions or stroke) and in likelihood (*e.g.* from very common to very rare). They also vary in the opportunities for risk minimisation.

Generally, risks result from how the medicine works, how the body metabolises or removes the medicine or how it is used in practice. Some risks are completely preventable while others can have their likelihood or severity reduced. Not every patient benefits from a medicine or gets side effects; so, we talk about potential benefits and potential risks to make it clear that they may happen but not for everyone.

In many countries, a regulator needs to authorise a medicine before a HCP can prescribe it or a patient can buy it. For any authorised medicine, the potential benefits must outweigh the potential risks to the intended patients when the medicine is used as authorised. Evidence on benefits and risks is obtained from laboratory experiments and animal studies, and clinical trials, as well as knowledge continuously gathered from post-authorisation studies and the medicine's use in clinical practice. Since every medicine has risks, the

balance of benefits and risks can be improved by minimising the risks, especially those that are serious and have substantial impact on patients' wellbeing.

HCPs have a vital role in passing on information to patients about a medicine's risks, crucially about how to minimise or avoid the risks. Face-to-face encounters with a HCP allows the patient to fully understand the nature of the risks and how to prevent harm from such risks.

In this chapter, 'medicine developer' refers to the company or institution responsible for generating the evidence needed for the medicine to be authorised. In the European Union (EU), the medicine developer that applies for authorisation is called the marketing authorisation applicant (MAA). If the medicine is authorised, the company or institution is known as the marketing authorisation holder (MAH).

### 8.1.1 How risk is minimised

The overall aim of risk management is to ensure that the benefits of the medicine exceed the risks by the greatest achievable margin.[1] The ultimate goal of risk minimisation is to ensure that the right patients get the right dose of the right medicine under the right conditions at the right time. The 'right patients' are those for whom the potential benefits outweigh the potential risks. 'Risk minimisation' includes both risk prevention and risk mitigation.[2,3] Risk minimisation measures (RMMs), also known as risk minimisation activities, include tools intended to prevent a risk or reduce how often it occurs, or mitigate a risk (reduce the severity when it occurs) or both.[2,3] RMMs can apply to prescribing, dispensing or using a medicine, the circumstances in which it is used, patient selection, and patient monitoring or evaluation.

Risk minimisation measures are classified as routine or additional[1] (see also Annex 2 to this chapter and the 2014 CIOMS report, *Practical approaches to risk minimisation for medicinal products*).[2] Every medicine has routine risk minimisation measures – such as the routine information provided to healthcare professionals and patients. Additional RMMs (aRMMs) are used when routine RMMs are not thought sufficient to reduce the risks to an acceptable level. They relate to a specific risk or set of risks.

aRMMs can be grouped into two broad categories:

- Communication and educational: providing information to heighten awareness or understanding about a risk and promoting attitudes or actions to minimise the risk.
- Controlled medicine distribution and use: measures to limit the medicine's prescribing, dispensing or access.

In some cases, aRMMs are an essential prerequisite for a medicine to receive regulatory approval or to maintain its marketing authorisation. Without these measures, the medicine's benefits would not exceed its risks and so would not be authorised for treatment.

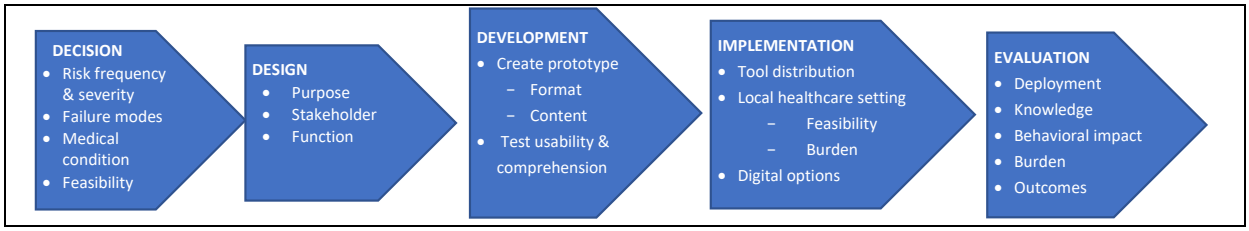
## 8.2 Patient involvement in additional risk minimisation

### 8.2.1 When to involve patients in additional risk minimisation

Patients can be involved throughout the aRMM process (Figure 7) by providing valuable input on the decision, design, development, implementation and evaluation of aRMMs. Patients' input can inform the relevance and functionality of the aRMMs and the acceptability and feasibility for implementation.

***Figure 7: Framework for patient involvement in additional risk minimisation measures***

Source: CIOMS Working Group XI




### 8.2.2 Ways of involving patients in additional risk minimisation measures

Patient input on risk minimisation can be collected in a variety of ways. Also, collection of patient perspectives can be incorporated into clinical trials (see section 4.4).

***Table 8: Methods to collect patient experience data***

Source: CIOMS Working Group XI

| Qualitative research | Quantitative research |
|---|---|
| • Individual and group interviews with patients<br>• Focus groups<br>• Patient panels<br>• Patient advisory boards<br>• Analysis of social media postings in response to specific topics | • Survey to obtain targeted information from patients |
| Open-ended questions (see example for aRMMs in Annex 3 to this chapter) to elicit information from patients' experiences and perspectives 'in their own words'. | Closed questions with distinct response options to quantify responses. |

Surveys can be conducted as follows:

- in-person paper questionnaires
- by an interviewer
- over the phone
- by email
- online or using a mobile device
- using automated telephone or voice response system

These research approaches can be combined, in the same patient encounter, to collect different types of patient experience data.

To ensure that the research participants are representative of the target patient population, the following factors should be considered when selecting patient representatives for input or experience data:[4]

- demographic background (*e.g.* age, sex, race or ethnicity)
- socioeconomic background
- cultural background
- geographical area
- health literacy (*e.g.* level of education, level of reading, writing, problem- solving abilities, speaking ability, understanding of the medical condition and of healthcare system)
- functional status (physical, cognitive)
- severity of medical condition; co-morbidities
- severity of signs and symptoms
- duration of disease (for example, time since diagnosis).

## 8.3 How to involve patients at each step of the additional risk minimisation process

### 8.3.1 Decision to introduce additional risk management measures

The first step in the process is to determine whether risks can be managed by routine risk minimisation or whether aRMMs are needed.

Whether a medicine needs aRMMs can be determined at various stages in the medicine's life. t may become obvious during clinical trials that aRMMs will be needed to manage a particular risk post-authorisation.. When identified early enough, clinical trials provide an opportunity to design and pilot an aRMM. More often, the need for an aRMM is decided closer to the time of marketing authorisation.

Sometimes, important new risks which have (or may have) a major impact on the benefit-risk balance are identified after authorisation. Additionally, a known risk can be found to be more serious or more frequent than was seen previously during clinical trials; this may necessitate introduction of aRMMs to manage the risk. Evaluation of an aRMM's impact may lead to it being revised or discontinued.

#### Factors involved in decision making on additional risk management measures

Deciding whether a medicine merits aRMMs is complex. Regulators and medicine developers consider a number of factors to make this decision:

- severity and frequency of the risk (or set of risks)
- healthcare professional (HCP) familiarity with the relevant risk and of managing it
  - For example, a cancer doctor will be very familiar with prescribing medicines which substantially lower white blood cell levels and will know how to manage the risk, whereas a generalist less familiar with such medicines will not be as alert to the risk and will be less confident about managing it.
- whether the product requires a new (complex) method of administration
- is the medicine a new substance which raises questions such as:
  - will the medicine have risks or be given in a way that is different from existing treatment options?
  - can the medicine be given in different ways or doses which could lead to confusion?
- seriousness of the medical condition
- expected benefit of the medicine
- target population size
- special population use (*e.g.* children, pregnant or breast-feeding women, the elderly, visually impaired or cognitively impaired patients)
- expected duration of treatment
- medicinal forms (*e.g.* solutions or suspensions that may require preparation, dilution or reconstitution) or use of dosing devices
- potential for abuse and for off-label use (using the medicine outside the circumstances for which it is authorised)
- opportunities for, and feasibility of, minimising the risk within the healthcare setting
- Whether the risk justifies the extra burden placed on the patient and/or healthcare system by the aRMM.

Patients can provide regulators and MAHs unique and valuable perspectives on the above factors. For example, if a medicine's dose needs to be measured, they can provide insights on how easy it is to understand what dose is needed, how easy it is to measure the correct dose, and whether there are ways to make it easier.

#### Integrating the patient perspective in decision making

The patient perspective on what can go wrong, when and where, is an important factor in the decision on what risks require aRMMs. The general patient care pathway and the questions based on it (described below) identifes areas which patients consider particularly important for minimising a risk.

Patients can be included in conducting a failure mode and effects analysis (FMEA).[5–7] FMEA is a standardised risk evaluation method used in a variety of settings, such as aeronautics, military, engineering, and manufacturing, to identify potential failures (before they occur) and mitigation options. In these risk intensive settings, lives are at stake if certain failures occur. 'Failure mode' describes how something might fail; this can be departure from ideal actions. 'Effects analysis' assesses the consequences of the failures; it considers the seriousness and frequency of the consequences and how the failures could be minimised. This systematic approach can also be used to evaluate risks and risk minimisation of medicines (details and examples provided in Annex 4 to this chapter and in the CIOMS report, *Practical approaches to risk minimisation for medicinal products*).[2]

Patients can advise medicine developers on realistic ways to reduce the risk of aRMM failure while taking into account that humans will make mistakes.

### 8.3.2 Designing additional risk management measures

When one or more aRMMs are considered necessary, the choice and design of the aRMM needs to be made. Typically, the design of aRMMs is based on three key specifications:

- Purpose: what is the aRMM trying to achieve?
- Stakeholder: who is the target for the aRMM?
- Function: how will it be achieved?

Patients can provide important insights into each specification.

For the first specification, it is essential to be clear on what is intended. The outcome or goal of a given aRMM might be achievable in different ways. Being clear on the objective of the aRMM will allow the appropriate choice of aRMMs.

For example, for a medicine which causes birth defects, the goal of aRMMs might be to avoid any child being born with the defect. In theory this goal could be achieved by offering pregnancy termination if a defect were detected in an unborn child. However, most people would consider this an unacceptable aRMM! Changing the objective of the aRMM to preventing the fetus from coming into contact with the medicine, means the goal can be achieved by a pregnancy prevention plan. The pregnancy prevention plan would ensure that women are not pregnant when they start treatment with the medicine and do not become pregnant during treatment. In this example, the goal may be the same but the objective of the aRMM and ways of achieving it are very different. Once the objective is clear, how, when and whom to target are next steps.

Patients can provide useful input into helping frame the objective of an aRMM. In the above example, patients could also provide input into how to make pregnancy prevention plans effective and what is acceptable in a particular culture or region.

#### Using the general patient treatment pathway

When designing aRMMs it is essential to think about the general treatment pathway (Figure 8) for the medicine. Patients can provide insight into how the pathway works for them and their disease. The pathway may vary depending upon the condition being treated, the region including associated cultural aspects, local, national and international treatment guidelines and the healthcare system in the country or region.

***Figure 8: General patient treatment pathway***


For products which include a device, additional aspects may need to be included (*e.g.* installation, maintenance, service and shipping).

The general patient treatment pathway can help patients think about the circumstances in which a risk might arise and what measures can reduce the severity or likelihood of the risk occurring. For example, patients could suggest appropriate actions for a patient or caregiver that could minimise risk at various points along the treatment pathway. They can also suggest actions they would like from their healthcare providers (or other stakeholders involved in the care pathway) to help minimise risk. This information can be applied to the design of an aRMM.

Patients can be asked for their viewpoint on who the key stakeholders are along the care pathway. The key stakeholders will vary according to how healthcare is delivered in the specific healthcare system. The most common stakeholders include:

- Prescribing physician
- Other healthcare providers (*e.g.* others doctors, pharmacist, nurse, physical therapist)
- Patient
- Patient caregiver
- Product distributor

Patients can also be asked their opinions on various questions based on each phase of the care pathway to inform aRMM purpose and function (Table 9). For some medical conditions, obtaining information from caregivers based on the Pathway would also provide useful information to optimise the design of additional RMMs.

***Table 9: Questions based on the general patient treatment pathway to obtain patient perspectives***

Source: CIOMS Working Group XI

| **Patient and treatment selection** | **Dispensing of product** | **Product use** | **Follow-up** |
|---|---|---|---|
| • What does a patient need to know about how a patient is selected for treatment?<br>• How does the prescriber select suitable treatment for the patient?<br>• What do patients need to know about testing (e.g., screening or biomarker) to identify those more vulnerable to a risk?<br>• What do patients need to know about vaccinations before and during treatment?<br>• Do healthcare providers other than the prescriber interact with the patient? | • Does the patient or caregiver need pre-treatment instructions?<br>• Should the patient be counselled about:<br>○ Nature of the risks?<br>○ Signs and symptoms of the risks?<br>○ How to take the product?<br>• Will patients or caregivers receive the medicine on time?<br>• What do patients think about the product being dispensed in a specific healthcare setting (*e.g.* inpatient or infusion centre)? | • How is the product administered?<br>• What is the treatment setting?<br>• Can a patient self-administer the product (*e.g.* when medicine needs to be reconstituted or Injected)?<br>• Does the amount of medicine needing to be taken change over time (*e.g.* weight based dosing)?<br>• How difficult is it to follow the instructions for using the product?<br>• Will patients understand and follow product use instructions?<br>• Should patients be observed or monitored during administration? | • Are patients aware of the risks?<br>• Are patients aware of signs and symptoms of risks?<br>• Would early recognition of signs and symptoms enable the patient to act to reduce severity of the risk?<br>• Can the patient act to prevent the risk?<br>• Will the patient attend monitoring appointments, follow-up visits?<br>• Will the patient adhere to laboratory testing and monitoring requirements? |

### 8.3.3 Developing additional risk management measures

#### Options and formats for additional risk minimisation measures

Patients can provide ideas or feedback on specific aRMM options. For example, patient educational information can be developed in multiple formats, such as print, downloadable files, interactive applications, and webpages. With growing access to, and familiarity with, information technologies that allow instant access to information, there is a need to move beyond paper-based tools and use digital tools, accessible via a variety of devices – from handheld ones to personal computers.

MAHs are making efforts to provide interactive learning tools, digital options and innovative aRMMs which can be customised for specific patient groups (for example, tools for patients with visual or hearing impairment or patients with mobility limitations). Patients can advise on the most appropriate formats for a particular target audience and can provide valuable perspectives on:

- Tool prototypes
- Tool format appropriateness (format preferences may vary according to factors such as age, educational level, and geography)
- Tool feasibility and acceptability (would the tool be used, and how)
- Tool design to enhance utility and ease of use, and therefore, adherence
- Tool design to limit burden

#### Content for additional risk minimisation measures

Patients can provide information about aRMM content that can be important for the success of aRMMs. Patients or caregivers can make valuable recommendations on what information is suitable for children (including suitability for different age groups). What is suitable may also depend upon region and culture. If patients consider a specific tool irrelevant or unappealing then it is unlikely to succeed in reducing the risk.

Similarly, educational material that patients cannot understand will be ineffective and possibly detrimental. Patients with varying educational and cultural backgrounds can help to evaluate the suitability of material, based on both readability and comprehension. The ability to understand numbers can also be relevant in information for patients; understanding of numbers (numeracy) may be different from reading ability (literacy).[8] Because risks (and benefits) may be expressed as percentages or ratios, inability to understand the size or frequency of a risk could lead to patients either rejecting the medicine or not realising the importance of risk minimisation.

### 8.3.4 User testing additional risk minimisation measures

A prototype of an aRMM tool can undergo user testing (also known as usability or human factors testing) with patients and other target user groups. Patient participants in user testing should be representative of the target group and be members of the general public rather than 'expert patients' (see section 4.6). User testing can also be undertaken with the intended end users (often patients) in simulated-use conditions that mirror real-world-use circumstances as much as possible, taking into consideration users' perspectives, the medicine, its function, and the use environment. The testing will indicate the likelihood of the tool achieving its intended purpose.

User testing of the information or tool is most valuable if it includes people who might be most challenged when using it. For example, if a medicine is for the elderly, it might be helpful to include people with reduced vision to check if the information is readable or

whether another format is better suited. For educational tools, the testing can assess readability and comprehension of the educational information.

User testing is designed to be both diagnostic and iterative. The results can inform what aspect of the tool's design, format or content could be modified to improve its usefulness. After each round, good practice in information writing (using plain language principles) and overall tool design is applied to address deficiencies and then retested in a new group of participants. Additionally, patients could do a trial run using a tool before full implementation (for example, before launching a new medicine). Test results can be provided to regulatory authorities as evidence of the tool's usefulness and appropriateness.

### 8.3.5 Implementing additional risk minimisation measures

Patients can provide valuable input on how to implement aRMMs for both patient-focused aRMMs and aRMMs for other stakeholders (*e.g.* physicians, nurses, pharmacists). In some countries, the regulatory authority must review or approve the aRMM implementation plan. The aRMM should also fit in with local healthcare and social practices.

Patients can provide information on:

- Local standard practice procedures
- Cultural aspects
- Local feasibility for implementation approaches
- Distribution of tool for aRMM: how to optimise delivery of tools to patients or other stakeholders (for example, who provides the tool, where its provided and when)
  - Frequency of distributing (or replenishing) the tool
- How patients are introduced to the tool and its purpose (tool instruction for use)
  - Use of visual aids, infographics, videos to aid implementation
- aRMM translation (language) options
- Local healthcare setting implications such as availability of laboratories and screening services
- Ways to lessen burden, enhance adherence or use of aRMMs
- Use of online or other digital options to implement or distribute tools for aRMM

If feasible, implementation or use of aRMM prototypes can be tested during clinical trials (see Chapter 4) to inform implementation strategies when launching the medicine after approval.

#### Assessing the burden of additional risk minimisation measures

An important caveat in additional risk minimisation planning is to determine if an aRMM places undue burden on the patients, caregivers, healthcare providers and the healthcare system, and how well the aRMMs can be integrated into healthcare delivery. Any additional burden affects the ease of implementation and the adoption of the aRMM by target stakeholders. For example, a requirement for magnetic resonance imaging (MRI) before the medicine is prescribed is unlikely to be implementable where MRI facilities are limited or absent. Where implemented, the screening could place a large burden on the healthcare system (by using up scarce MRI time) and on patients who may have to travel long distances to centres which have MRIs. In these circumstances, there is a risk that either this aRMM will be ignored or a potentially beneficial medicine is not used because the aRMM is too burdensome.

Patients can offer insights on such burdens and recommend how to avoid or lessen them. For example, if a test is necessary before prescribing a medicine, patients could suggest how this could be integrated into their daily routine to avoid long waits at hospitals or multiple visits. Understanding how an aRMM impacts on the life of a patient is important for determining whether a particular aRMM is likely to succeed in its objective.

### 8.3.6 Evaluating additional risk minimisation measures

Evaluating aRMM effectiveness in minimising risk and its impact on healthcare system burden and patient access to a medicine is important. Additional RMMs are put in place to reduce risk. If aRMMs are not effective, then there is an increased likelihood of harm to patients. aRMMs use resources – this can be financial in the costs to the medicine developer, time for HCPs and patients, healthcare resources such as laboratory testing and clinical tests and screening. If aRMMs are not working, it is important to modify them to prevent patient harm and waste of resource. It is also important to ensure that aRMMs are not so burdensome that access to the medicine in question is prevented.

The evaluation can focus on individual aRMMs, across multiple measures as part of a single aRMM programme, or across multiple aRMM programmes for a class of medicines. Regulatory authorities often require the medicine developer to include effectiveness evaluation as part of the overall additional risk minimisation programme. [2,3,9,10] Patients can provide ideas for designing the effectiveness evaluation and they can participate in the evaluation.

Patients can help interpret the evaluation results, and when warranted, advise on improvements to the aRMMs, based on the evaluation findings. Patients can also advise whether an aRMM can be decommissioned if it is no longer needed.

#### Evaluating effectiveness

The key measure of risk minimisation is whether it prevents or reduces the frequency and severity of a risk. An evaluation may involve counting both the number of adverse reactions, over a period and assessing their severity; however, it may be difficult to collect the necessary data outside a clinical trial setting. Sometimes a more formal evaluation is needed, and it may be a requirement by certain regulatory authorities.

#### Evaluating implementation

The implementation process can be evaluated in different ways, such as:

- Tool delivery and distribution
  - Distribution within a given timeframe to targeted recipients
  - Frequency of distribution
- Awareness of the tool
- Usage of the tool
- Acquired knowledge about the risk
- Impact on activities: desired actions versus deviations from ideal actions
- Burden on stakeholders, clinical practice and on healthcare setting

Patients can provide their perspectives on how well the aRMM is being implemented, and whether the aRMM is needed, once they have used it as part of their treatment.

#### Evaluating knowledge, attitudes and actions

Sometimes patients participate in a questionnaire (or survey) evaluation to collect information about the aRMMs to assess their knowledge, attitudes, and medicine-use practices. This approach can collect information from patients living in diverse locations and can be conducted in a variety of ways, such as by phone, mail, email or online. Patients should be involved in the design of the questionnaires and in testing prototype questionnaire to ensure that the questions are relevant, appropriately phrased and understandable. Surveys have some challenges, such as recruitment of representative patient samples that adequately reflect the target patient population, lack of objective criteria for measuring knowledge, and reliance on self-reporting and recall rather than direct measurement of knowledge, attitudes and/or behaviours.[11]

#### Online evaluation

Some medicine developers use online aRMMs, allowing stakeholders another way to access the aRMM before or during use of the medicine. Web-based aRMMs can include built-in analytics to collect ongoing real-world effectiveness information, based on reported actions, comprehension, or even satisfaction with the aRMM, from a range of patients. Information can be collected on the number of downloads, the sections of educational material viewed, the time spent by a stakeholder using a tool or reviewing certain sections of educational material. Patients are being invited to advise on the development of these innovative tools and on how they are evaluated for effectiveness.

## 8.4 How regulators involve patients in additional risk management measures

With the aim of managing serious or frequent risks, many regulatory authorities have legislated for the use of aRMMs and have produced guidance on them (see Annex 1). Regulators can enforce the requirement for aRMMs by making them a condition of the marketing authorisation, as in the EU. Although the specifics of the legislation vary between regulators, in all jurisdictions aRMMs are ultimately intended to improve a medicine's balance of benefit over its risks.

### 8.4.1 European Union

In 2004, the EU introduced the concept of risk management system (Directive 2004/27/EC). Medicine developers were required to describe the risk management system in the form of a risk management plan (RMP) when they applied to have a medicine authorised.[1] If additional risk minimisation activities were likely to be required, companies had to submit a risk minimisation plan as part of the RMP. Since July 2012, all medicines are required to have a RMP which includes a risk minimisation plan.[1]

There are 4 possible routes for medicines to get authorised in the EU: the centralised procedure, mutual recognition, decentralised procedure, and purely national procedures (see Annex 1). The following description applies to medicines that the European Medicines Agency (EMA) evaluates through the centralised procedure, which applies to the vast majority of innovative medicines authorised in the EU.

Patients have an important role in advising the EU regulators on aRMMs. Sometimes EMA sets up scientific advisory groups to discuss aspects of whether a medicine should be authorised and under what conditions. The groups often include representatives from patient organisations who can advise on the practical aspects of living with a disease and what matters to them. They can also comment on proposed aRMMs and their practicality.

The EMA's safety committee, the Pharmacovigilance Risk Assessment Committee (PRAC), which has the responsibility for making recommendations on RMPs – and hence aRMMs – includes patient representatives and it also holds public meetings to interact with patient representatives.

A medicine that involved considerable discussion with patients was thalidomide which the EMA evaluated for treating multiple myeloma, a bone marrow cancer. In the late 1950s and early 1960s, thalidomide was used for treating morning sickness during pregnancy. Unrealised at the time, thalidomide causes serious birth defects when fetuses are exposed to it in the womb. Its use led to a large number of babies being exposed to the medicine and, as a result, many babies were born with serious birth defects before it was withdrawn from use.

However, many years later, research found thalidomide very effective in treating multiple myeloma (a form of blood cancer) and also some severe skin conditions. Given thalidomide's history, reintroducing it, albeit for another use, ignited concerns over risks for patients and potentially unborn children.

In Europe, the EMA organised a series of meetings with the victims of thalidomide –children of women who had taken it during pregnancy – and multiple myeloma patients for whom thalidomide was proving to be of major benefit in clinical trials. The two groups discussed the medicine in sometimes intense and painful meetings. The thalidomide victims understood the need to license thalidomide for treating multiple myeloma but wanted to ensure that no child should ever suffer the severe effects that they had suffered. Consequently, aRMMs were agreed to prevent any fetus from being exposed to thalidomide.

### 8.4.2 United States

In the US, the FDA can require companies to develop and implement a risk evaluation and mitigation strategy (REMS), a required additional risk minimisation plan, to ensure the benefits of a medicine outweighs its risks. The Food and Drug Administration Amendments Act of 2007 (FDAAA) established FDA's REMS authority (see Annex 1 to this chapter).[12–14]

The FDA seeks patient input in several ways on proposed strategies to mitigate a specific medicine's risks. It seeks input from patients on medicines under review and is discussed at Advisory Committees through the open public hearing session during which patients may present their views on the proposed risk minimisation strategy. FDA also encourages medicine developers to seek patients' and healthcare providers' input on a proposed risk minimisation strategy during the development of the REMS, after implementation or if the REMS undergoes a major modification.

Patient input was important during the review of Palynziq (pegvaliase), an injectable medicine for treating adults with phenylketonuria (PKU), to understand patient's perception of benefits and burden that may be associated with certain risk minimisation strategies. Palynziq's manufacturer sought input from the national organisation of patients with PKU during the clinical trials. Patient input included discussion of the burden of monitoring associated with the medicine as well as with the perceived risk of anaphylaxis, including the decision to continue treatment if it occurred. Ultimately, the FDA and the manufacturer considered the patient input and implementation of measures during the trials in the development of the REMS. The Palynziq REMS includes patient education and counselling on the signs and symptoms of anaphylaxis, as well as the necessity to have auto-injectable epinephrine (adrenaline) available at all times.

Patients' perspectives can also be provided to FDA once the REMS has been approved and implemented. The Center for Drug Evaluation and Research's Division of Drug Information

welcomes patients' questions and feedback on REMS programs. Additionally, the FDA encourages companies to include patient input when evaluating burden as part of a REMS effectiveness assessment.

### 8.4.3 Japan

In Japan, the industry is mandated to prepare an RMP for medicines. This applies to medicines whose application for marketing authorisation was after 1 April 2013, or if any new safety concerns arise after authorisation. Additional risk minimisation activities may be included for any authorised medicine (even if the marketing authorisation application preceded 1 April 2013). The RMP may include additional risk minimisation activities if they are considered necessary.[15]

Japan's Pharmaceuticals and Medical Devices Agency (PMDA), the agency responsible for reviewing medicines and medical device applications in Japan, issued guidance on patient participation in September 2021.[16] The following cases illustrate patient involvement in additional risk minimisation activities in Japan.

The first case is similar to the experience described above in Europe. Thalidomide was marketed in Japan in the 1950s as an antiemetic, hypnotic and sedative, particularly for pregnant women. The medicine was recalled in Japan when it became clear that it caused birth abnormalities when taken during pregnancy. When studies found thalidomide to be effective for multiple myeloma, it was authorised for again in 2008 for this disease. Moreover, lenalidomide and pomalidomide, both chemically similar to thalidomide, were developed subsequently for treating multiple myeloma and were approved in Japan in 2010 and 2015, respectively. As expected, animal studies identified birth defects as an important risk for these medicines.

In granting marketing authorisation for thalidomide (Thaled), lenalidomide (Revlimid), and pomalidomide (Pomalyst), the Ministry for Health, Labour and Welfare (MHLW), which develops and implements safety standards for medicines and medical devices in Japan, required additional risk minimisation programmes [thalidomide education and risk management system (TERMS) and proper control procedures for Revlimid/Pomalyst (RevMate)]. Aimed at preventing fetal exposure to these medicines, these programmes, directed at prescribing physicians and medical institutions, include educational measures and measures to restrict distribution and use. Representatives of a multiple myeloma patient group and a group of thalidomide victims were on the committee for the preparation and review of these additional risk minimisation programmes.

Another example involved methylphenidate (Ritalin), a stimulant approved in Japan in 1957 for treating depression and depressive neurosis. In 2007, Ritalin was authorised and marketed for the treatment of narcolepsy (a disorder that causes a person to fall asleep suddenly and unexpectedly), refractory depression (depression that doesn't respond well enough to antidepressants), and prolonged depression. By then, inappropriate use or abuse of Ritalin had become a problem. Of note, other medicines were available in Japan for treating depression. The MAH of Ritalin proposed to MHLW to remove depression as an indication and to restrict distribution. At that time, review of the marketing authorisation application of Concerta, a long-acting version of methylphenidate, was underway for treating childhood attention deficit/hyperactive disorder (ADHD). The MHLW decided that restrictive distribution was necessary to prevent off-label use and unauthorised distribution of both Ritalin and Concerta. In making this decision, the MHLW had solicited opinions from patient organisations and healthcare professionals. As a result, MHLW accepted the removal of depression as an indication of Ritalin and mandated measures to restrict distribution, including restricting prescribing by physicians and medical institutions, for both medicines.

Lisdexamfetamine (a form of amphetamine) was approved in Japan in 2019 (as Vyvanse) for treating childhood ADHD. MHLW sought patient input on the additional risk minimisation programme for the medicine. This patient perspective was used to develop the final programme which included measures to allow only doctors who have undertaken e-learning on the risk of drug dependence to prescribe the medicine, only registered pharmacies with pharmacists who have taken the same e-learning to dispense the medicine, and patients to be followed in a register to prevent duplicate prescribing and inappropriate distribution. In addition, a third-party committee was established to confirm that the medicine was properly distributed and prescribed.

## 8.5 Conclusions and recommendations

Additional risk minimisation measures (aRMM) aim to optimise the balance between a medicine's benefits and risks. This is generally achieved by patient selection, treatment management (*e.g.* through monitoring, screening, testing and patient follow-up, as well as modifying how a medicine is used) and prompt recognition and treatment of specific harms.

Involving patients throughout the aRMM process helps to determine if such additional measures are needed and provides valuable input into the design, development, implementation and evaluation of the specific measures.

Patients should be invited to provide ideas or feedback on specific aRMM options, taking into account different educational and cultural backgrounds and health literacy. Patients can provide input on the approaches to implement aRMMs, offering ideas on customising their implementation, according to local social, legal and healthcare circumstances.

Patients can provide an important perspective on how aRMMs may be accepted and used. They can also help determine whether a given aRMM will place an unacceptable burden on themselves, carers and the healthcare system.

Finally, patients can offer ideas on evaluating the effectiveness of aRMMs and, importantly, participate in the evaluation itself.

# Chapter 8 – Annex 1:
# Additional details of the risk minimisation process in the EU and US

## European Union

There are 4 possible routes for medicines to get authorised in the EU: the centralised procedure, mutual recognition, decentralised procedure and national. Certain categories of medicines have to be authorised through the centralised procedure. Via this process, a single marketing authorisation is granted for a medicine valid throughout the EU, Iceland, Lichtenstein and Norway. In the centralised procedure, the European Medicines Agency (EMA) assesses the evidence and provides an Opinion to the European Commission on whether a medicine should be authorised and also what conditions should be attached to the license. For other medicines where authorisation is sought in more than one EU country, the EMA acts as a coordinator of the process.

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) is charged with assessing the risk management plan (RMP) which includes decisions about aRMMs and the effectiveness of aRMMs. The PRAC makes recommendations either to the Committee for Medicinal Products for Human Use (CHMP) for medicines in the centralised procedure or, for medicines authorised outside of the centralised procedure, to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh). PRAC's membership includes representatives from the 27 EU countries, from Iceland and Norway, independent healthcare professionals and patient representatives. PRAC advises on what the RMP should contain and whether aRMMs are necessary. EU legislation requires the regulatory authorities to state, at the time of the marketing authorisation decision, if any measures are required for the safe use of the medicine and what they should be.

In the centralised procedure, when the CHMP (following advice from the PRAC) decides that aRMMs are needed, the key requirements are included as draft conditions of the marketing authorisation in the Opinion sent to the European Commission. The European Commission makes the final decision on whether or not to accept CHMP's Opinion and their suggested conditions of the marketing authorisation. If accepted, the aRMMs become legally binding.[1,3]

The aRMMs are written in the Commission Decision in the form of key elements which state what is required, but not how it should be implemented. For example, the Decision may say that every physician who might prescribe the medicine shall be provided with educational material and describe the key messages to include in it. Using this framework means that both the language of the educational material and how it is provided to healthcare professionals and patients can be customised to the country. These key elements apply to all the EU countries, Iceland, Liechtenstein and Norway.

After authorisation, the MAH discusses implementation of aRMMs with each EU country where it intends to market the medicine. It may also provide (as required) the final proof of the educational material to the country's regulatory authority for approval.

Whatever the route of authorisation, how the aRMMs are actually implemented in each country is a matter for discussion between the MAH and the national regulatory authorities. This is necessary because countries have different health care systems and so how an aRMM will actually work is often country specific. For this reason, in the centralised procedure, by stating in the conditions of the authorisation what is required but not how it should be achieved, there is enough flexibility to accommodate the different health care systems.

## United States

Before 2007, the FDA worked with MAHs to develop special safety programmes called Risk Management Programs or Risk Minimization Action Plans (RiskMAPs) for specific medicines. RiskMAPs included restrictions on medicine use or distribution to minimise serious risks for a limited

number of medicines that offered substantial therapeutic benefits.[17] Many of the principles described in the RiskMAP Guidance are reflected in the Risk Evaluation and Mitigation Strategy (REMS) provisions in the Food and Drug Administration Amendments Act (FDAAA) and have been incorporated into FDA's REMS decision-making process.

REMS can be required before approval of the medicine to ensure the benefits outweigh the risk or after approval if the FDA becomes aware of new safety information and determines that a REMS is necessary to ensure the benefits outweigh the risks.[18] A REMS may include a communication plan for healthcare providers, certain packaging and safe disposal technologies for medicines that pose a serious risk of abuse or overdose, elements to assure safe use (ETASU), and an implementation plan. ETASU include requirements or other actions that healthcare providers or patients need to take before dispensing the medicine. Specific ETASU include:

- certification and specialised training of prescribers
- certification of pharmacies or other dispensers of the medicine
- dispensing or giving the medicine in limited settings (*e.g.* hospitals)
- dispensing or giving the medicine only on fulfilling safe-use conditions (*e.g.* specific medical testing like a pregnancy test)
- specified monitoring of each patient using the medicine
- enrolment of treated patients in registries.

The ETASU are not mutually exclusive and are often used in combination. FDA acknowledges that a REMS can impact the healthcare delivery system and patient access to medicines (especially REMS with ETASU) and recommends that MAHs assess the impact of their REMS on patient access.

# Chapter 8 – Annex 2:
# Detailed information on routine and additional risk minimisation

Routine risk minimisation measures (routine RMMs) apply to every medicine. These measures include information about the specific risks, information on correct use of the medicine to minimise risks, and physical presentation of the medicine. For most medicines, application of routine RMMs is sufficient to minimise risks.[1,2]

For some medicines, routine RMMs are not sufficient to optimise the balance between a medicine's benefits and risks. These risks require an extra level of risk minimisation known as additional risk minimisation measures (aRMMs).[1–3] The United States Food and Drug Administration (FDA) refers to aRMMs as Risk Evaluation and Mitigation Strategy (REMS).[12,13] In some cases, aRMMs are necessary to improve the benefit-risk profile sufficiently to allow market authorisation of the medicine or to maintain the medicine's market authorisation.

Table 10 shows routine risk minimisation measures and additional risk minimisation measures.

***Table 10: Types of risk minimisation***

| Routine risk minimisation | Additional risk minimisation* | |
|---|---|---|
| ***Sufficient for most products***<br>• Product Information<br>○ Professional information e.g. summary of product information (SmPC), US Prescribing Information (USPI)<br>○ Patient information e.g. package information leaflet, patient package inserts (PPI)<br>Medication Guide<br>○ Information on the packaging or carton<br>• Pharmaceutical form<br>• Pack size and design<br>• Legal (prescription) status | **Communication / Education**<br>Measures to:<br>• raise awareness or understanding<br>• impact behaviour<br>*Examples:*<br>○ 'Dear Healthcare Professional' letter<br>○ Educational guide<br>○ Patient card<br>○ Checklist of actions to take before prescribing | **Controlled Product Distribution / Use**<br>Measures to support appropriate prescribing, dispensing or accessing a product<br>*Examples:*<br>○ Attestation<br>○ Certification<br>○ Tests which must be done before a prescription is issued |

*A condition of approval; required to support product marketing and distribution



## Description of routine risk minimisation measures

The different types of routine RMMs are described below:

### Product information

Information for healthcare providers and patients is presented in product information (product label); details about patient involvement in assembling the product label are provided in Chapter 5.

Table 11 shows examples of product information.

***Table 11: Examples of product information***

| Product information | EU | US | Japan |
|---|---|---|---|
| For healthcare providers | Summary of product characteristics (SmPC) | Prescribing information (USPI)<br>Package insert | Package insert |
| For patients | Package leaflet (patient information leaflet in UK) | Patient package insert (PPI)<br>Medication guide | Drug guide for patients |

**Product labelling**

Information provided with the medicine.

- Outer labelling: information on external packaging (*e.g.* on the carton such as 'Keep out of the reach of children')
- Inner labelling: information on packaging in contact with the medicine (*e.g.* on the vial or blister pack)

**Pack size and design**

- The amount of medicine (*e.g.* number of tablets) in a pack, selected to support correct use. In some cases, limiting the doses in a pack or a packaging design feature is intended to reduce the risk of medication error, overdose or abuse.
- Limiting available doses may also increase the frequency of interactions between the patient and healthcare provider.
- A common example is restrictive packaging design (*e.g.* childproof containers and tamper-proof packaging)

**Pharmaceutical form**

- The size, shape, and colour of the medicine intended to reduce medication error due to confusion with other medications or other strengths.
- Specific medicinal forms (*e.g.* solutions or suspensions that may require preparation, dilution or reconstitution, or use of dosing devices), especially important for children's medicines.

**Legal (prescription) status**

Typically, this is availability of a medicine only with a prescription. Further restrictions may include (and vary across different regions):

- Specialist prescriber only
- Hospital use only (*e.g.* use in a setting where resuscitation equipment is available)
- Limiting prescription validity to a certain time period (*e.g.* medicine must be dispensed within 7 days of prescribing to ensure monitoring [such as pregnancy test result] is still valid at time of dispensing)
- Limiting number of automatic refills or repeat prescription
- Need for a special medical prescription (*e.g.* due to abuse potential)

### Description of additional risk minimisation measures (aRMM)

aRMMs can be grouped into two broad categories:

- **Communication and educational material:** This includes measures that provide information to raise awareness or understanding about a risk and promote behaviours or behavioural changes to minimise the risk.
- **Controlled product distribution and use**: This includes measures to limit medicine prescribing, dispensing or access.

Of note, certain aRMMs may not apply in some localities or countries for legal issues.

Communication and educational measures are used to enhance understanding (and knowledge) about:

- A specific risk and recommended actions to minimise the risk (supplementary to information in the medicine label)
- Patient selection criteria (such as selection on the basis of biomarkers or contraindications (*e.g.* contraindication for pregnant women to avoid fetal harm)
- Complicated medicine use procedures
- Recognition of important signs and symptoms (so that either preventive measures or pre-emptive treatment can be instituted])
- Treatment management (*e.g.* dosing, testing, monitoring, follow-up) which is likely to be unfamiliar to the target healthcare provider or falls outside standard care practices.

Sometimes the communication and educational materials are designed to help:

- Provide reminders (what to do, what not to do)
- Provide advice on patient counselling: information that needs to be discussed with the patient and caregivers before treatment is started
- Influence and reinforce certain actions.

Examples of communication and educational aRMMs include:

- ‘Dear Healthcare Provider (Professional)’ letter
  Sent directly to health care providers likely to prescribe the medicine
- Educational material
- Counselling guide
  (to guide healthcare provider on information to give to patients)
- Patient ‘wallet’ or ‘alert’ tool
  The tool instructs patients to alert any healthcare provider of the risk and risk minimisation actions
  May include contact details of treating physician or healthcare facility and dates or results of key tests
  Designed to fit inside a wallet or handbag; digital version may be available for handheld devices
- Checklist and treatment algorithm
- Dosing guide

Printed versions have been the mainstay for communication and educational aRMMs. Increasingly, more user-friendly forms are being used.

Examples:

- Digital or online versions
  (for easy download or on-line viewing)
- Audiovisual options
  (such as smartphone applications, video for procedural instructions)
- Interactive formats and computer simulations
- Reminder systems
  Designed to enhance compliance with actions to minimise risks, such as monthly monitoring or testing (*e.g.* liver transaminase level testing or pregnancy testing)
  Include options to send reminders to the healthcare provider or the patient via various means, such as email, text, phone or direct mail

Some types of communication and educational materials can be linked to controlled medicine distribution and use options (described below) (*e.g.* a training programme can link to certification).

The design and preparation of communication and educational aRMMs should consider the health literacy of the target user. These materials may require periodic updating (*e.g.* to align with current medicine information).

### Controlled medicine distribution and additional risk management measures

Controlled medicine distribution and use aRMMs are used to:

- Limit access only to appropriate patients (*e.g.* patients with a specific medical profile or genetic testing results, exclusion of pregnant women)
- Limit prescribers and pharmacies that can prescribe and dispense the medicine
- Limit dispensing to certain healthcare settings

### Types of controlled medicine distribution and additional risk management measures

**Attestation:** Prescribers, other healthcare providers, or patients acknowledge (in writing) that they understand and accept the risk (or set of risks) and agree to comply with actions to minimise the risk. Healthcare provider and patient could co-sign and commit to the risk minimisation actions.

Example: A woman patient and her healthcare provider commit to monthly pregnancy testing

**Certification:** Healthcare providers or pharmacists are certified by fulfilling certain requirements (*e.g.* undertaking training and passing a knowledge test)

Examples:

- Physicians are certified after completing specialised training
- Pharmacists register into a restricted dispensing programme which involves confirming laboratory test results or delivering specific counselling before dispensing a prescription for the medicine

**Patient monitoring and surveillance:** Monitoring may be recommended or required before starting treatment or at specified time periods during treatment to permit continued use of the medicine. It can entail monitoring for adverse effects, laboratory tests or screening (*e.g.* pregnancy test, blood cell counts, liver transaminase levels or ECG).

**Supply chain measures:** A centralised or specialty pharmacy could be used to distribute the medicine to avoid use of wholesalers and supply to large numbers of pharmacies. Special control over the supply chain can facilitate tracing medicines with potential for misuse or abuse.

# Chapter 8 – Annex 3:

## Example of interview questions to collect patient views on additional risk minimisation

The following are examples of questions to gain a patient's perspective on the usability and understanding of additional risk minimisation measures (aRMMs) for a particular risk associated with a medicine. In this example, they have an educational booklet and a patient alert card.

1. Imagine you are taking this medicine 'Tradename' and you are given this educational booklet. Why do you think you have been given this educational booklet?
2. Have you seen a patient educational booklet before?
    a. If you received a patient educational booklet before, did you read it?
    b. If you have used a patient educational booklet before, how helpful was it?
    c. What would you have changed about the patient educational booklet that you used?
3. Please read the educational booklet – what are your overall impressions?
    a. What do you like about the educational booklet?
    b. What would you change about the educational booklet?
4. Has the information in this educational booklet helped you understand more about the medicine?
    a. What do you think are the most important risks of this medicine?
    b. Is there any information you feel is missing? (If it raised any questions, what are they?)
    c. Is there any information that you feel is not necessary?
    d. Does the information in this educational material make sense? (Were there any words or phrases that you did not understand?)
5. When and why would you show a healthcare professional the patient alert card?
6. How do you feel about the design of the educational booklet and patient alert card?
    a. Is the patient alert card something you would carry around with you?
    b. Was the educational booklet appealing and well laid out? How could it be improved?
    c. What would you change about the design of either the educational Booklet or patient alert card?
    d. What do you like about the design of the educational booklet and patient alert card?

# Chapter 8 – Annex 4: Failure modes and effects analysis for risk minimisation

The key steps for application of failure modes and effects analysis (FMEA) in pharmaceutical risk minimisation include:

- Define the typical process steps and sub-steps in the use of a medicine (*e.g.* treatment selection, patient selection, prescription, dispensing, use of the medicine by the patient, follow-up or monitoring, discontinuation)
- Identify end users (*e.g.* prescriber, nurse, pharmacist, patient, caregiver) and use environments (*e.g.* hospital, retail pharmacy, patient's home)
- Identify all failure modes (Ask, 'What could go wrong? How could the user depart from ideal actions for using the medicine? How could a medicine or process fail?')
- Identify potential causes of each failure mode. (Ask, 'Why or how can the failure occur?')
- Identify effects (consequences) of each failure mode. (Ask, 'What could happen if the failure occurred?')
- Prioritise the potential failure modes. This can be done by using a scoring system to address severity, frequency, importance of the failure mode effects, detectability of the failure mode.
- For the failure modes with the highest priority (for example, the top 75%) identify actions, processes or attitudes that can decrease severity and frequency of the failure mode's effect or increase detectability of the failure mode.
- Decide if special additional risk management measures could minimise the failure modes (ideally at multiple points along the process) for the various users.

Examples of failure modes and specific risk minimisation approaches (in addition to routine measures such as labelling, safe packaging and formulation etc.) are presented in Table 12.

***Table 12: Examples of failure mode and effects analysis and risk minimisation***

Source: CIOMS Working Group XI

| **Failure modes** | **Consequences** | **Risk minimisation activity (additional or routine)** |
|---|---|---|
| Prescriber fails to screen for existing condition (*e.g.* infection for a medicine that weakens the immune system) | Patient who should not receive the treatment receives the medicine which could lead to certain side effects (*e.g.* opportunistic infection) | • Reminder for specific testing (screening, laboratory testing) |
| Prescriber prescribes wrong dose (*e.g.* a dose that should be taken **every week** is instead prescribed to take **every day**) | • Overdose and increased adverse reactions<br>• Underdose and lack of treatment | • Educational material<br>• Reminder system<br>• Alert cards advising patients to contact the prescriber if certain side effects occur |
| Healthcare provider fails to monitor for important side effect (*e.g.* liver failure) | Early signs of side effect are not detected, and patient develops severe damage. | • Educational material for healthcare providers and patients<br>• Reminder system |
| Prescriber forgets to counsel the patient on dosing instructions for the medicine | Patient takes a wrong dose of the medicine or takes it at wrong time or at the wrong frequency, which could reduce treatment effect or increase side effects | • Provide relevant healthcare professionals background information and a counselling script<br>• Reminder tool<br>• Provide extra information to the patient on correct dosing |

(continued)

| Failure modes | Consequences | Risk minimisation activity (additional or routine) |
|---|---|---|
| (Table 12, continued)<br>Pharmacist dispenses the wrong medicine (*e.g.* dispensing a medicine with a very similar name) or wrong strength | • Lack of efficacy<br>• Unexpected side effects | • Communication material to alert of this issue<br>• Use of Tall Man lettering (writing part of a medicine's name in upper case letters to help distinguish sound-alike medicines from one another, *e.g.* 'cycloSERINE' vs 'cycloSPORINE') – link<br>• Name change<br>• Different colour packaging for different strengths |
| Patient fails to disclose relevant medical conditions or use of other medicines as well as relevant herbal remedies and foods | Unexpected side effects or unwanted effects from an interaction between the new medicine and other foods or medicines | • Provide the patient with information on why it is important to tell the prescriber about conditions, other medicines and particular foods they normally eat that might interfere with the medicine<br>• Reminder to healthcare professionals to ask patients. |
| Patient forgets to take the medicine as prescribed | Loss of treatment effect<br>Excessive side effect if the patients takes an incorrect dose or takes doses too frequently | • Reminder tool to aid correct timing and frequency of dosing<br>• Educational material for caregiver |
| Pharmacist fails to tell the patient or caregiver of important side effect | Increased likelihood of the side effect's importance being overlooked and medical advice not being sought | • Educational material for healthcare professionals and patients<br>• Reminder system |
| Patient fails to take the medicine correctly because the dosing instructions are unclear or not legible | Lack of treatment effect<br>Increased likelihood for side effects | • Redesign package so that dosing regimen is clear (*e.g.* calender blister pack identifying the days and times for taking the medicine)<br>• Redesign the label so that dosing instructions are clear<br>• For patients with vision impairment, design package instructions with large readable font; offer access to audible instructions |



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# Chapter 9: Clinical practice guidelines

In this chapter we talk about patient and public involvement in developing clinical practice guidelines (treatment guidelines).

**Key points**

1. Involving patients or members of the public is important for creating a clinical practice guideline of high quality.
2. An effective process for involvement ensures that patients or members of the public are able to share their views – and that the guideline takes account of these views.
3. The principal steps of involving patients and members of the public in the guideline development process are:
   - Informing them about the guideline for making health decisions;
   - gathering the views of a broad group of patients or members of the public; and
   - inviting patients and members of the public to join the group that creates the guideline.
4. There are several ways to achieve effective patient and public involvement. The choice of the path depends on the guideline developer's goals and resources.
5. Effective processes to recruit and support patients or the public are vital to make sure that patients can contribute their views freely. The recruitment process should be transparent and selection should follow pre-set criteria.

## 9.1 Introduction

This chapter covers patient and public involvement activities and methodologies for developing clinical practice guidelines (also called treatment guidelines). Rather than detailing the different methodologies, it refers to international guidance from the Guidelines International Network (GIN) and its patient and public involvement working group (GIN PUBLIC working group).

## 9.2 Guidelines

Many organisations issue different types of guidance or best-practice advice, which they call guideline. In this chapter, 'guidelines' refers to 'clinical practice guidelines' (CPGs) as clinical decision-making tools to support healthcare professionals and patients. The US Institute of Medicine defines these as follows:

> Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.[1]

CPGs are issued by specialty societies and health institutions to aid clinical decision-making. Ideally, they are developed by multidisciplinary panels that include representatives of all healthcare professions involved in the condition in question as well as patients and carers. This multi-stakeholder approach is why patient and public involvement – implemented in many different ways – has become important for CPG development since the late 1990s.

## 9.3 A quality criterion for clinical practice guidelines

Patient and public involvement (PPI) is considered a key component and a quality criterion in CPG development. As early as 2003, the international AGREE Instrument, a tool to assess

the quality of CPGs, listed 23 items in six domains that describe a high-quality guideline. Item 5 is relevant to PPI: [2]

> The patients' views and preferences have been sought

These views can be identified through different methods. The essential underlying idea is that informing guideline recommendations by patients' experience makes recommendations more relevant to patients. This is a good characterisation of the purpose of PPI in CPG development. Other publications have advanced the idea that PPI is essential in guideline development and that high-quality guidelines need to take account of patients' or consumers' views when weighing the evidence and formulating healthcare recommendations.[3,4]

## 9.4 Core principle

Patient and public involvement in the development of clinical guidelines must not be tokenistic but meaningful; it is not about 'ticking the box' by involving just any patient on a panel. Therefore, the core PPI principle for guideline developers is that patient and public involvement must be realised – through different methods – to ensure that:

- patients and members of the public are able share their views and experiences and are encouraged to do so; and
- these views and experiences have an impact on CPG development in ways that matter.

Not every guideline developer will have the resources for a sophisticated PPI process. However, even limited resources can achieve effective PPI, by using cost-conscious methods (*e.g.* using free online training instead of offering in-house training). How patients or consumers are involved depends on the guideline developer's goals and rationales as well as on the developer's budget. Hence, a one-size-fits-all approach is inappropriate and there is no 'right method'; instead, a variety of measurements and methods need to be considered.

## 9.5 Rationales and methods

A systematic review of methods documents from guideline organisations has shown that they involve patients and consumers for a variety of reasons:[5]

- to increase legitimacy and credibility
- to foster implementation and adherence to recommendations
- to inform scope and content by patient values and perspectives to make guidelines more relevant to patients.

Depending on the rationale, different involvement methods may apply.[6] Guideline-developers have to choose carefully their methods of involvement, such as recruitment strategies and involvement techniques, with respect to the goals to be achieved and the patient or public input expected. That requires reflection and strategic planning before starting the development process.

## 9.6 Involvement strategies

The Guidelines International Network Patient and Public Involvement (GIN PUBLIC) working group offers a framework to conceptualise different approaches and methods that may apply in different stages of guideline development based on the flow of information between the organisation (or guideline panel) and the public (Figure 9).[7,8]

### 9.6.1 Consultation strategies

Consultation strategies involve collecting information from patients and the public. This can include surveys, focus groups, individual interviews, online consultation, use of primary research on patients' needs and expectations, or use of a systematic review of studies on patients' and the public's perspective.

### 9.6.2 Participation

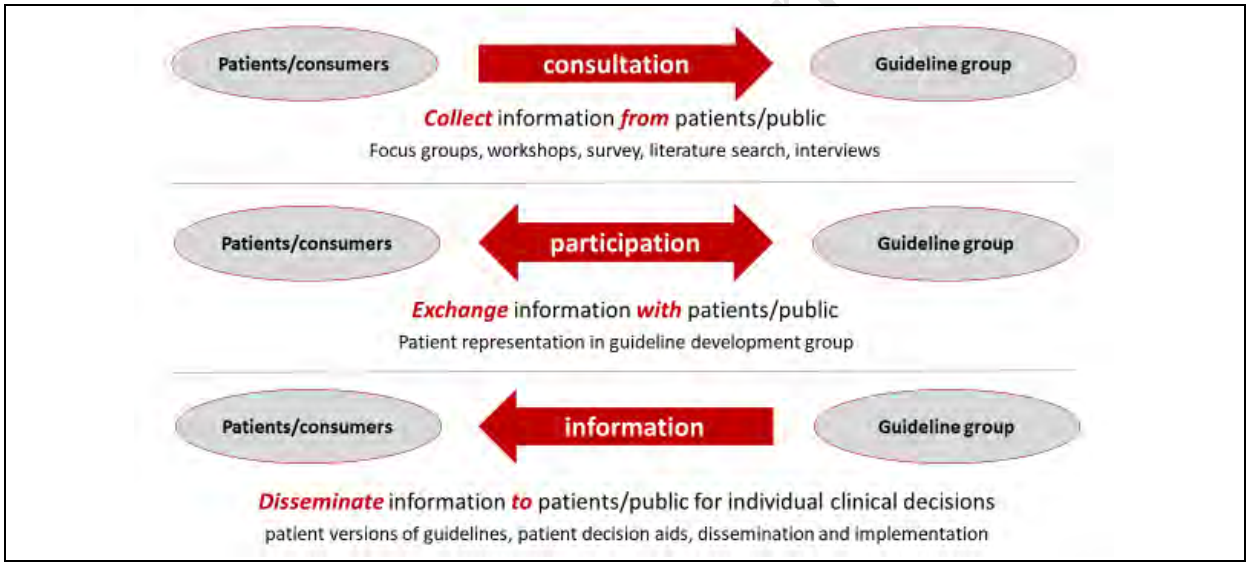
Participation involves the exchange of information between guideline developers and the public. The appropriate method is to invite patient and public representatives into guideline development groups.

### 9.6.3 Communication

Communication strategies involve the communication of information to patients and the public to support their individual healthcare decisions and choices. This can include the production of plain-language versions of CPGs or the development of patient decision aids or education material.

***Figure 9: A framework of patient participation techniques***

Source: CIOMS Working Group XI




These three strategies can and should be combined throughout the development process. Where a broader range of views is required (for example to prioritise endpoints or collect key questions), consultation methods are helpful. When it comes to discussion in the guideline panel, participation is needed.

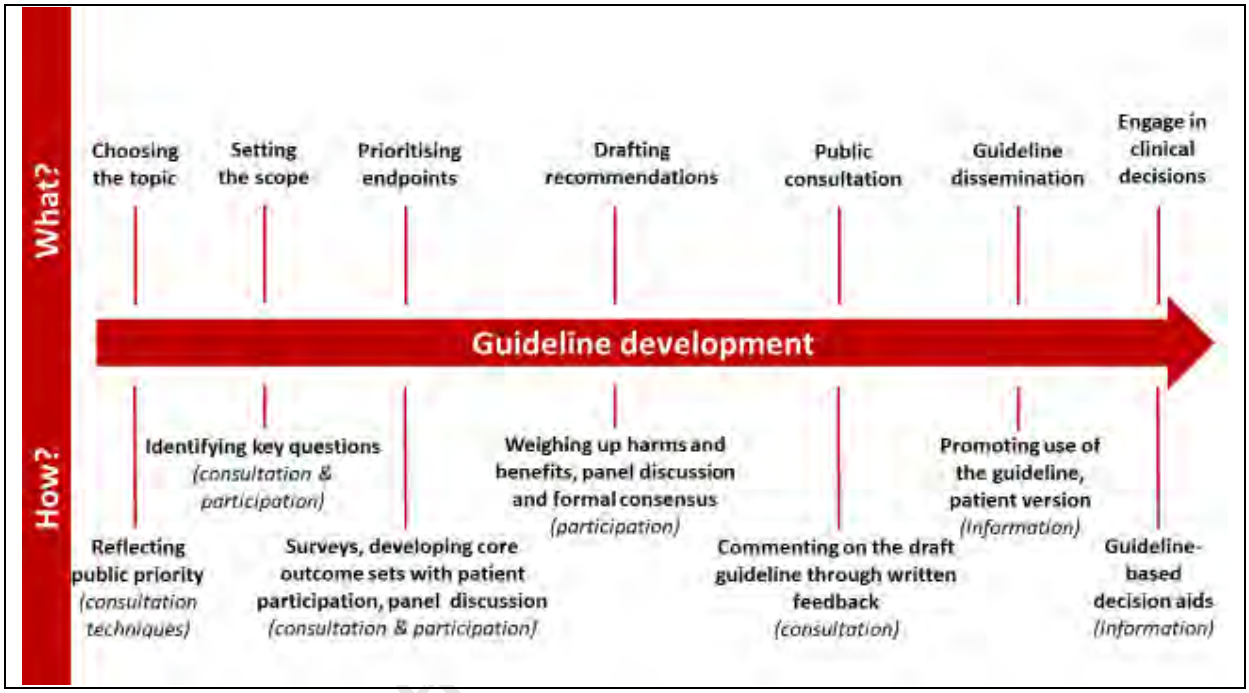
A recent survey among GIN members indicated that most guideline developers use more than one strategy to involve patients and the public.[9] These organisations are based in different countries and health care settings, thus showing that many developers seek an elaborated approach to PPI, independent of financial and organisational circumstances.

## 9.7 Patient and public involvement in guideline development

Patient or public representatives can contribute relevant insights at all stages of guideline development and they influence the guideline as well as its dissemination and implementation. When starting the development process, it is important to anticipate the different ways of obtaining patient input and plan methods and patient input according to the needs of the guideline topic, scope and purpose. The presence of one or two patients on the guideline development panel may not be sufficient to capture the different types of input. Figure 10 provides an overview:

***Figure 10: Patient and public involvement during guideline development***

Source: CIOMS Working Group WG XI




## 9.8 Patient and public involvement: effective recruitment

When recruiting individuals from the public to support the guideline process, a transparent and defined recruitment process is key. It is important to ensure that the guideline developer selects patients according to their ability to present their perspective rather than individuals that it prefers. The two recruitment strategies discussed below – nomination and open recruitment – differ in resource and setting requirements, but most probably not in their potential to provide a transparent and unbiased recruitment process.[10]

Evidence is lacking on the best way to recruit patients or consumers. International experience and best-practice examples from GIN indicate that both strategies have their advantages and disadvantages and that both may be appropriate to assure a robust and non-tokenistic recruitment process.[10]

### 9.8.1 Nomination

Nomination describes a process where guideline developers formally ask consumer organisations or patient associations to nominate individuals most suited to bringing in the patient perspective. This is similar to the nomination process for health professional representatives. The guideline developer has no influence on the individuals nominated and the responsibility for nominating suitable persons is completely delegated to consumer organisations and patient associations.

### 9.8.2 Open recruitment

Open recruitment means that guideline developers advertise broadly for patient and public members on a guideline group, providing a distinct role and person specification (like a job description). The guideline developer has to consider applications from anyone who meets the set criteria, invite individuals and select them according to defined criteria. The selection process needs to be very transparent to choose individuals who best meet the defined criteria. Open recruitment requires more resources but offers the chance to recruit people who have personal experience of a disease and not necessary of healthcare policy.

In specific situations, such as involving children or people who face language barriers (for example migrants), these strategies need to be adapted to reach appropriate groups or to choose suitable individuals.

## 9.9 Training and support

Patients or consumers who participate in a guideline group require adequate training and support to enable them to fulfil their assigned tasks in a meaningful way. Training should provide a basic insight of the principles of guideline development and evidence-based medicine. It is crucial for patients to understand that their experience and expertise is appreciated and welcomed but that guideline development is a scientific process that has follow certain rules to generate results in a potentially unbiased way.

International experience from guideline developing groups indicates that it is helpful for patients to understand why their individual experience matters to the process but may not influence a guideline recommendation (*i.e.* someone having experienced cure after taking a specific medication but large and robust trials showing insufficient benefit).

Training may include in-house or online courses and should cover basic skills in evidence-based medicine, guideline methodology and consensus techniques. In-house training may be tailored to the specific needs of the individuals but requires human and financial resources. On the other hand, some very valuable online training resources (mostly in English) are freely available.

See also section 3.4.2 for a general discussion on training for patients.

Guideline developers also need to offer practical support to ensure that patients or consumers can attend meetings, videoconferences or teleconferences and access documents. Patients or consumers may not be used to long consensus meetings or scientific jargon, and they may have physical and mental impairments. Support must be tailored to individual requirements and should include providing a coach or someone from the guideline organisation with responsibility for patient or consumer group members. Plain-language material, interpreters, considerate scheduling of sessions, and all other physical or psychological requirements need to considered. Experience from the UK shows that with adequate support, even vulnerable groups like children or people with mental illness can be involved effectively.[11] See also section 3.1.2.

Patients or consumers differ from healthcare professionals in that they volunteer to participate in guideline groups without any academic or professional benefit. Reimbursement of travel costs and adequate financial compensation for their time spent enable more individuals to participate (see section 3.3.2).[10]

## 9.10 Documenting and managing conflict of interest

Whichever involvement methods a guideline developer uses, it is crucial to document transparently the process and the impact of patients and consumers involved. This can be achieved via the guideline report and should be freely available. Documentation should cover:

- PPI methods used
- recruitment process and selection or nomination of guideline group members
- impact of patient or consumer feedback on guideline content

Furthermore, international standards require transparent conflict of interest (CoI) management for all members of a guideline panel, including patients and consumers.[12] Not only do CoIs have to be disclosed but they also need to be managed. If moderate or relevant CoIs are identified, the consequences have to be discussed; these may include abstention from voting, exclusion from discussion of specific topics or – in individuals with very serious CoIs – exclusion from the guideline group. Typically, patients or consumers do not have relevant individual CoI. However, they may come from patient organisations that may be conflicted *e.g.* receiving industry funding. In these cases, the same management rules must apply for all panel members regardless of their status as medical experts or patients or consumers. CoI disclosures and management should be documented.

## 9.11 Barriers to patient and public involvement

Even though patient and public involvement is now regarded a quality criterion for guidelines, both patients and guideline developers face considerable barriers to successful involvement. A 2017 workshop of the GIN PUBLIC working group assembled a framework of barriers to effective PPI related to the guideline itself, to the development process, or to participants (patients or consumers and healthcare professionals). Furthermore, patients and guideline developers face different barriers. Table 13 outlines these barriers. Understanding them and addressing them in individual involvement strategies may help guideline developers to implement PPI successfully.

5174 ***Table 13: Barriers to patient and public involvement. Results from GIN PUBLIC workshop (2017)***

5175 Source: CIOMS Working Group WG XI

| | Guideline-related | Process-related | Patient-related | Expert-related |
|---|---|---|---|---|
| Barriers perceived by guideline developers | **Scope**:<br>Is the scope relevant to patients? | **Recruitment**:<br>How to select patients?<br>**Uncertainty:** How many patients should be on the panel? Which is the right recruitment strategy?<br>**Documentation:**<br>Additional workload to adequately document the process<br>**Absence of evidence:** No reliable data: Does PPI make a difference?<br>**Living guideline:** continuous process that requires constant exchange and availability<br>**Confidentiality:** of underlying data and draft guideline content | **Health literacy**:<br>How to find patients with high levels of health literacy?<br>Lack of methodological expertise:<br>How to train patients on weighing anecdotal experience and robust evidence? | – |
| Barriers percieved by patients | – | **Awareness**:<br>How do patients learn of guideline groups looking for patients?<br>**Training**:<br>Can crucial training on guideline methodology be offered to participants?<br>**Practical support:**<br>Can specific patients requirements (*e.g.* to overcome physical or other impairment] be overcome?<br>**Scheduling / planning:**<br>compatibility of guideline engagement and patient's job or other duties; tight timelines, long meetings<br>**Reimbursement**:<br>Compensation may be needed if patients have to take time off work and incur travel costs | **Health literacy:**<br>Good level of health literacy expected to follow discussions<br>**Lacking peers:**<br>How to learn from other patients that have already served on a guideline panel? How to speak up as a single patient representative among a large group of experts. | **Respect**:<br>Not feeling welcomed and respected by professional experts of the group as equal members<br>**Uncertainty:**<br>Feeling intimidated; how to talk to 'experts'?<br>**Influenceability**:<br>Reduced trust in experts *i.e.* due to experts' conflicts of interest<br>**Lacking acknowledgement:**<br>Patients not being treated as equal members of group (*i.e.* no authorship, no right to vote)<br>**No positive feedback**<br>Patients' contributions not being valued |

## 9.12 International patient and public involvement activities

Many guideline-developing institutions internationally involve patients and consumers. However, a recent survey among guideline developers indicates considerable uncertainty about where to find the 'right' person and what training and support to provide.[9] Inviting patients or consumers to a guideline panel raises questions around their role and who they should represent.[10] It is an ongoing issue whether an 'advocate' or an 'affected individual' might be the right choice for a guideline panel. A solution might be to invite both and use further consultation to gain a broader insight on patients' perspective.

It remains unclear to what extent guideline developers involve patients and consumers internationally. Studies looking into national guideline programmes found modest to poor participation. A recent study focusing on Germany and based on the national guideline registry found that 58% of 270 German high-quality guidelines had patients on their panels.[13] Given that PPI is considered mandatory, this level of PPI represents only modest success. Only 35% provided guideline information in plain language, a key element for successful participation. An analysis of the method papers of all US guideline organisations found that only 8% described PPI as mandatory and 15% as optional.[14]

In a recent survey among GIN members, many guideline organisations see a lack of resources and funding as the most important barrier to initiate PPI.[9]

## 9.13 Effect of patient and public involvement

PPI in guidelines is a resource-demanding process that requires commitment, strategic planning and dedication. So, the key questions for many guideline developers are: 'is it worth it?' and 'does it make any difference?'. These questions are not easy to answer.

It is unclear, which endpoints can adequately measure the difference PPI makes. Does it refer to the guideline as a product or to the process? Researchers have recently tried to answer this question in a parallel group experiment (similar to a RCT) where two guideline panels worked on the same guideline topic, one had patients on the panel and the other did not.[15] Although the emerging evidence is tenuous due to inherent study limitations, the trial indicates that in the process investigated, PPI did make a difference: PPI influenced the conduct of guideline development, scope, inclusion of patient-relevant topics, outcome selection, and planned approaches to recommendation development, implementation, and dissemination with implications for both guideline developers and the guideline development process.

The UK National Institute for Health Care and Excellence (NICE) consistently evaluates its patient and public involvement programme. A qualitative study from 2016 evaluating PPI in nine NICE appraisal panels shows the areas in which PPI was most appreciated and made a real difference.[16] The following quotes from healthcare professionals illustrate the value of patient input and describe the impact it had on the development process:

> "From time to time, what patients have said has been an absolute lightbulb moment, a fantastic insight that you wouldn't get from anywhere else."

> "There was a patient who said 'I'm taking this drug, but I've had to stop it for a couple of days, because it gives me such bad diarrhoea that I wouldn't have been able to come to this meeting…' It was that insight - on the page they [the manufacturers] say 'Side-effects-X% of people get gastrointestinal problems', but actually that illustration was wow, this is much more important than it appears on a list of adverse effects."

> "Without the patient's voice, it's easier to be a little bit more dismissive if you're looking at clinical data … rather than hearing what effect it had on the individual patient."

5222 "On occasions there's a discrepancy between the clinicians and the patients … what clinicians
5223 think is important and what patients think is important is not always the same. Sometimes what
5224 clinicians think is terribly important, patients will say 'I've learned to live with that'."

## 5225 9.14 Key components of successful patient and public involvement

5226 Patient involvement is a core element in high-quality clinical practice guidelines and can be
5227 achieved through a variety of methods. The most important aim of all methods is to ensure
5228 that patients or consumers speak up and have their say. Key components of PPI are the
5229 following:

5230 • clarity on what is expected of patient and public members (precondition to choose the
5231 right involvement strategy)
5232 • a specified, effective recruitment processes and CoI management
5233 • transparent reporting
5234 • good chairing
5235 • induction, training, support and financial compensation
5236 • continuous evaluation and refinement of processes

5237 PPI that follows these rules will have an impact that matters.

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# Chapter 10: Low and middle-income countries

In this chapter we explain why involvement of patients in the development, regulation, and safe use of medicines can be challenging when they live in remote or deprived communities. By overcoming the barriers, patients in these communities can be involved more fully, as described in the other chapters of this report.

**Key points**

1. The principles for involving patients in low and middle-income countries should be no different from that in high-economy countries.
2. There are specific challenges in low and middle-income countries – making it difficult to fully involve patients in the development and safe use of medicines.
3. Civil society, people working in medicine research and development, government, international institutions, and non-governmental organisations can all support patient involvement in low and middle-income countries.
4. The following actions can improve patient involvement in low and middle-income countries:
   a. Improved health literacy of the general public and respect from healthcare providers for patients as equal partners in the fight against disease
   b. Communicating openly and in public-friendly language that encourages two-way discussion
   c. Developing laws and policies that fully involve the participation of patients in healthcare decisions that affect them and their communities.
   d. Sharing knowledge and success stories between patient organisations locally and internationally.
   e. Enforcing highest ethical standards for medicines research that fully respect patients' needs.
   f. Building capacity by engaging with international patient organisations – as well as learning from experience in high-economy countries.

## 10.1 Background

The importance of involving patients in medicine research and development through to facilitating access to safe and appropriate treatment is beyond question. However, a large proportion of the global population remains disenfranchised when it comes to meaningful involvement in research, regulation and access to medicines. These are people in low- and middle-income countries (LMICs) and even some in more affluent countries who live in remote or deprived communities – resource-limited settings (RLS).

Poverty and deficient legal and societal structures prevent patients from fully engaging in decisions about medicine development, regulation and safe use.

Low-income and lower-middle-income economies (as defined by the World Bank) suffer a greater burden of disease than countries with higher economies. Both communicable and non-communicable diseases are more prevalent in LMICs, also, healthcare systems in these countries are often not sufficiently developed or are dysfunctional. Box 3 shows important health challenges in LMICs.

***Box 3: Health challenges in LMICs***

Source: CIOMS Working Group WG XI

- High burden of disease
- Unaffordability of effective medicines
- Shortage of appropriately trained healthcare providers
- Fragile governance and insufficient priority given to healthcare
- Underdeveloped regulation of medicines and research and poor law enforcement
- Weak pharmacovigilance systems
- Diseases and treatments poorly researched because disease only prevalent in LMICs
- Absence of substantial local pharmaceutical manufacturing
- Rural population too distant from treatment centres
- Underdeveloped logistics infrastructure
- Lack of local health research
- Low health literacy and paternalistic relationship between patients and healthcare providers

It is vital for patients in LMICs to be involved in driving the development and regulation of medicines and in their safe and proper use. The more the healthcare and regulatory systems develop, the easier it becomes to engage patients and foster trust. Other chapters of this report largely focus on patient involvement in the development, regulation, and safe use of medicines in high-income economies. In LMICs, the same guiding principles and goals apply, but there are also unique challenges and opportunities to take into consideration, and this chapter focuses on those.

## 10.2 Barriers to patient involvement in LMICs

LMICs face many impediments to the full involvement of patients in research, medicine development and regulation and healthcare decisions. They are grouped under the following headings.

### 10.2.1 Governance structures

Regulation of healthcare professionals and of medicines in LMICs still lags far behind that in the most advanced economies. Regulatory procedures in LMICs typically omit the patient perspective. Programmes such as medicine-safety monitoring, in which patients can play a very active role, are either missing or very restricted because of financial constraints; and when patients are involved, they may be used simply for 'rubber-stamping' decisions.

In some LMICs, political fragility – characterised by unstable governance arrangements, civil strife and war – severely disrupts civil structures; people are left without access to a functioning healthcare system. It is impossible to plan and implement sustainable patient engagement activities in these circumstances. In some LMICs, patients may be fearful of voicing opinions that expose failings or weaknesses in the healthcare and governance structures.

Absence of ethical standards or ineffective enforcement where they exist, work against patients playing their full part. In medicines research, poor adherence to established ethical principles can mean that patients' views are overlooked, diminished, or misrepresented.

In *Ethical challenges in study design and informed consent for health research in resource-poor settings*, Marshall recommended applying certain principles when obtaining patients' consent; they include:[1]

- respecting cultural traditions;
- using appropriate documentation for the consent form;
- applying appropriate standards of care and provisions for medical treatment;
- developing plans for resolving conflicts surrounding research implementation.

Adherence to these principles increases the likelihood of patient involvement in decisions on medicine development, regulation and safe use.

LMICs may not have the capacity to fund or support the establishment of patient organisations. Policymakers and funders may regard the involvement of patients a luxury without having fully considered the benefits of a strong patient voice in decision-making. In some settings, patients may be seen as threats to the status quo because they might expose deficiencies of the system.

### 10.2.2 Population circumstances

Levels of literacy and particularly health literacy – the ability to understand health information and navigate healthcare services – are highly variable in LMICs. Patients' health literacy affects their capacity to understand a disease and to engage in patient groups.

Patients in many LMICs are in a subservient role and in arenas such as research and medicine development, their voice is absent or only just beginning to be heard. People may not be aware of their legal rights and entitlement to healthcare. In LMICs, healthcare professionals often discourage patients from participating in clinical decisions and so reinforce a paternalistic ('doctor-knows-best') attitude.

Paternalistic healthcare practice results from the educational disparity between healthcare providers and patients in LMICs and from the seemingly vast gap between the large establishment behind the provider and the lone patient. The power differential diminishes the patient's voice at every level of interaction in medicine development and use.

Community structures, traditions, and cultural values in LMICs can limit meaningful involvement of patients in, for example, advocating about health issues. Leaders and other influential figures in the community are susceptible to manipulation by misleading information and media reports; misinformation can affect how the community responds to requests for collaboration on health or medicine research.

Communities in LMICs may be suspicious of health interventions and of healthcare providers. In many parts of the world – and not just in RLS – there is mistrust, scepticism, and hostility towards, for example, vaccination programmes.[2] Such misgivings lead to the community drawing away from healthcare systems and diminishes the prospects for patient involvement in decision-making.

Patients' circumstances also reduce the possibility of involvement; constraints include: their medical condition, lack of time, reticence to engage with the 'establishment', and unawareness of how to provide input. Severity of their health conditions and co-existence of multiple diseases can affect patients' ability and motivation to engage with health researchers, government agencies and healthcare providers.

The scarcity of patient organisations in LMICs, combined with a lack of local models of patients forming a coherent body, leads to the absence of an effective patient voice in activities related to medicine use.

### 10.2.3 Medicine research and development and health systems

The 2021 CIOMS publication, *Clinical research in resource-limited settings* sets out in Chapter 4 and elsewhere how to safeguard patients in RLS and how to engage them in the research environment.[3]

Research on treatments of diseases prevalent mainly in LMICs needs to occur in LMICs. Some of these diseases are 'neglected tropical diseases', so-called because they affect poverty-stricken people in low-income countries; in the past, these mainly parasitic and microbial diseases received little research attention.

Researchers for diseases that affect LMICs and high-income countries alike – such as COVID-19, HIV/AIDS, malaria and tuberculosis – were traditionally based in high-income countries; this limited LMIC patients' influence. Encouragingly, however, many initiatives now increasingly support the involvement of local researchers.

Underdeveloped research capacity in terms of expertise and laboratory and computational facilities also hinders research in LMICs.

Apart from the low proportion of clinical trials in LMICs, the quality of studies may fall short of recognised best practice. Inadequate adherence to ethical principles can mean that patients' rights and wishes are not properly considered. Regrettably, this means that the opportunity to design scientifically better trials may be lost because patients are not properly involved.

Deficient regulations also open the possibility of promotional activities disguised as post-marketing research. In developed economies, codes of conduct for pharmaceutical companies prevent such 'research'.

Absence of significant pharmaceutical industry in LMICs means that almost all innovative medicines are developed, manufactured, and regulated in higher-income countries. This deprives LMIC patients the opportunity for involvement in bringing a medicine to the market and getting it used appropriately. Where regulation requires a contract between patients and industry, the terms of the contract may prevent meaningful collaboration.[4]

Health services are improved by learning from patient experience, but in LMICs, healthcare providers are under considerable strain to attend to these learning opportunities; treatment is often delivered in ill-equipped facilities and with too few trained health professionals. The services are unlikely to have the capacity to learn about the benefits of involving patients in policy decisions on the safe and effective use of medicines.

## 10.3 Improving patient involvement in LMICs

Civil society, researchers, medicine developers, government agencies, non-governmental organisations and international institutions have a part to play in enabling LMIC patients' involvement in the development, regulation, and safe use of medicines. The aim should be to accelerate patient involvement so that LMIC patient organisations are on the same footing as those in more developed economies.

Patient organisations can nurture future community advisory board patient members to contribute to research on many health issues and benchmark institutions in developing protocols for clinical trials. The organisations have the potential to influence government bodies to strengthen regulatory frameworks, and to control and supervise comprehensive health services. Patient organisations in high-income countries could work with sister organisations in LMICs to develop and foster the creation of collaborative international organisations.

Activities to improve patient involvement in LMICs are set out below.

### 10.3.1 Education

Improving health literacy is a key intervention for patient engagement. People should be knowledgeable about their rights to healthcare, including their right to decide – with their healthcare provider – on the most appropriate course of treatment. WHO considers that improving health literacy is important for achieving the United Nations' sustainable development goals.[5]

The relationship between the patient and the healthcare provider should be regarded as a partnership; it should not be paternalistic.

Healthcare education and improvement of health literacy can start in schools and be reinforced each time a patient engages with the healthcare system. By understanding patients' beliefs about their treatment and their attitude to healthcare, healthcare providers can resolve misunderstandings and increase trust. Special activities and campaigns aimed at community leaders will promote an understanding of the aims and workings of healthcare systems.

For involvement in policymaking, patients should acquire adequate understanding of the disease, research methods and treatments, as well as of regulatory and healthcare systems. This will enable more effective engagement with decision-making in medicine research, development and use.

Hand in hand with the education of patients, healthcare providers should be taught to respect patients as equal partners in the management of disease and in healthcare decisions. They should also be taught to seek patients' feedback on treatments and on the use of medicines. A relationship built on trust and respect facilitates patients' involvement in policy decisions.

### 10.3.2 Communication and digital technology

Through good communication, healthcare systems should encourage patients to become involved in decision making within their communities. Healthcare bodies should help patient groups share knowledge and experience so that they can extend the scope of their activities to participate in research and development of treatments, regulation of medicines and their effective deployment and monitoring.

Sharing success stories of patient participation in mainstream and social media can further empower patients, counter the stigma associated with certain conditions and lead to the formation of active associations as well as umbrella patient organisations that facilitate sharing of knowledge (such as on diseases, treatment, research, regulation, and treatment access) and strategies.

Mass communication – whether through radio, television or the Internet – can inform community influencers in LMICs about health matters and how the influencers can promote greater community participation in healthcare decisions.

'Call for Life Uganda' helps HIV patients manage their disease through mobile phones that connect to a central computer.[6] Using text and voice messages in local languages, the phone can remind patients to take their medicine, keep their clinic appointments, and easily report their symptoms.[7] This or similar technology could be extended to promote and maintain patient communities that can engage with research, development and safe use of medicines.

### 10.3.3 Research and development

There is increasing recognition that clinical research should be strengthened in LMICs but the solutions recommended focus mainly on academics and institutions increasing research capacity but do not specifically address how LMIC patients can be better drawn into the research.[8],[9] CIOMS has drawn up recommendations on involving LMIC patients in research (see Box 4).

***Box 4: CIOMS recommendations on patient involvement in research in LMICs***

Source: CIOMS Working Group report on Clinical research in resource-limited settings [3]

- Prioritize research that answers questions definitively and is relevant to the specific setting and to health care systems of the communities involved.
- Educate, empower and support patient organisations and communities to foster an understanding of the value of clinical research.
- Establish and enforce effective regulations for ethical review; ensure appropriate protection—which does not mean exclusion—of vulnerable persons and groups in research.
- Support the establishment of platforms for researchers to engage with patient representatives and communities, *e.g.* community advisory boards; request and consider formal communication plans as part of applications for clinical studies.
- Invest in constructive dialogue with stakeholders, including patients and communities, on research priorities and methods to generate relevant evidence, including in specific populations such as children; ensure that the research findings are implemented in national health systems to advance evidence-based health care delivery.

Researchers and medicine developers should subscribe to the ethical guidelines developed in high-economy countries. The CIOMS publication *International Ethical Guidelines for Health-related Research Involving Humans*[10] covers important issues, including research in low-resource settings. Ethical considerations on patient involvement are discussed in the Foreword and throughout this report.

Researchers and medicine developers should help form a patient body that can articulate participants' needs to researchers. These bodies can seed patient organisations that then provide input into all the different stages of medicine development and safe use. Care must be taken that barriers such as the need for travel and financial outlay or inaccessible language do not hinder patients' participation (see Chapter 3).

### 10.3.4 Governance, healthcare systems and legislation

Governments and healthcare systems should actively involve patients in decision-making bodies. Appropriate regulation and healthcare structures create opportunities for patient involvement. This entails creating positions for patient representation in different forums and recruiting patients who can properly represent their communities.

Legislation should require patient organisations to participate in decision-making bodies, including medicine-regulating bodies. The legislation should be backed by effective enforcement to ensure meaningful patient involvement. Patient organisations – including umbrella organisations – should receive official recognition.

Drawing on the experience of well-established regulatory and healthcare authorities, LMIC governments should legislate for the highest ethical standards in research and clinical trials which involve effective patient representation in the planning of clinical studies (see section 4.3).

The African Union, through the African Medicines Agency Treaty, recognises the role of African civil society and patients within research and development and in medicines regulation.[11] The research and development environment in Africa is set to change as the Agency takes control and fully implements the Treaty.

### 10.3.5 International collaboration

International organisations working in LMICs can help to set up patient organisations locally and create international networks of organisations to help LMICs build their capacity through knowledge transfer. Giving LMIC patient organisations exposure to international events can also help to consolidate their role.

By sharing knowledge and experience, international bodies – such as WHO and the United Nations (UN), as well as non-governmental organisations – can facilitate patient involvement and help with local adaptations of models developed globally. WHO's monograph, *Patient Engagement*, outlines strategies to strengthen the involvement of patients in primary healthcare.[12]

The United Kingdom government and others have proposed collaboration to protect against future pandemic threats and to slash the time to develop and deploy new diagnostics, therapeutics, and vaccines to 100 days.[13] The '100 Days Mission' puts LMICs – especially those that are potential reservoirs of pathogens involved in international public health emergencies – at the centre of a pandemic preparedness response. Patients in LMICs therefore have an opportunity to shape public health measures and be involved in programmes for research and development of medicines, vaccines, medical devices, diagnostics and assistive products.

The 2020 UN General Assembly resolution on *Comprehensive and coordinated response to the coronavirus disease (COVID-19) pandemic* calls for a transformation of how LMICs are engaged and supported. The resolution's preamble emphasises that civil society – patients – in LMICs must be included in all decision-making.[14]

Product-development partnerships (PDPs) also create opportunities for patient participation. A PDP brings together public, private, academic, and charitable bodies to fund the development of medicines, vaccines, and other products for public good.[15] The main beneficiaries of PDPs are resource-limited settings that lack the capacity for research or for funding access to treatment. These international partnerships can be structured to involve the LMIC patient voice into all decisions – from the development of a treatment to its use and monitoring.

Diseases of international concern such as HIV infection and the COVID-19 pandemic offer excellent opportunities to create patient organisations with international links. International bodies should ensure that these organisations are established, and they thrive in LMICs. In this way, LMIC patients can be involved in addressing challenges such as development of new medicines, vaccine hesitancy, problems of ineffective, dangerous, substandard and falsified medicines, and securing access to effective interventions.

The Solidarity Trial for COVID-19 treatments, set up by WHO and its partners has enrolled patients in over 30 countries. It has enabled patients and hospital teams in LMICs to work together on medicines, vaccines, medical devices, diagnostics, assistive products, research and development.[16] International scientists have committed themselves to collaborate on accelerating research in resource-limited settings.[17] LMICs can use the experience of patient involvement in this work in the context of other existing and emerging diseases.

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# Chapter 11: Pandemic considerations

In this chapter we consider the impact of the COVID-19 pandemic and the voice of the patient.

**Key points**

1. Previous pandemics and the current severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic have highlighted the need for patient involvement in their management.
2. There is much experience of patient involvement in the human immunodeficiency virus (HIV), which emerged in the 1980s. Here, the patient voice had a great impact on therapeutic interventions and clinical trials.
3. Public health measures to stop the spread of SARS-CoV-2 have been challenging because of how people behave and because of miscommunication.
4. Several factors have led to vaccine hesitancy and antivaccination attitudes. This makes it likely that the virus will continue to circulate.
5. There will likely be another pandemic, possibly an entirely new infection. We must make use of what we have learned so far to develop more effective ways of communicating about pandemics across the world.

## 11.1 Introduction

The 1918 influenza pandemic (misleadingly called 'Spanish flu'), and the human immunodeficiency virus (HIV) pandemic, which emerged in the early 1980s, pointed to the threat of other deadly infectious disease pandemics looming over the world.

Two recent coronavirus diseases – Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) – both spread to over 20 countries and led to 866 and 774 deaths respectively.[1] These coronaviruses heralded a new disease called COVID-19 (coronavirus disease 2019), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). COVID-19 has affected every country in the world, and by January 2022, it had caused well over 5.5 million deaths.[2]

This report discusses the unique expertise and perspective gained from patient involvement, but mostly this has been in 'normal times'. However, in this chapter we explore how the situation changes under pandemic circumstances.

Patient involvement has been dramatically affected by the sheer size of the population infected with SARS-CoV-2 and has in fact laid down the groundwork for the necessary public health and medicine development actions to deal with future pandemics with other infectious agents, including the likely mutation of SARS-CoV-2 into a more infectious or virulent strain.

Since their discovery in the 1960s, coronaviruses that infect humans have been challenging regarding the development of medicines and vaccines.[3] The common cold is often caused by coronaviruses and since it causes only temporary and relatively mild symptoms, it is usually perceived as an inconvenience rather than an infection to be feared. No antiviral medicines have been developed against the common cold; instead, medicines have mostly been used to relieve the usual symptoms of the condition.

However, when the SARS CoV-2 pandemic emerged, science had to rapidly refocus on developing a vaccine and medicines to treat it. Initially, medicines established for other diseases were used to treat severe COVID-19. They were often used haphazardly and in the initial absence of formal studies to establish their efficacy due to the urgency of the rapidly

growing pandemic. Such 'off label' use of medicines – developed for other diseases such as autoimmune diseases – and interventions like the use of convalescent plasma (plasma collected from patients who had survived SARS CoV-2 infection) are borne of empirical research rather than robust clinical trial data, and of desperation to manage severely ill patients with this potentially lethal new disease. Therefore, patients were exposed to medical management that was somewhat precarious and uncertain in effect by healthcare providers keen on helping their patients. As far as patient involvement was concerned, there was room for improvement.

## 11.2 The patient voice and public health management of SARS-CoV-2

Vaccine development and clinical trials of anti-SARS-CoV-2 vaccines proceeded at an unprecedented speed, with vaccines being introduced in just a few months. However, vaccine availability at a global level has been suboptimal, and consideration is needed on the best method of vaccine availability and distribution, *e.g.* allowing countries to manufacture vaccine with IP rights waivers as was the case with HIV medicines, and extending clinical trials and pragmatic clinical trials (see Glossary) to include patient involvement in given regions. An important aspect has been not just lack of availability of vaccine, but emerging patient attitudes including anti-vaccination stances resulting from fear and misinformation. By involving patients at the regional level as part of vaccine expansion and study, there is the potential to allay vaccination fears and miscommunication.

From the onset of the HIV pandemic, the HIV patient voice in some countries has been dominant and impactful for expediting the development of antiretroviral medicines. Nevertheless, about 36 million people have died from HIV/AIDS since 1981 and 38 million people were infected in 2019; and new infections continue to arise,[4] and the healthcare provision burden due to the SARS-CoV-2 pandemic has likely reduced access to testing for HIV, resulting in people with new HIV infection being unaware of their infectious status.

The medical, social, and people-centred management of the HIV pandemic has important relevance to the SARS-CoV-2 pandemic. It is highly likely that SARS-CoV-2 will not be eliminated, and society will have to develop strategies to learn to live with it, similarly to HIV. The emergence of new SARS-CoV-2 variants is the challenge that differs from HIV in view of the rapidity of spread and highlights the urgency of appropriate vaccine distribution and application the global population as the hope would be that the development of variants would be suppressed. Strategies for dealing with the disease must extend to developing countries especially in view of their very vulnerable healthcare systems.

Public health strategies are likely to involve regular vaccinations adapted to emerging SARS-CoV-2 variants as with current annual influenza vaccination strategies, use of effective medicines for those who become ill, perhaps prophylactic medicines in certain exposure scenarios, and social restrictions when outbreaks occur.

With almost the entire global population directly or indirectly impacted by SARS-C0V-2, this pandemic has catapulted patient participation in healthcare and healthcare policy to the front of the global agenda (see also Appendix 3). The global population has been subjected to public health risk-minimisation measures that include travel bans, social distancing, 'lockdowns' (that restrict presence in public areas), quarantines (after any potential exposure), and the wearing of masks, along with diligent handwashing, and strict isolation for those most vulnerable to serious consequences of COVID-19. Of note was the socially tragic effect of strict isolation on the people most at risk for fatal outcomes, in particular the elderly and those with underlying diseases such as diabetes, who sometimes died alone without the presence of family or friends due to restrictions in the hospitals.[5]

Measures against the spread of infection are not possible or applied in every country due to a lack of resources and healthcare infrastructure, other barriers including ineffective or unclear communication, poor economic support for individuals, late or poor decisions by policymakers and ineffectual enforcement of the measures. As a result, many groups are at higher risk of suffering the consequences of SARS-CoV-2 infection.

In a crisis, the normal rules and healthcare planning procedures do not apply – for reasons of speed and efficiency, decision-making can often become centralised with little public involvement. Unfortunately, established patient and community advisory groups were suspended in many cases, resulting in a lack of patient input in crisis management measures. Patient organisations were rarely involved in crisis decision-making.[6–9]

Arguably, some of the more undesirable impacts on patients such as from blanket application of visiting restrictions even for end-of-life patients, could have been mitigated had patients and family members been included as part of the care teams.

Despite being overlooked, patient organisations were active during the pandemic, providing information updates and support to their members, calling attention to inequalities, and gathering rich information on the impacts of the pandemic on patients.[10] Analysis from Ireland showed that patient and public involvement (PPI) contributors are helping COVID-19 research teams. Patient organisations such as the Irish Platform for Patients' Organisations, Science and Industry (IPPOSI) who are advocating for their members and supporting them to move to virtual environments and to continue to work with researchers.[11]

As the research community responds to funding and implementing research rapidly, it is easy to overlook PPI or regard it as unessential. However, researchers cannot afford to lose the important insights of patients, especially as COVID-19 is expressing clinical long-term impact on many individuals – the Irish researchers called them 'nuggets of gold'. Other examples include: the establishment of a national PPI panel to support COVID-19 research in Australia; and Health Data Research UK establishing a PPI group to work with UK researchers, with the UK National Institute for Health Research agreeing new commitments for PPI.[12–15]

## 11.3 Impact on healthcare systems

The SARS-CoV-2 pandemic has added burdens on the healthcare systems in many countries. Diagnoses and interventions have been delayed for patients with other diseases, including for patients with HIV, cancer, rare hereditary and metabolic diseases, and for those needing elective surgeries. This continues to have detrimental consequences on patients' health and on the ability of healthcare systems to care for all the patients who developed severe COVID-19, which represent the most apparent effects of the pandemic.[16,17] Beyond these implications, it is still too early to determine the extent of the overall impact of the pandemic on treatment and prevention of other disease.

The departure from routine medical care and specialty medical care because of the pandemic for patients with diseases that they had before the SARS-Cov-2 pandemic is especially worrisome when hospitals in certain regions could barely accommodate the flood of COVID-19 patients. Paradoxically, patients with those underlying diseases are often those at greatest risk for severe and fatal COVID-19 and will require hospitalisation; possibly more of these patients could have survived the infection – or have been less severely affected – if the routine management of their diseases had not been interrupted by the pandemic. The patient voice is important for ensuring that the healthcare system provides effective routine medical care while making adequate provisions for managing the pandemic.

The unique circumstance and additional burden on healthcare systems with healthcare workers themselves becoming infected and dying added to the desperate situation of this pandemic. SARS-CoV-2 mutation variants emerging in various countries may be more infectious (transmissible) or virulent (increased disease severity or higher potential for harm); these variants are set to become the dominant strains, further increasing the burden on healthcare systems and society.

Additionally, incomplete understanding of how this virus acts in the body, its potential for disease, and long-term consequences of infection places many countries' healthcare systems in dangerous and overwhelming predicaments.

The near-collapse of some healthcare systems in early 2021 exemplifies how incomplete understanding of the effects of the virus can contribute to an already dire situation.[18] Medical facilities were overwhelmed by a surge in SARS-CoV-2 infections driven by a variant (the delta variant) that seemed more infectious and possibly more virulent. With poor communication to the public, these factors may have had a profound effect on people getting appropriate and prompt attention for COVID-19 and for controlling the spread of the virus. Early and effective risk-minimisation measures could have mitigated this catastrophic eruption of infection and allowed time to build up vaccination capacity. Importantly, the experience is a lesson learned as the SARS-CoV-2 will mutate as it already has with Omicron variant, and possibly with a more virulent strain in future.

## 11.4 Impact of COVID-19 and public health measures on patients and patient care

Public authorities have communicated their concern that people were not seeking acute medical care because the fear of becoming infected in the hospital, which may well have been the case for many patients with chronic conditions who are vulnerable to infections. In addition, simply getting an appointment for non-COVID related care has been particularly challenging for patients.[19]

The adage, 'prevention is better than cure', holds true for pandemics. There is clear and robust evidence that the public health risk from the spread of infectious diseases, in general through contact and by the respiratory route, has been managed adequately with hand washing, use of face masks, and social distancing.

Cooperation from affected populations and a strong governmental public health stance enabled infectious disease outbreaks such as Ebola virus in Africa to be brought under control. Moreover, risk prevention with Ebola vaccine has enabled healthcare systems to better control outbreaks. Due to the relatively well-managed public health actions on Ebola outbreaks, there was no major impact on society and everyday life returned to normal. But as a zoonotic virus (a virus that has jumped from animals to humans), re-emergence is always possible if populations are not vaccinated sufficiently with an effective vaccine.

SARS, caused by a coronavirus related to SARS-CoV-2, which emerged in 2004, was rapidly controlled because it was managed effectively.[20] By contrast, for SARS-CoV-2, in many countries, lockdowns and controls of its spread have been irregular and often mismanaged; this may reflect an incomplete understanding of the epidemiological behaviour of SARS-CoV-2 despite lessons learned from the earlier SARS outbreak.

Modifying human behaviour is extremely challenging, especially since it relies on the robustness of policymaking and capable political and public health leadership. Incorporating the patient voice will help in the public health strategies and communication allowing for increased acceptance of measures taken.

## 11.5 Patient communication

The CIOMS report *Practical approaches to risk minimisation for medicinal products*[21] describes risk minimisation using risk prevention and risk minimisation strategies. These strategies can be applied to the SARS-CoV-2 pandemic for patient communication and use of plain language (message presented and organised in a way that the audience can readily understand at the first reading or hearing).[22]

We have yet to coordinate our efforts to learn from each country's mistakes and successes regarding the implementation and effectiveness of appropriate communication. The evolving flow of advice to the public from multiple sources about protective measures against infection has been inconsistent and often contradictory, which unsurprisingly will have dented confidence in the advice. This will have confused and angered the public and given rise to divergent behaviour over pandemic mitigations.

Given the restrictions imposed because of this pandemic, it is not surprising to see reports of increasing obesity, drug and alcohol use, and domestic violence, while limited socialisation, especially amongst children and adolescents, may have contributed greatly to worsening mental health.[23] These are not a direct consequence of SARS-CoV-2 itself. We must ask questions about the effects of risk-minimisation measures, from appropriate lockdowns[24] to the distribution and use of vaccines.

One of the first public health risk-minimisation methods was to apply lockdowns. Governments applied the strictest control over the movement of people. Data clearly showed a drop in virus transmission following lockdowns, but the measure was stopped prematurely in some countries resulting in a resurgence of infection rates – the most notable consequence was the emergence of SARS-CoV-2 variants.[25] However, at the time the appropriate duration or extent of the lockdowns was not known because the virus was novel and there was paucity of scientific data.

Healthcare providers started using established medicines such as hydroxychloroquine and ivermectin outside the clinical trial setting in the hope of reducing the severity of SARS-CoV-2 infection. Similarly, convalescent plasma has been used based on experience of managing other infections for which there was no reliable treatment; its value in treating serious COVID-19 remains unproven.[26,27]

Fortunately, vaccines, and medicines such as molnupiravir and monoclonal antibodies against SARS-CoV-2 were developed at an unprecedented rate. Accumulating experience on the use of vaccine vectors and on research on mRNA vaccines contributed to their rapid development. Clinical trials demonstrated efficacy of these vaccines in a truly short period, matched by equally unprecedented speed of regulatory authorisation.

The remarkably rapid approval and deployment of SARS-CoV-2 vaccines has surpassed the 'fast-tracking' of medicines for other health emergencies, including the ongoing HIV pandemic.

Over recent years, the public has become more aware and knowledgeable about clinical trials and regulatory processes. The speed of vaccine development and authorisation has led some to question the robustness of the vaccines' safety and efficacy evaluation. Such doubts may have contributed to hesitancy over receiving vaccination. This highlights the need for effective communication and accessible information to enable people to make informed decisions.

The deployment of COVID-19 vaccines has been erratic and dependent upon geopolitical aspirations and views, in contrast to their relatively quick and smooth development.[28] There have been marked differences in how groups are prioritised for vaccination including who can or should receive the vaccine; such prioritisation has sometimes been determined

at the political level. The procurement of vaccines has also become politicised, further damaging global cooperation in fighting this pandemic.

The imperative to prevent progression of the pandemic was influenced by individual and group leadership in some countries. For example, when societies pleaded to reopen schools to understandably bring back a sense of normality, teachers were not prioritised for vaccination in some countries whereas they were in others.

On the other hand, healthcare workers have been prioritised in some countries to preserve the stability of the healthcare system so that patients with other diseases could still receive healthcare.

Also, patients were reluctant to engage with healthcare systems because of the fear of becoming infected or the (often misplaced) intention of not wanting to place an additional burden on the system. This reluctance likely contributed to the delay in diagnosis or essential treatment.

In some cases, alternative methods were developed such as increased use of telemedicine, which led to healthcare professionals and patients having to adopt to a new model of healthcare delivery. While this may be seen as a positive step, there are limitations in terms of assessing, monitoring, and treating patients remotely. Telemedicine can also create barriers for some patients due to lack of access to relevant facilities and digital exclusion.[29]

Furthermore, healthcare systems have had to adapt to prioritising patients according to criteria such as age and disease state for admission to hospital, including intensive care units. This ethical predicament is driven by government and to some degree public health and payer regulations either preceding the pandemic or created during the pandemic to meet the needs of the healthcare systems. This becomes another ethical consideration as a form of adaptive legislation that aims to meet the dynamics and needs of the moment.

The additional ethical requirement of obtaining informed consent for treatment options in the setting of an ongoing pandemic involving overwhelming numbers of patients may cause difficulties. This is especially so for a critically ill patient whose family is not allowed into the hospital and who could very possibly die alone as a result. The use of deferred informed consent will likely increase and needs to be addressed.[30]

Due to the chaos created by the difficulty of communicating information, lack of standard of care for treatment, and the potential variability of health literacy, even family members or caretakers who can usually help decide treatment options for a critically ill patient may be challenged by the circumstances created by the pandemic.

## 11.6 Vaccines

Mass vaccinations that need to be delivered in a short period require advance planning with local governmental logistical support, overall healthcare system preparedness, and cooperation from the population.

Vaccines in general are not 100% effective, and we can expect SARS CoV-2 to circulate, especially if other measures are not used effectively. Complete eradication of the virus is unlikely probably due to the delay in recognising the initial impact of the outbreak, erratic public health management, and the resistance to these measures by various stakeholders.

The vaccines developed thus far have demonstrated clear effectiveness in preventing severe COVID-19.[31] However, at the time of this writing, they do not prevent infection and consequent transmission, which means that SARS-CoV-2 will continue to circulate and infect people and likely mutate, thereby likely necessitating the development of modified or different vaccines. Current vaccination programmes are reducing the burden on healthcare systems allowing people with other diseases to receive adequate care.

Moreover, those who have received booster doses of vaccines (or have had natural infection as well as vaccination) are likely to develop robust protection against hospitalisation or severe consequences of the infection; this will also reduce that amount of SARS-CoV-2 circulating in the community. Therefore, this will be part of finding an acceptable way for the global community to exist with the virus.[32]

While moving out of the pandemic situation, with its sole focus on medical therapy, sociological aspects related to 'normal life' should also be addressed in the global conversation. This calls for a diverse and large range of stakeholder groups, including patient groups, at the table to achieve a representative and meaningful dialogue.

Vaccine hesitancy and antivaccination views have likely emerged as a result of poor communication and misinformation.[33] The identification of severe but rare side effects of vaccines in a situation where vaccines are still scarce raises the discussion of how and who decides the best vaccination strategy.

Ongoing investigations have led regulatory authorities in Europe and the US to warn that certain vaccines may lead to rare but severe side effects.[34] Some health authorities advise against the use of certain vaccines in specific groups of people despite the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) concluding that the vaccines' benefits outweigh the risks in these people.

Whether an individual can choose to be vaccinated or not is a public health determination that will likely change the dynamic of global goal to stop transmission; if enough people refuse to be vaccinated, more infectious and more virulent SARS-CoV-2 variants may emerge. This would prolong the pandemic and its perilous impact on society and global health. Importantly, inadequate distribution and deployment of vaccines to developing countries can have a similar outcome.

## 11.7 The impact of COVID-19 infection on patients

The SARS-CoV-2 virus has demonstrated an ability to spread worldwide and develop variants that are potentially more infectious and more virulent. Scientists and healthcare providers are still trying to understand the clinical repercussions of an infection in patients, with growing evidence that infection can lead to long-term disease of varying severity and clinical features, the exact implications of which are still unknown.[35]

Patients who survive treatment in the intensive care unit may develop post-intensive care syndrome (PICS), which involves cognitive, psychological, and physical complications on discharge from hospital. PICS and post-intensive care syndrome-family (PICS-F) can also affect COVID-19 patients and their relatives.[36] Acute infection may also lead to a chronic COVID-19 disease syndrome, and 'long-term COVID' in millions of people, which could produce the largest single-disease group in recent history.

As it stands currently, 7 out of 10 patients who were hospitalised for COVID-19 continue to experience symptoms months after the acute infection and 1 in 10 patients who had mild infections experience symptoms months after acute infection.[37,38] These consequences will need intense study and ongoing healthcare provision. Disconcertingly, many countries are not able to manage these long-term effects appropriately given socioeconomic and geopolitical barriers. However, efforts should be made to organise and enhance the voice of afflicted patients at the international level since healthcare and scientific study will have to coalesce into unified global action.

Implications of 'long-COVID' and other complications will involve not only medical aspects, but also affect other domains of patients' lives, *e.g.* employment, social, emotional and spiritual wellbeing, and costs of healthcare provision for the patient, payers, and healthcare systems such as hospitals and clinics.[39] The costs are, and inevitably will be, enormous; the

burden is mostly on the individual patient, even amongst those who live in countries such as the US where COVID-19 survivors face unbearable financial debt. An effective rehabilitation programme should consider these factors and can therefore only be established after thorough understanding of the full presentation of long-COVID.

We should start by capturing the long-COVID patients' perspective on the most impactful effects of their condition, together with their healthcare providers' perspective to map the path towards recovery. Establishing an overarching patient organisation for long-COVID patients will be of utmost importance: by allowing the patient voice to transcend anyone's individual perspective, remaining up-to-date and being representative and advocative, such a framework could establish effective and appropriate communication that would otherwise be substantially harder to achieve. Furthermore, collecting and analysing data from a patient-driven source, such as a patient registry, will further enrich our knowledge of the still rather unknown health consequences and inform future action.

The world must learn lessons from this pandemic to be better prepared for the inevitable next one. Risk minimisation measures cannot be successfully and effectively implemented if communication is inadequate and worse, if the means and methods to counter misinformation are lacking.

## 11.8 Future goals

The future goals for managing pandemics must include a roadmap that our children and grandchildren can follow, alter, and amend as new findings emerge.[40] We must bequeath to them:

1. A fully independent, enduring international infrastructure for disaster preparedness and oversight which, by design, includes a strong societal representation, as well as the patient voice.
2. A fully independent international patient organisation centred on global COVID-19 health impact and management.
3. An international COVID-19 patient registry, because it is unlikely that SARS-CoV-2 and its effects will be eliminated and will likely continue to produce more variants of concern.
4. A renewed commitment to international approaches for all microbial threats and the means and methodologies to support all countries, ensuring that the necessary tools and capabilities are readily available internationally.
5. As the foremost priority, availability of a singular international source of authoritative scientific advice from clinicians, epidemiologists, allied health professionals, patients, and political entities that draws on the latest evidence and represents the consensus of best thinking and practices including:
   - disease detection and information about its transmission
   - disclosure of options for managing transmission and the likley impact of each risk-management mesure
   - discussion of candidate medicines and the risks and potential benefits
   - vaccine development with disclosure of any innovatie elements and what is known about the safety and possible concerns about what is not known
6. Active patient engagement in global risk monitoring and data-sharing networks to detect and engage these threats more rapidly.
7. Improved development approaches with collaborative endeavours that fully adhere to rigorous scientific standards.
8. Effective communication channels should be laid down in anticipation of a health emergency to pass on authoritative advice and information, and to foresee and counteract misinformation and disinformation.

Our battle against SARS-CoV 2 will be judged by history, but an honest and introspective analysis of our current successes and failures must act as a roadmap to protect future generations from this infectious disease and others that will surely emerge.

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# APPENDIX 1: Glossary

**Academia**

The environment or community concerned with research, education, and scholarship.

Modified from: Lexico.com (a collaboration between Dictionary.com and Oxford University Press). (Online dictionary accessed on 6 December 2021)

**Acceptable risk**

The degree of risk (likelihood of an adverse event or outcome) that a person or group is prepared to take or considers reasonable. However, what may be acceptable for one person or group may not be to another.

Proposed by CIOMS Working Group XI.

**AGREE Instrument**

A tool that assesses the methodological rigour and transparency in which a guideline is developed.

Adopted from: AGREE Next Steps Consortium (2017). The AGREE II Instrument Electronic version. (PDF accessed 7 October 2021)

**Burden to patients**

The additional load that a clinical activity imposes on patients above that which would be experienced under normal clinical practice.

Modified from: CIOMS Working Group IX, Glossary definition of 'Burden of a risk minimisation activity'.

**Caregiver**

A person who helps a patient with daily activities, healthcare, or other activities that the patient is unable to perform because of age, illness or disability, and who understands the patient's health-related needs. This person may or may not be a family member and may or may not be paid.

Modified from: Patient-Focused Drug Development: Collecting Comprehensive and Representative Input, Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. U.S. Department of Health and Human Services Food and Drug Administration. June 2020. (PDF)

**Civil society**

Communities and groups that work outside of government or commercial bodies.

Modified from: Commission on Social Determinants of Health: Civil Society Report, WHO. October 2007. (Webpage accessed 16 January 2022)

**Claims data**

(In the US) The compilation of information from medical claims that health care providers submit to insurers to receive payment for treatments and other interventions. Medical claims data use standardized medical codes, such as the World Health Organization's International Classification of Diseases Coding (ICD-CM), to identify diagnoses and treatments.

Source: U.S. Food and Drug Administration. Framework for FDA's Real-World Evidence Program. December 2018. (PDF)

**Clinical development**

The research performed in humans that increases knowledge about the safety and efficacy of a medicine in a particular indication.

Proposed by CIOMS Working Group XI.

**Clinical development plan**

A master document which outlines the research strategy to progress a medicine from first in human man to authorisation.

Modified from: CIOMS Working Group IX

**Clinical practice guidelines (synonym: clinical guidelines)**

Recommendations on how to prevent, diagnose and/or treat a medical condition. A clinical practice guideline should summarise current medical knowledge, the pros and cons of the scientific evidence supporting different options and how the authors reached their recommendation.

Modified from: InformedHealth.org, Institute for Quality and Efficiency in Health Care (IQWiG, Germany). (Webpage accessed 6 December 2021)

**Clinical trial**

A research study, in a defined and controlled setting, where participants are assigned prospectively to one or more (or no) interventions to evaluate the effects of the intervention on biomedical or health-related outcomes. The research is performed according to a written protocol. The intervention may be a medicine, vaccine, device, diagnostic or surgical procedure, or change in behaviour (*e.g.* diet).

Modified from: ClinicalTrials.gov. Glossary of Common Site terms. definition of 'Interventional study (clinical trial)'. (Webpage accessed 14 December 2021)

**Conflict of interest**

A situation where a person's judgement, decision or action may be unduly influenced (or seen to be influenced) by circumstances such as the person's or family member's employment, investments, scientific work or invention.

Proposed by CIOMS Working Group XI.

**Contract research organisation (CRO)**

(See Research organisation)

**Consensus techniques**

Methods or processes used to reach agreement, or a mutually acceptable solution, between a group of individuals.

Modified from: American Heart Association: Consensus-Based Decision-Making Processes. (PDF accessed 6 December 2021).

**Current practice**

(See also Normal clinical practice)

A diagnostic, monitoring, or therapeutic procedure can be considered current practice in a particular geographic area if at least one of the following is fulfilled:

- Routinely performed by a proportion of healthcare professionals and is not deemed obsolete;
- Performed according to evidence based medicines criteria;

- Defined in guidelines issued by a relevant medical body;
- Mandated by regulatory and/or medical authorities;
- Reimbursed by the national or private health insurance.

Current practice may or may not be considered as Standard of care.

Modified from: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). ENCEPP considerations on the definition of non-interventional trials under the current legislative framework ("clinical trials directive" 2001/20/EC). 22 November 2011. (PDF)

**Diversity**

The degree to which individuals in a group (*e.g.* participants in a trial) have differences in characteristics such as age, race, gender, and disease severity. Diversity may also relate to individuals with differing beliefs, customs, habits, or social and economic status.

Proposed by CIOMS Working Group XI.

**Endpoint**

In clinical trials, an event or outcome that can be measured to determine how beneficial and/or harmful an intervention is.

Modified from: National Institutes of Health, National Cancer Institute. (Online dictionary accessed 6 December 2021).

**Endpoint prioritisation**

The process that guideline developers go through to decide which endpoints in a study or trial are most important. Importance is determined by the question being asked.

Proposed by CIOMS Working Group XI.

**Epidemiology**

Epidemiology is the study, in populations or defined groups of individuals, into how, how often, when and why health-related events occur.

Proposed by CIOMS Working Group XI.

**Evidence-based medicine**

The conscientious, explicit and judicious use of current best scientific evidence in making decisions about the care of individual patients.

Modified from: Sackett DL *et al.* Evidence based medicine: what it is and what it isn't. BMJ 1996;312.71. doi: 10.1136/bmj.312.7023.71

**Family caregiver**

(See Caregiver)

**Health literacy**

An individual's capacity to access, understand, appraise, and apply health information.

Modified from: Sørensen, K., Van den Broucke, S., Fullam, J. *et al.* Health literacy and public health: A systematic review and integration of definitions and models. BMC Public Health 12, 80 (2012). doi: 10.1186/1471-2458-12-80

**Health technology**

Any intervention to promote health, prevent, diagnose or treat disease, or for rehabilitation or long-term care. This includes medicines, vaccines, devices, procedures and organisational systems used in health care.

Modified from: EUPATI. Health Technology Assessment: Key Definitions. (Webpage accessed 8 October 2021).

**Health technology assessment**

Health technology assessment is a multidisciplinary process to determine the relative value of an intervention developed to prevent, diagnose or treat medical conditions; promote health; provide rehabilitation; or organize healthcare delivery. The intervention can be a test, device, medicine, vaccine, procedure, program or system.

Modified from: International Network of Agencies for Health Technology Assessment (INAHTA). (Webpage accessed 16 January 2022)

**Healthcare system**

An organised structure designed to promote, restore or maintain health in populations defined by geographical region, insurance coverage or employment.

The term is frequently used to mean how services are provided to the population of a particular country.

Proposed by CIOMS Working Group XI.

**Immunization anxiety-related reaction (synonym: Immunization stress-related reaction)**

A range of symptoms and signs that may arise around immunization that are related to the stress around the procedure and not to the vaccine itself or the immunization programme, a defect in the quality of the vaccine or an error of the immunization programme. These reactions may include vasovagal-mediated reactions, hyperventilation-mediated reactions and stress-related psychiatric reactions or disorder.

Modified from: WHO Vaccine safety basics e-learning course, Module 3: Adverse events following immunization. (Webpage accessed 29 January 2022)

**Industry, pharmaceutical**

Companies whose primary functions include one or more of the following: research, development, manufacture, and marketing of medicines and/or vaccines.

Proposed by CIOMS Working Group XI.

**Informed assent**

Informed assent means that a child or adolescent who will possibly participate in a research study is meaningfully engaged in the research discussion in accordance with their capacities. Assent must be considered as a process, and is partnered with the informed consent acquired from the parents or legal guardian; it is not merely the absence of dissent. It is of major importance to inform the child or adolescent and obtain assent preferably in writing at an age appropriate level for children who are literate. The process of obtaining assent must take into account not only the age of children, but also their individual circumstances, life experiences, emotional and psychological maturity, intellectual capabilities and the child's or adolescent's family situation.

Informed assent can be applied to adults who do not have the legal capability to give consent.

Modified from: CIOMS. International Ethical Guidelines for Health-related Research Involving Humans. 2016. (PDF)

**Informed consent**

(See also Informed assent)

A process by which a potential participant (or a responsible proxy – *e.g.* a parent) voluntarily confirms willingness to take part in a study, after having been informed of all aspects of the study relevant to the person's decision to participate. This must be recorded in the appropriate format.

A type of informed consent is sometimes used as a risk minimisation tool for an authorised medicine to ensure that the patient has had the potential risks of the treatment, and other

important information, explained to them by the healthcare professional who is prescribing, dispensing or using it.

Modified from: ICH Harmonised Guideline. Integrated Addendum to ICH E6(R1): Guideline for good clinical practice. E6(R2). International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH); 2016. (PDF)

**Investigational product (synonym: investigational medicinal product)**

A medicine, vaccine or placebo which is being tested, or used as a comparison, in a clinical trial.

Modified from: European Parliament and the Council of the European Union. Regulation (EU) No 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Article 2(2)(5) (PDF)

**Low- and middle-income countries (LMIC)**

Countries with gross national income (GNI) per capita below a set threshold, which is defined periodically using GNI data from the World Bank, the Development Assistance Committee of the Organisation for Economic Co-operation and Development.

Modified from: Organisation for Economic Co-operation and Development (OECD): Development Assistance Committee (DAC) list of Official Development Assistance (ODA) recipients. (Webpage accessed 16 January 2022)

**Manufacturer (pharmaceutical)**

A legal entity (e.g. pharmaceutical company) that is engaged in the industrial scale synthesis, formulation, production or preparation of pharmaceuticals and/or vaccines.

Proposed by CIOMS Working Group XI.

**Marketing authorisation applicant (MAA)**

A company or other legal entity seeking authorisation from a regulatory authority to market a medicine or a vaccine in a national or regional territory.

Modified from: European Medicines Agency, About us, Glossary of regulatory terms: 'Marketing authorisation holder'. (Webpage accessed 10 December 2021)

**Marketing authorisation holder (MAH)**

A company or other legal entity that has been granted permission by a regulatory authority to market a medicine or a vaccine in a national or regional territory.

Modified from: European Medicines Agency, About us, Glossary of regulatory terms : 'Marketing authorisation holder'. (Webpage accessed 10 December 2021)

**Medication guide**

Printed document supplied with many prescription medicines that contains U.S. FDA-approved information on particular issues and that can help patients avoid serious adverse events.

Modified from: U.S. FDA website. Drug safety and availability. Medication Guides. (Webpage accessed 10 December 2021)

**Medicinal product**

Any substance or combination of substances:

- presented as having properties for treating or preventing disease in humans; or
- which may be used in or administered to humans either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

Modified from: European Parliament. Directive 2001/83/EC of the European Parliament and the Council of 6 November 2001 on the Community code relating to medicinal products for human use. (PDF) Article 1(2).

Note: In other jurisdictions, this may be called a medicine, medical product or a drug, and may include biologicals and vaccines.

**Medicines developer**

The company/institution that is responsible for, and may perform, the research necessary to get the evidence needed for the medicine to be authorised and made available to patients.

Proposed by CIOMS Working Group XI.

**Medicine life-cycle**

The time between the first discovery of a potential medicine to when the medicine, once developed, is no longer available to patients.

Proposed by CIOMS Working Group XI.

**Medicine or vaccine use within label (synonym: On-label use)**

(See also antonym: Off-label use)

Use of a medicinal product in accordance with the terms of the marketing authorisation.

Proposed by CIOMS Working Group XI.

**Minimal risk**

The probability, and the potential seriousness, of harm or discomfort anticipated in the research are no more than ordinarily encountered in daily life or the performance of routine physical or psychological examinations or tests.

Modified from: Federal Policy for the Protection of Human Subjects, U.S. FDA. (Website accessed 14 December 2021)

**Natural history study**

A study that follows a group of people over time who have, or are at risk of developing, a specific medical condition or disease. A natural history study collects health information in order to understand how the medical condition or disease develops and how to treat it.

Adopted from: National Institutes of Health, National Cancer Institute Dictionary of Cancer Terms. (Webpage accessed 14 December 2021)

**Non-interventional study**

A study is non-interventional if it is:

i. Carried out in a database or other form of secondary data or is
ii. A review of records where all the events of interest have already occurred or
iii. When all the following conditions are met:

- The medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation;
- The assignment of the patient to a particular strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study; and
- No additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data.

Interviews, questionnaires, taking of blood samples and patient follow-up may be performed as part of normal clinical practice.

Modified from: European Medicines Agency Guideline on good pharmacovigilance practices (GVP) – Module VIII (Rev 3)
EMA/813938/2011 Rev 3. 9 October 2017; page 4. (PDF)

**Non-randomised study**

A study in which the allocation of treatment is NOT decided by chance. Single arm clinical trials and observational studies are examples of non-randomised studies.

Proposed by CIOMS Working Group XI.

**Normal clinical practice**

(See also Current practice)

Medical care typically used in a particular country, region or hospital to treat, prevent, or diagnose a disease or a disorder.

Modified from: European Parliament and the Council of the European Union. Regulation (EU) No 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. (PDF) Article 2(2)(6)

**Off-label use**

(See also antonym: Medicine or vaccine use within label, *i.e.* on-label use)

Use of a medicine or vaccine in a way that is not in line with its authorised use.

Proposed by CIOMS Working Group XI.

Note: Use of a medicine for an unapproved indication or in an unapproved age group, dosage, or route of administration.

**Package leaflet**

(Also called Patient product information)

A leaflet containing information for the user, which accompanies the medicinal product.

Modified from: European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (Rev 4). 9 October 2017. (PDF)

**Patient**

A person who has, or had, a health condition whether or not they currently receive therapy to prevent or treat it.

Modified from: National Health Council. Glossary of patient engagement terms. 13 February 2019. (Webpage accessed 14 December 2021)

**Patient-centered outcome**

Outcomes the population of interest notices and cares about (*e.g.*, survival, functioning, symptoms, health-related quality of life) and that inform an identified health decision.

Source: Patient-Centered Outcomes Research Institute (PCORI). PCORI Methodology Standards. (Webpage accessed 29 January 2022)

**Patient-focused drug development (PFDD)**

A systematic approach to capture patients' experiences, perspectives, needs and priorities, and to incorporate them meaningfully into the development and evaluation of a medicinal product throughout its lifecycle.

Modified from: U.S. Food and Drug Administration. Patient-Focused Drug Development Glossary. (Webpage accessed 16 January 2022)

**Patient engagement (synonym: Patient involvement)**

The active, non-tokenistic and collaborative interaction between patients, the patient community and other stakeholders, where decision making is guided by patients' contributions as partners, recognising their unique experiences, values and expertise.

Modified from: Harrington RL, Hanna ML, Oehrlein EM, Camp R, Wheeler R, Cooblall C, *et al*. Defining Patient Engagement in Research: Results of a Systematic Review and Analysis: Report of the ISPOR Patient-Centered Special Interest Group. *Value Health*. 2020 Jun;23(6):677-688. doi: 10.1016/j.jval.2020.01.019.

**Patient expert**

A person living with a health condition whose knowledge and experience enables the person to take more control over personal health by understanding and managing the health condition.

Expert patients may also act as advocates for their condition and help other patients with the same health issue.

Proposed by CIOMS Working Group XI.

**Patient information leaflet (PIL)**

(See Package leaflet)

**Patient labelling**

(See Package leaflet)

**Patient ombudsman**

A neutral person (or body) responsible for receiving, investigating and responding to patients' complaints on health services or other support services provided to patients.

Modified and combined from:
- Patient Ombudsman. Vision, Mission, and Values. Toronto, Ontario, Canada. (Webpage accessed 14 December 2021)
- Parliamentary and Health Service Ombudsman, UK. (Webpage accessed 14 December 2021)

**Patient organisation (synonym: Patient group)**

An institution that represents the interests and needs of patients (and their families and caregivers) who have a particular disease, disability or group of diseases and disabilities. Patient organisations may engage in research, education, advocacy and fundraising to further the needs of their patient group.

Proposed by CIOMS Working Group XI.

**Patient group**

(See Patient organisation)

**Patient Package Insert (PPI)**

(See Package Leaflet)

**Patient preference**

(See Patient preference studies)

**Patient preference studies**

The qualitative or quantitative assessment of the desirability, or acceptability to patients of choices of outcomes or other attributes, that differ among alternative health interventions.

Modified and combined from:
- U.S. Food and Drug Administration. Advancing Use of Patient Preference Information as Scientific Evidence in Medical Product Evaluation, Collaborative Workshop hosted by Centers of Excellence in Regulatory Science and Innovation (CERSIs) and the Food and Drug Administration. December 7-8, 2017 . (Webpage accessed 14 December 2021)
- U.S. Food and Drug Administration. Patient Preference-Sensitive Areas: Using Patient Preference Information in Medical Device Evaluation. (Webpage accessed 14 December 2021)

**Patient registry**

An organised system that collects uniform data on specified outcomes in a population defined by a particular disease, condition or exposure.

Modified from: European Medicines Agency Guideline on good pharmacovigilance practices (GVP). Annex I - Definitions (Rev 4). (PDF)

**Patient-reported outcome**

Data reported directly by the patient about aspects of their health without prior interpretation of the patient's response by a clinician or anyone else.

Modified from: FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016. Glossary. 2016 Jan 28 [Updated 2021 Nov 29]. (Webpage accessed 29 January 2022)

**Patient safety organisation**

A group, institution, or association that improves patient care by reducing medical risks and hazards.

Modified from: Agency for Healthcare Research and Quality. Guide to Improving Patient Safety in Primary Care Settings by Engaging Patients and Families. Appendix E : Category Definitions. (Webpage accessed 14 December 2021)

**Patient voice**

The input and perspective of patients on their needs and what is of value to them, which can differ from needs identified by other stakeholders (*e.g.* medicine developers, physicians, regulators, and payers).

Modified from: National Health Council (NHC). *The patient voice in value: the NHC patient-centered value model rubric*. 2016. (PDF accessed 10 March 2021)

**Pharmaceutical industry**

(See Industry, pharmaceutical)

**Pharmacology**

The scientific study of the properties of drugs and their effects on the body.

Modified from: Oxford concise medical dictionary, 8th edition, 2010. (Webpage accessed 17 January 2022)

**Pharmacoepidemiology**

(See also Pharmacology and Epidemiology)

The study of the use and effects of drugs (including biologicals and vaccines) in large* numbers of people using methods, analyses and reasoning based on general epidemiology.

* 'Large' is dependent on the study and the disease.

Modified from: International Society of Pharmacoepidemiology. About Pharmacoepidemiology. (Webpage accessed 10 December 2021)

**Plain language**

Communication that the audience can understand the first time they read or hear it.

Modified from: plainlanguage.gov. What is plain language? (Webpage accessed 14 December 2021)

**Post-authorisation efficacy study (PAES)**

A study conducted after a medicine is authorised to address scientific uncertainties around how well a medicine works in its authorised indication.

Note. For a medicine to be authorised, the benefit risk balance must be positive. PAES are required when there is some uncertainty on the level of the benefit that can only be addressed after the medicine is authorised, or when there is new information suggesting that previous assumptions may need to be revised.

Proposed by CIOMS Working Group XI ((based on Scientific guidance on post-authorisation efficacy studies. EMA/PDCO/CAT/CMDh/PRAC/CHMP/261500/2015)

**Post-authorisation safety study (PASS)**

Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures [DIR 2001/83/EC Art 1(15)].

A post-authorisation safety study may be an interventional clinical trial or may follow an observational, non-interventional study design.

Adopted from: European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (Rev 4). 9 October 2017. (PDF)

**Pragmatic trial**

A randomised controlled study designed to evaluate the effectiveness of interventions in real-life routine practice conditions.

Modified from: Patsopoulos NA. A pragmatic view on pragmatic trials. Dialogues Clin Neurosci. 2011;13(2):217-24. doi: 10.31887/DCNS.2011.13.2/npatsopoulos

**Prevalence**

Number of existing cases of an outcome or disease in a defined population at a given point in time. Prevalence is calculated as a proportion (cases divided by the total defined population) and is often expressed as a percentage, or as the number of cases per 10,000 or 100,000 people.

Modified from: CIOMS Working group report on Drug-induced liver injury (DILI). 2020. (PDF)

Note: Prevalence should be distinguished from Incidence, see CDC Web Archive*: 'Prevalence and incidence are frequently confused. Prevalence refers to proportion of persons who have a condition at or during a particular time period, whereas incidence refers to the proportion or rate of persons who develop a condition during a particular time period.'

**Real-world data (RWD)**

Health care data gathered from routine clinical practice in a non-interventional setting. RWD can come from wide variety of sources such as electronic claims and health records, registries,

* Centres for Disease Control (CDC). Principles of Epidemiology in Public Health Practice, Third Edition
An Introduction to Applied Epidemiology and Biostatistics. Lesson 3: Measures of Risk, under 'Properties and uses of prevalence'. (Webpage accessed 9 February 2022).

patient reported outcomes, digital tools/mobile devices. Data collected include clinical and economic outcomes, patient-reported outcomes (such as disease activity and quality of life) and resource utilisation.

Source: Report of CIOMS Working Group XIII on Real-World Data and Real-World Evidence in Regulatory Decision Making (work in progress).

**Real-world evidence**

The evidence derived from the review and analysis of Real-world data.

Source: Report of CIOMS Working Group XIII on Real-World Data and Real-World Evidence in Regulatory Decision Making (work in progress).

**Regulator, medicines (synonyms: regulatory authority, health authority)**

A legally mandated body concerned with ensuring the quality, safety, efficacy, manufacture, sale or marketing of medicines including biologicals and vaccines.

Medical regulators can be regional, national (for example FDA, PMDA or MHRA), or supranational (for example EMA).

Proposed by CIOMS Working Group XI.

**Research organisation**

A body that performs one or more activities in relation to the development of medicines or other treatments, or for investigating the causes, prevention, progression and treatment of diseases.

A research organisation may be academic, not-for-profit or for-profit. It may perform research for itself or on behalf of another organisation.

Proposed by CIOMS Working Group XI.

**Resource-limited setting (RLS)**

A country or locale where the capability to provide care for life-threatening illness to most of the population is limited to basic critical care resources, with no or very limited possibility of referral to higher care capability.

Modified from: Geiling J, Burkle FM Jr, Amundson D, *et al.* Resource-poor settings: infrastructure and capacity building: care of the critically ill and injured during pandemics and disasters: CHEST consensus statement. *Chest.* 2014;146(4 Suppl):e156S-67S. doi: 10.1378/chest.14-0744

**Risk**

The probability of an adverse event, or an outcome, in a defined population over a specified time interval.

Modified from: A dictionary of Epidemiology. 6th edition. Miquel Porta (editor). Oxford University Press; 2014. (Online content accessed 8 February 2022)

**Routine pharmacovigilance**

The set of pharmacovigilance activities required by a regulatory authority for every medicinal product they authorise.

In many regions, these minimum requirements are laid down in law or regulations.

Proposed by CIOMS Working Group XI.

**Serious adverse event**

Any untoward medical occurrence that:

- results in death;

- is life-threatening;
- requires hospitalisation or results in prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- is a medically important event or reaction.

Modified from: ICH harmonised tripartite guideline. Post-approval safety data management: Definitions and standards for expedited reporting. E2D. 12 November 2003. (PDF)

Note: In pharmacovigilance, the term "event" is used when it is not known or suspected that the occurrence or effect was caused by the medicine.

**Shared decision making**

In medicine, a process in which both the patient and healthcare professional work together to decide the best plan of care for the patient. When making a shared decision, the patient's values, goals, and concerns are considered.

Source: National Cancer Institute. NCI Dictionary of Cancer Terms. (Webpage accessed 23 February 2022)

**Signal**

Information on a new or known side effect that may be caused by a medicine and is typically generated from more than a single report of a suspected side effect. It's important to note that a signal does not indicate a direct causal relationship between a side effect and a medicine, but is essentially only a hypothesis that, together with data and arguments, justifies the need for further assessment.

Source: Uppsala Monitoring Centre (UMC). What is a signal? (Webpage accessed 9 February 2022)

**Signal detection**

The act of looking for and/or identifying signals using event data from any source.

Adopted from: CIOMS. Practical Aspects of Signal Detection in Pharmacovigilance. Report of CIOMS Working Group VIII. 2010.

**Special populations**

(See also Vulnerable populations)

Populations to be considered should include (but might not be limited to):

- Children;
- The elderly;
- Pregnant or lactating women;
- Patients with relevant co-morbidity such as hepatic or renal disorders;
- Patients with disease severity different from that studied in clinical trials;
- Sub-populations carrying known and relevant genetic polymorphism;
- Patients of different racial and/or ethnic origins.

Adopted from: ICH harmonised tripartite guideline. Pharmacovigilance Planning. E2E. (PDF)

**Sponsor**

An individual, company, institution or organisation that takes responsibility for the initiation, management and/or financing of a clinical trial.

Modified from: CIOMS Working Group IX.

**Stakeholder**

Individuals or organisations involved in the development, regulation and safe use of a medicine during its life-cycle. These may include:

- Medicine developers (pharmaceutical and healthcare industry and academia);
- Patients, patient organisations and patient advocates;
- Regulators;
- Health Technology Assessment bodies;
- Payers; and
- Healthcare professionals

Modified from: Innovative Medicines Initiative (IMI), Patients Active in Research and Dialogues for and Improved Generation of Medicines (PARADIGM). *D4.1 Recommendations on the required capabilities for patient engagement*. 2018. (PDF)

**Standard of care**

(See also Current Practice and Normal Clinical Practice)

Medical care that is the customary treatment, diagnosis or prevention of a disease or disorder in a particular region or setting. This may be as defined in guidelines issued by a relevant medical body, mandated by regulatory and/or medical authorities or as routinely performed by a reasonable proportion of healthcare professionals.

Proposed by CIOMS Working Group XI

**Systematic review**

An organised evaluation with the aim of collating all scientific evidence and experience that fits the pre-specified eligibility criteria in order to answer a specific research question.

Modified from: Cochrane Training, Handbook, Chapter 1. (Webpage accessed 14 December 2021)

**Unmet medical need**

An unmet medical need is a condition whose prevention, treatment or diagnosis is not addressed adequately by what is available.

Modified from: U.S. Food and Drug Administration. Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics. May 2014. (PDF)

**Vaccine hesitancy**

The delay in acceptance or the refusal of vaccination despite availability of vaccination services.

Modified from: MacDonald NE; SAGE Working Group on Vaccine Hesitancy. Vaccine hesitancy: Definition, scope and determinants. Vaccine. 2015 Aug 14;33(34):4161-4. doi: 10.1016/j.vaccine.2015.04.036.

**Vulnerable populations**

Persons who are relatively or absolutely incapable of protecting their own interests.

This may occur when persons have relative or absolute impairments in decisional capacity, education, resources, strength, or other attributes needed to protect their own interests.

In other cases, persons can also be vulnerable because some feature of the circumstances (temporary or permanent) in which they live makes it less likely that others will be vigilant about, or sensitive to, their interests.

Modified from: Guideline 15. In: CIOMS. International Ethical Guidelines for Health-related Research Involving Humans. 2016. (PDF)

# APPENDIX 2:
# Case studies

# A. Medication formulation created to meet patients' and doctors' needs (AdrenalNET)

### Purpose/objective of the case study

This case study provides an example of patient involvement in medicine (re)formulation by a pharmaceutical company, that was initiated by a thorough inventory of needs and worries of health care professionals and patients by AdrenalNET (Dutch Adrenal network expert organisation)

Source information only available in Dutch: https://www.bijniernet.nl/kwaliteit-zorg-kwaliteit-leven/kwaliteitsstandaard-bijnieraandoeningen/nulmeting-volledige-rapportage/

### Pharmacology

Hydrocortisone

Used as supplementation therapy in patients with a deficiency of adrenal cortex hormone, due to adrenal disease (prevalence in the Netherlands of around 10 000).

Narrow therapeutic window, requires frequent dosage adjustments in individuals

### Indication/disease treated

Adrenal disease leading to deficiency of adrenal cortex hormone

### Stage of the drug development life cycle

Patient organisations NVACP and NHS joined the initiative and were among the driving forces within multistakeholder organisation, AdrenalNET, throughout the process of medicine formulation (or reformulation) by pharmaceutical companies. Pharmaceutical companies were approached by AdrenalNET after receiving complaints of periodic shortages, unpleasant taste and inconvenient dosage forms of available tablets on the market.

### Why were patients involved?

Patients were, like all other stakeholders, fully involved throughout this activity. The purpose of their involvement was to state their concerns about existing formulations of hydrocortisone and make suggestions for dosage forms that are better adapted to their needs.

### How was contact established with the patients?

Patients were involved from the launch of AdrenalNET in all processes. For this activity they were co-initiator and driving force.

The patient organisations NHS (pituitary disease) and NVACP (adrenal disease) were able to speak on behalf of the larger adrenal patient community in the Netherlands after performing a survey. Both patient organisations remained 'at the table' for every decision-making) step of the project. The two patient organisations have about 4000 members in the Netherlands and maintained close involvement via their respective board members and representatives, as well as with their constituencies via website and social media.

### What did the patients do?

- Nurses, medical specialists and patients addressed the issue and were able to pinpoint the exact needs and worries of the patient community.
- AdrenalNET brought all relevant stakeholders (incl. NHS & NVACP) to the table and facilitated a project team with the appropriate expertise.

### Was the process adjusted to the patients' needs?

This initiative resulted in newly formulated hydrocortisone tablets, adapted to patients' and doctors' needs: by developing increasing dosage strengths in different (and 'logical') colours and with acceptable shape, as well applying a coating to mask the bad taste, both patient compliance and safety will benefit. The final steps in the regulatory process (approval of 2- and 3-mg strengths plus the hydrocortisone drink) were ongoing at the time of writing this report.

### If patients were asked to help disseminate information, please give details.

AdrenalNET facilitates the multi-stakeholder process as well as incoming and outgoing communication via various websites and social media.

### Did the patients receive payment or compensation?

All parties covered their own costs (mainly travel expenses). Ace Pharmaceuticals covered the costs for innovation and market readiness. Patients, health care professionals and employees of AdrenalNET received no financial compensation for their contribution in this project.

### Did you discard any patient requests or recommendations and why?

In order to prepare for any complaints from patients, healthcare professionals, or other stakeholders, AdrenalNET consulted the Dutch Pharmacovigilance Centre Lareb at an early stage. Lareb, as an independent party, received nearly 200 signals or complaints and published a report on these. Some of the complaints were flagged as potentially insincere (*e.g.* competing commercial interests).

### Conclusion

This initiative resulted in newly formulated hydrocortisone, adapted to patients' needs: by developing increasing dosage strengths, in small steps, in different (and 'logical') colours and with acceptable shape, as well applying a coating to mask the bad taste, both patient compliance and safety will benefit.

Key learnings:

- Know your facts: make sure that you know exactly what the problem is and what solution might address the needs of patients in your community.
- Invest in a strong and durable network, this will provide timely support if there is a problem.
- Bring all relevant stakeholders to the table and aim for a collaboration based on equality. Do not settle for 'second-best': serious issues like these require a team with professionals.
- Project management is crucial to handle a process of long duration that involves a trajectory with many hurdles and considerable financial risks for some partners.

### Contact details

Coor@BijnierNET.NL -> e-mail address of the manager/coordinator.

For more details, please visit:

www.bijniernet.nl (Dutch)
www.adrenals.eu (European multilingual)
www.nvacp.nl
www.hypofyse.nl

# B. A regulatory agency involving patients; public hearing on valproate (EMA)

### Purpose/objective of the case study

This case study demonstrates the value of input from patients in shaping the review outcomes during the post-authorisation safety review of valproate by the European Medicines Agency (EMA).

### Pharmacology

Valproate and related substances (sodium valproate, valproate magnesium, valproate semisodium, valproic acid and valpromide)

- Valproate is thought to reduce overactivity of some brain cells by an effect on the neurotransmitter gamma-aminobutyric acid (GABA).
- Valproate medicines, when used in pregnancy, are associated with a higher risk of certain birth defects. Data have also suggested an association between valproate use during pregnancy and developmental disorders (frequently associated with craniofacial abnormalities), particularly of verbal intelligence quotient (IQ).

### Indication/disease treated

Valproate medicines have been widely in use in Europe since 1967. They are authorised for treating epilepsy, bipolar disorder, and in some European member states, for preventing severe migraine headaches. For some patients with serious conditions, valproate may be the best or only treatment option. Most patients are long-term users and may begin treatment well before reaching their childbearing age, when a revision of valproate treatment may be necessary.

### Stage of the drug development life cycle

Pharmacovigilance Risk Assessment Committee (PRAC) was asked to review existing measures to minimise harm from valproate to unborn babies, and to determine if more should be done to prevent or minimise harm, considering the specific situation in the different Member States.

- This review started in March 2017 and concluded in May 2018.
- Patients were involved and consulted at several timepoints during the review, using a variety of engagement methodologies.

### Why were patients involved?

Patients are systematically involved in EMA's work to incorporate their input throughout the medicine's regulatory lifecycle. They are voting members of several EMA scientific committees (including PRAC), they participate in expert meetings called by the committees and are also regularly consulted in writing. They review all written material intended for patients (*e.g.* package leaflets, safety communications).

During its evaluation of the risk minimisation measures for valproate, EMA determined it essential to take in the views and experiences of patients, affected families and the wider EU public. The goal was for PRAC to gather as wide a range of views as possible to ultimately support better regulation of valproate medicines across Europe. EMA recommendations were the basis for national action to further protect patients across Europe. To do so each EU Member State considered the specific circumstances in their territory. EMA used all available options for engaging with patients; a written consultation in March 2017, a public hearing in September 2017, a stakeholder meeting with patients and healthcare professionals in October 2017 and a final written consultation in December 2017.

### How was contact established with the patients?

The public hearing was announced on EMAs website, and its twitter and LinkedIn platforms, together with an online application form for participants to register. The announcement was also disseminated via EMA's network of patient and healthcare professional organisations, and the network of medicines regulatory authorities across Europe.

Applicants applied to participate as observers or speakers. EMA selected as many speakers as possible to include diverse affiliations and countries; there were 65 attendees, including 28 patients/patient representatives (12 as speakers), 19 healthcare professionals and academics, 11 from pharmaceutical industry and 7 from media.

The hearing was broadcast live and the recording published afterwards. Written input received from non-speakers was also considered and published for full transparency.

As for the public hearing, for the initial written consultation, the stakeholder meeting and the final written consultation, those invited to participate or contribute and provide input and experience comprised: patient organisations representing epilepsy, bipolar disorder and migraine, as well as organisations representing patients, carers and victims affected by valproate.

### What did the patients do?

During the initial 'scoping' written consultation, patients and their organisations were asked if they were aware of the risks of taking valproate while pregnant; and if and how they received relevant information from their healthcare providers. Healthcare professionals also participated in the survey. The information collected at this early stage indicated that the effectiveness of the risk minimisation measures which were in place at the time were not optimal and this helped in identifying the problems and shaping the focus of the public hearing.

For the public hearing, EMA asked the public to address a list of questions, about their views of the risks, the current measures to manage them, and, more importantly, for suggestions on how the measures could be strengthened.

During the hearing, 12 patients gave 8 oral presentations to the PRAC, about their personal experiences, and those of others in their organisations. They also gave important practical suggestions for enhancing the existing risk minimisation measures.

Patients highlighted that the problem was that known information on risks was not reaching the right people at the right time and that risk-minimisation measures needed strengthening. They suggested that in addition to communication and knowledge there was a need to think about other ways to effect change, such as:

- reminders of the risks on the outer packaging of valproate medicines;
- women receiving information and discussion of the risks when receiving valproate (with alert prompts embedded in prescribing and dispensing software);
- regular (at least annual) reviews for all women receiving long-term valproate and a record that they had been counselled about the risks;
- registers of women receiving valproate and of children who had been exposed to valproate during pregnancy;
- further development of professional education to increase healthcare professionals' awareness of the risks;
- more coordinated care services nationally, to ensure individualised care plans for those affected; and
- public awareness campaigns.

To build on the information gathered from the public hearing a stakeholder meeting with patients and their families, healthcare professionals, academics and PRAC members led to a build-up of useful information, especially on tangible actions to strengthen existing measures and propose new ones.

Having evaluated all the information from the public hearing and the stakeholder meeting, PRAC's proposals were put out for public consultation to ensure they addressed the concerns and concrete suggestions raised by patients (and others) during the preceding public hearing, stakeholder meeting and written consultation.

### Was the process adjusted to the patients' needs?

This was the first public hearing organised at EU level and the regulatory process was adapted to accommodate this important new tool. Detailed practical guidance was provided to facilitate attendance.

The announcement and application form were designed to be easily read, completed and submitted by any member of the public.

Speakers who attended the public hearing and the stakeholder meeting were provided with one-to-one support by an EMA staff member.

Public hearing speakers were given the option of using a translator for their presentation.

Disability assistance was provided where needed.

### If patients were asked to help disseminate information, please give details.

Relevant patient organisations helped disseminate the written consultation (survey), the public hearing announcement and the concluding written consultation via their membership, using their websites and social media platforms.

### Did the patients receive payment or compensation?

Travel, accommodation and a daily expense allowance were provided to the public hearing speakers and to the stakeholder meeting participants.

### Did you discard any patient requests or recommendations and why?

All the information received from patients was taken into consideration, although some aspects were outside EMA's remit, *e.g.* care services at national level

### Conclusion

On 21 March 2018 the CMDh* endorsed PRAC's proposed new measures to strengthen previous restrictions on valproate use.

The input received from the patients and the public was instrumental in the assessment of valproate and the new measures introduced to protect women and their babies.

PRAC outcomes developed with input from patients (and other stakeholders) include:

- Restrictions on use: Contraindication for use in pregnancy and in women of childbearing potential for bipolar disorders, migraine prophylaxis and epilepsy (unless no alternative treatment and conditions of pregnancy prevention programme (PPP) met. Establishment of a PPP and initiation and supervision of treatment by specialists.
- Development of educational materials: A direct to healthcare professional communication (DHPC), patient card, patient guide, healthcare professional guide and annual risk acknowledgment form.

* The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) is a medicines regulatory body representing the European Union (EU) Member States, Iceland, Liechtenstein and Norway.

- Promotion of effective communication of warnings: Recording of passing on of risk information to patients, introduction of smaller pack sizes, patient card in outer carton, warning of pregnancy risks (in boxed text and warning symbol) on medicines packaging, warnings on patient cards attached to box and supplied each time dispensed, annual reassessment of patients
- New research and databases: Effect of valproate to offspring of treated father and in third-generation offspring (post-authorisation safety study) and register(s) on epilepsy and valproate including mothers and affected children
- Public hearings give a voice to patients and citizens in the evaluation of medicines and empower them to share their views on issues related to the safety of certain medicines and the management of risks. This platform allows EMA to reach out to the wider public and complements its established methods to engage with patients.
- Inviting people into the public meeting and broadcasting this live, demonstrates the regulator's disposition to transparency and can engender better understanding and trust in the regulatory process.
- In turn, this enables EMA to increase its understanding of how medicines are used in the real world and helps make sure that the committee's recommendations are appropriate, relevant and feasible. It also illustrates how EU central regulatory recommendations can be implemented at national level in an harmonised manner, taking into account the specific circumstances of each Member State.
- Following the public hearing (which was EMA's first) a 'first-experience and lessons-learnt' document was published.

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# C. Pilot collaboration between Lareb and a patient organisation in communicating a signal (Lareb)

### Purpose/objective of the case study

The case study illustrates a pilot collaboration between Lareb and a patient organisation in communicating a signal about levothyroxine and panic attacks through the patient organisation to reach the right target group.[1]

### Pharmacology

Levothyroxine is a thyroid hormone used to treat hypothyroidism. It is a generic medicine marketed by multiple several companies worldwide.

### Indication/disease treated

Hypothyroidism (underactive thyroid) is a condition in which the thyroid gland doesn't produce enough of certain crucial hormones.

Hypothyroidism may not cause noticeable symptoms in the early stages. Over time, untreated hypothyroidism can cause health problems such as obesity, joint pain, infertility and heart disease.

### Stage of the drug development life cycle

Post-marketing safety communication

### Why were patients involved?

A patient organisation was involved in the communication of this signal because Lareb wanted to explore if collaboration with a patient organisation would provide an effective means to communicate a signal to a certain target group.

### How was contact established with the patients?

In the Netherlands there have been quite some problems with the use of levothyroxine. The Dutch Thyroid Organization and Lareb had frequent contacts about them. When the idea arose for this pilot study, the person in Lareb who is responsible for contacts with patient organisations asked the director of the Dutch Thyroid Organization if they were interested in this pilot study. They were interested, and to give shape to the pilot study, Lareb mainly collaborated with the communications team of the Dutch Thyroid Organization during the study.

### What did the patients do?

The patient organisation played a role in tailoring the message of the safety signal to a to make it relevant to their members. They also drew up communication strategy to communicate this signal, distributed the written materials through their communication channels, and moderated discussions around the signal on their social media channels.

### Was the process adjusted to the patients' needs?

As the collaboration was with a patient organisation and not with individual patients, Lareb did not need to adjust its process to address the individual patient's need.

### If patients were asked to help disseminate information, please give details.

The patient organisation distributed the signal communication through their print magazine, website, newsletter, Twitter and Facebook.

A representative from the patient organisation moderated the social media channels, and if topics arose which the representative did not feel competent to answer, Lareb provided support.

### Did the patients receive payment or compensation?

No payment or compensation were offered. The project had mutual benefits for both parties.

### Did you discard any patient requests or recommendations and why?

When drafting the communication there were multiple discussions between the Lareb author and the person from the patient organisation about the message of the article and the language used. In the end, both parties were satisfied with the text.

### Conclusion

This pilot could not have been done without the collaboration of the patient organisation. Based on the pilot, Lareb concluded that it is possible and valuable to communicate signals through patient organisations to reach the desired target audience. The social media posts about the signal generated more engagement than other communications from the patient organisation, indicating a strong interest from the patients about information on safety signals. The additional patient experiences that were shared in the comments on social media further strengthened the original signal and its relevance to patients, creating an interesting feedback loop.

The results of this study have also been published in a peer-reviewed journal.[2]

### Contact details

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# D. Creating partnerships between industry and patient groups for therapy development (Roche)

## Purpose/objective of the case study

This case study demonstrates the value of integrating the patient and caregiver voice into the decision-making process in all phases of medical product development. The early and systematic partnerships between the spinal muscular atrophy (SMA) community and Roche helped shape the company's clinical development programme in SMA and was central to ensuring faster and broader patient access and improving outcomes.

## Pharmacology

The medicine, Evrysdi (risdiplam) is a survival motor neuron-2 mRNA splicing modifier designed to treat SMA.[1] In August 2020 FDA approved risdiplam for the treatment of SMA in adults and children.[2] This was followed by approval from the European Medicines Agency (EMA) in March 2021[3] and Japan's Pharmaceuticals and Medical Devices Agency (PMDA) in June 2021. The development of risdiplam is part of a collaboration between Roche, PTC Therapeutics and the SMA Foundation, which started in 2011 with the goal of delivering a life-saving treatment for SMA patients.[1]

## Indication/disease treated

SMA is a genetic disease affecting the central nervous system, peripheral nervous system, and voluntary muscle movement (skeletal muscle).[4]

## Stage of the drug development life cycle

The SMA patient-and-caregiver community (patient advocacy groups [PAGs], patient experts, patient advocates, carers and individual patients from around the world)[5] were involved at every stage of the clinical development programme: from discovery to clinical trial planning and design, through to submissions to health authorities and access to treatment.

## Why were patients involved?

People with SMA and their caregivers are the experts when it comes to living with the condition. Their unique perspectives can change and advance drug research and development, resulting in improved patient outcomes. In order to bring meaningful treatments to patients, Roche embraced patient partnership across risdiplam's life cycle.

## How was contact established with the patients?

Ensuring that peoples' experiences, needs, and priorities were captured and meaningfully incorporated early and throughout risdiplam's life cycle required new ways of working. By listening to the community, Roche introduced a new operating model that focused on fostering trusted partnerships, facilitating continued dialogue and enhancing the way in which it received regular input from the SMA community to inform decision-making. These efforts included:

### 1. Strategic consultation

- Forming a one-of-its-kind Joint Steering Committee that oversees the clinical development programme, which also included members of the SMA Foundation, ensured that the community perspective was embedded in the nature of the programme and every decision made.

- Convening a standing patient advisory group with SMA Europe, partnering on strategic points with Cure SMA, and forming topic-specific working groups with members of the SMA patient-and-caregiver community.
- Hosting PAG webinars in response to questions and for feedback exchange – for example, to provide details on ongoing and/or new clinical trials and regulatory processes.

### 2. Transparent communication about the development programme

- Distributing 'Dear Community' letters with updates on activities and milestones, upon PAG request.
- Providing lay summaries of scientific publications, family-friendly posters for presentation at patient conferences, FAQs and other documents.
- Attending and/or co-hosting community webinars in partnership with PAGs.

### 3. Primary relationship manager model

- Critical for the SMA programme, Roche established the primary relationship manager (PRM) model. The PRM serves as the accountable point of contact between Roche and the patient community. This streamlines and enhances dialogue for community partners and creates a dynamic environment for seamless and mutually beneficial engagements.

Individuals touched by SMA have varying levels of input and experience into collaborative processes. Roche was inclusive in terms of who it engaged with, by forging strong and trusted partnerships with patient advocacy groups (including SMA Europe and Cure SMA), patient experts, patient advocates, carers and individual patients, from varied countries, ethnicities and socioeconomic backgrounds.

### What did the patients do? What were the outcomes?

As a result of these new ways of working, the patient-and-caregiver community helped shape every step of risdiplam's development journey, and regular exchanges ensured that community concerns, needs and expectations were understood and addressed by Roche.

### Trial design and strategy

The SMA Foundation (as a standing member of the JSC), SMA Europe and Cure SMA provided input on all elements of the Roche-sponsored SMA clinical trials from the earliest stages. This included helping to set research priorities, providing input on draft study protocols, and reviewing informed consent forms, assessment schedules and family guidance for self-administration. Their feedback led to developing seamless phase II/III clinical trial designs (combining phases II and III into one single, uninterrupted study conducted in two parts), including broader inclusion criteria and less restrictive exclusion criteria, and reducing trial burden to patients and their families.

In partnership with Cure SMA and SMA Europe, Roche developed a 'disease conceptual model' for SMA, which aimed at better understanding the core disease symptoms and impacts from the patient and family perspective. Insights generated from the qualitative interview study with SMA patients and caregivers helped inform the clinical development strategy, including selecting and developing patient-relevant study endpoints to ensure the assessment of concepts that matter to patients.

Many patients and caregivers who participated in the conceptual model study emphasised the desire to maintain independence in everyday life. This triggered the development of the SMA Independence Scale: a novel patient and caregiver-reported scale developed and validated with the continued input of SMA Europe and Cure SMA. The scale assesses the level of assistance required to complete activities of daily living in individuals with certain types of SMA (Type 2 and 3 non-ambulatory individuals).

The SMA Foundation and PAGs also worked with Roche on *how* to measure outcomes conveniently for patients and caregivers in the clinical trial setting - notably designing and deploying a mobile phone application to capture changes in day-to-day symptoms, which is used as an exploratory endpoint.

### Clinical trial participation

The support of PAGs helped facilitate international participation in the pivotal FIREFISH study (ClinicalTrials.gov identifier: NCT02913482), by enabling families to relocate to trial sites in other countries. Further, insights from the SMA community sparked the introduction of COVID-19 response measures that aimed at ensuring the continued safety and convenience of those involved in Roche clinical trials (*e.g.* home drug delivery using a contactless pickup and delivery process and home nursing services).

These efforts were fundamental in developing patient-centred trials, which resulted in expediting the timelines of the clinical programme's development and regulatory submissions, as well as generating more patient-relevant information on treatment effects in the population most likely to use the product if it were approved.

### Research beyond clinical trials

Feedback from SMA Europe inspired the conduct of a clinical meaningfulness study relating to the primary endpoint used in the pivotal SUNFISH trial (ClinicalTrials.gov identifier: NCT02908685) called the Motor Function Measure 32 (MFM32). The qualitative interview and survey study was designed in collaboration with a panel of SMA experts, which included members of SMA Europe and Cure SMA, and aimed to explore the relationship between the functional abilities assessed in the MFM32 and activities of daily living from the perspective of individuals with SMA and their caregivers.[6] The findings of this project are published, with the patient experts included as co-authors, and there is continued collaboration on other publications.

### Regulatory approval

PAGs advanced our understanding of the existing unmet need, and what treatment effects were most relevant, which helped prepare for interactions with health authorities. Members of the SMA Foundation attended FDA meetings alongside Roche, providing insights from people living with SMA directly. Patient views, published data from PAG-led surveys (*e.g.* Voice of the Patient report, EUPESMA) alongside the patient-reported outcome data from clinical trials, were also included in regulatory applications to capture the unmet need and real-life value that SMA treatments can bring to help support regulatory bodies in their review where possible.

### Product labelling

SMA Europe and Cure SMA provided valuable feedback on patient materials such as the risdiplam EU and US Instructions for Use, Patient Information Leaflet and Patient Package Inserts to ensure they were easy to understand for readers.

### Access to treatment

SMA Europe contributed to the design of a patient-centric pre-approval access programme. The SMA Europe standing advisory group and Cure SMA helped Roche to better understand the community's medical needs, validate ethical considerations and thus redefine the programme's inclusion and exclusion criteria and geographical reach. Ultimately, this input helped equitable access to patients most in need when no other treatment was available.

Regular input from the SMA Europe standing advisory group members helped inform the risdiplam market access and pricing strategy and helped to identify and understand potential barriers that might hinder reimbursement and future access to treatment. Patient-relevant evidence (*e.g.* existing unmet need, patient preference data) generated in partnership with PAGs supported access submissions and payer discussions.

### Supporting the safe and secure use of therapy, after approval

The community helped to develop non-promotional educational materials and design support services for the safe and secure handling of risdiplam. SMA Europe and Cure SMA helped identify which materials were most beneficial, and patients and caregivers ensured the content was accessible. These included welcome packs, 'Instructions for Use' videos and brochures, medication calendar reminders and cooling bags.

### Did the patients receive payment or compensation?

If allowed by local regulations, patients, caregivers and PAGs were compensated for their time and expenses for providing advice, with appropriate contracts put in place. The compensation was based on local fair market value guidance, in line with Roche policy and regional regulations.

### Did you discard any patient requests or recommendations and why?

Occasionally it wasn't feasible to incorporate all feedback, and in these cases, Roche reported this back to the community, sharing reasons why. Honest and timely discussions, with opportunities for questions, created a mutual understanding of the company and community stance, and ensured all views were acknowledged before any public announcements were made.

### Conclusion

Partnering with the community was essential to the development of risdiplam for SMA.

- Community expertise enriched the development process at every stage, leading to new ways of working, sharing information, making decisions, shaping strategies and co-creating solutions.
- Early and regular involvement of patients, caregivers and PAGs was critical to sustainably and effectively incorporate the patient voice throughout the life cycle of therapy development.
- Primary points of contact from Roche and PAGs helped to cultivate strong partnerships that fostered trust, allowing confidential information exchange, direct requests and open feedback.

Co-creation is about equal and active partnership and working together towards agreed principles and goals, while being open to feedback and embracing trust and transparency.

### Supporting quotes

> We are proud of the role we have played in the development of risdiplam, and of our partnership with Roche. It is vital that we continue to work together with health authorities, regulators and industry to help patients access the treatments they desperately need." Dr Nicole Gusset, President of SMA Europe.

### Contact details

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Senior Patient Partnership Director – Rare Diseases (SMA programme) at Roche

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# E. Example of a pharmaceutical company working with patients to develop an additional risk minimisation measure

### Purpose/objective of the case study

The purpose of this case study is to illustrate how a pharmaceutical company worked with patients to design an additional risk minimisation measure for a new osteoporosis medicine (Product X).

### Pharmacology

Product X inhibits the action of sclerostin, a regulatory factor in bone metabolism. It increases bone formation and, to a lesser extent, decreases bone resorption.

### Indication/disease treated

Osteoporosis in post-menopausal women at high risk for bone fracture.

### Stage of the drug development life cycle

During the end of the Phase 3 trials, the company sought to prepare for the potential of a Risk Evaluation and Mitigation (REMS) requirement in the United States in light of the serious risk of MACE (**m**ajor **a**dverse **c**ardiac **e**vents, including myocardial infarction, stroke and cardiovascular death), as well as the risks of osteonecrosis of the jaw and hypocalcaemia associated with the product. Patients were recruited to assist with the design of an additional risk minimisation measure (aRMM) during the end of the Phase III trials in about 8 months period before initial filing for marketing authorisation in the United States.

### Why were patients involved?

As part of the REMS planning, it was determined that a patient-physician benefit-risk counselling tool should be included as an aRMM. The purpose of the counselling tool was to provide the prescribing physician with key messages to convey to patients regarding the main benefit and key risks of using the medicine and what actions a patient could take to minimise the risks. The bottom half of the counselling tool had a tear-away section with a summary of the main counselling points for patients to keep for reference.

The trigger for involving patients was the company's desire to ensure that the aRMM was relevant, understandable, acceptable to patients and that it was feasible for use in real-world healthcare decision-making.

### How was contact established with the patients?

Patients were identified via various means: 1) the company's patient advocacy organisation had contacts within the osteoporosis patient community and conducted some outreach; 2) via a professional recruiting firm that used different social media forums to reach patients with osteoporosis at high risk for fracture.

Eight women ultimately participated in the study. Each woman came to the office of an academically-affiliated research firm where they were shown the counselling tool and interviewed for about an hour regarding their reactions to it. A standard interview guide was used to guide the questioning. None of the participants dropped out.

### What did the patients do?

Patient involvement occurred in two phases:

- In Phase 1, a group of 5 patients were asked to review the content, colour and layout of the benefit-risk counselling tool and patient tear-away section. They were asked whether they understood the information, what they liked and disliked about the tool, whether they would keep the tear-away sheet for future reference, whether it was clear as to what actions to take if symptoms of MACE presented, and to rate their overall impressions of the tool.
- In Phase 2 (which occurred after the initial set of interviews with 5 patients), the tool was redesigned to incorporate the feedback received and then a second group of 3 women reviewed the revised version of the tool and provided their feedback on the same questions.

### Was the process adjusted to the patients' needs?

Alternative dates and times were offered to accommodate patients' schedules.

### Did the patients receive payment or compensation?

Patients were compensated for their travel expenses and received payment for their time.

### Did you discard any patient requests or recommendations and why?

All patient feedback was reviewed and every effort was made to incorporate all of it.

### Conclusion

As a result of involving patients in the design of this aRMM, the company had enhanced confidence that the proposed aRMM would be an effective tool as part of a REMS. Although ultimately the FDA did not require a REMS for this product, the involvement of patients helped enhance the clarity of the information presented and the acceptability and usability of the tool to patients.

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# F. Takeda TAK-676 *Radiation Combination Cancer Therapy Patient and Care Partner Advisory Board* to inform early clinical development plans for a novel cancer therapy

## Purpose/objective of the case study

This case study describes a Takeda patient engagement (PE) activity involving oncology patients and their care partners in the early clinical development plans for a novel cancer therapy. The activity is entitled *Radiation Combination Cancer Therapy Patient and Care Partner Advisory Board*. There were two primary objectives:

1. To gain an understanding of patient and care partners' experiences in living with their disease and experience with therapy. Specifically, we wanted to understand their challenges, met and unmet needs.
2. To gather feedback and insights on a proposed Phase 1b clinical trial protocol from the patient and care partner perspective, including the risks and benefits advisors see in trial participation and how we might help support participants during the trial to decrease the burden of participation.

The patient and care partner insights gleaned from this PE activity were reviewed and several actions were taken as a result by the Takeda team, directly impacting the program's clinical development activities and strategy.

The *Radiation Combination Cancer Therapy Patient and Care Partner Advisory Board* described in this case study is part of an overall Patient Engagement Plan (PEP) that the program team developed to help ensure strategic and long-term considerations for patient and care partner involvement throughout the lifecycle of the medical asset.

## Stakeholders involved and representativeness of stakeholders

- **Takeda Global Program Team (GPT)** is a multi-disciplinary cross-functional team of subject matter experts that leads through a product lifecycle, from discovery through post-approval.
- **Takeda R&D Patient Engagement Office (PEO)** is a center of excellence for R&D PE within Takeda, working with internal and external stakeholders to co-create sustainable, systematic and fit-for-purpose PE plans to facilitate integrating patient perspectives in R&D.
- **Scientific and Clinical collaborator:** radiation oncologist from the Medical Center [name anonymized] in the North East who is a Takeda collaborator
- **Patient and care partners/advisers:** six individuals living with cancer and three care partners. Diversity, which is broadly defined, among the patient advisor groups is a high priority, and in its commitment to Diversity, Equity & Inclusion (DE&I), the Takeda PEO maintains awareness of the perspectives we are getting, and not getting, in each of our PE activities.
- **External partners:** an external vendor worked with the Takeda team to build the strategy and helped facilitate the meetings.

## Pharmacology

The molecule being used in this case study is a small molecule drug internally referred to as TAK-676. TAK-676 is part of a class of drugs known as immune agonists. TAK-676 "turns on" the immune system by specifically activating the STING protein. The signaling pathway mediated by activated STING is an important regulator in the human innate immune system. Radiation therapy, a well-established cancer treatment that can lead to tumor cell death, has recently been shown to induce changes in irradiated tumors which activate the human innate and adaptive immune systems. The process of immune system activation to target and destroy cancer is known as the "cancer immune cycle." However, for many cancer patients, their immune system is unable to mount a long-term

anti-tumor response due to the presence of specialized proteins known as “checkpoint proteins” on cancer cells which interact with T-cells, acting as “brakes” for the immune system and limiting the anti-tumor immune response. Multiple new checkpoint inhibitor drugs, including pembrolizumab used in this trial, have made significant progress to improve clinical outcomes. Unfortunately, many cancer types either don't respond to checkpoint inhibitors or become resistant, leading to renewed tumor growth.

In this trial, TAK-676 and radiation are being tested as combination partners to re-sensitize tumors to pembrolizumab checkpoint inhibitor therapy. TAK-676 has not been approved for the use or indications under investigation in the clinical trials (and there is no guarantee it will be approved for such use or indications). The information provided is only for the purpose of providing an overview of the clinical trial(s). Any claims of safety and effectiveness can only be made after regulatory review of the data and approval of the labeled claims.

### Indication/disease treated

The protocol discussed in the PE activity is the TAK-676-1003 clinical trial (NCT04879849 *A Study of TAK-676 With Pembrolizumab After Radiation Therapy to Treat a Number of Cancers*). This is a Phase 1b trial fast-following the FIH trial to the first-in-human trial TAK-676-1002 (NCT04420884). For this trial, there are three specific adult patient indications: Non-Small-Cell Lung Carcinoma, Triple Negative Breast Neoplasms, and Squamous Cell Carcinoma of Head and Neck. TAK-676-1003, NCT04879849, posted to CT.gov in May 2021 and is expected to begin in July 2021.

### Timeline of activities

- **2019 – November:** GPT and PEO come together to co-create a PE activity specific to the topic of the TAK-676-1003 *Radiation Combination Cancer Therapy Patient and Care Partner Advisory Board*
- **2020 – April:** Radiation Combination Cancer Therapy Patient and Care Partner Advisory Board is conducted virtually
- **2020 – April through present:** GPT in close collaboration with the PEO takes learnings from the *Radiation Combination Cancer Therapy Patient and Care Partner Advisory Board* and implements them, as appropriate, into the TAK-676-1003 trial design and execution.
- **2020 – September:** Takeda hosts an advisory board share back meeting with patient and care partner advisors. The purpose of the share back meetings is NOT to solicit new feedback from our advisors but to share with advisors some of the key insights we heard from them and the actions that were affected as a result of those insights. The share back is part of a respectful dialogue with our patient advisors and emphasizes the importance of translating patient and care partner insights, when appropriate, into tangible actions within the Takeda R&D organization.
- **2020 – November**: TAK-676 Patient Engagement Plan (PEP) development and the associated PEP workshop is conducted. The PEP is a roadmap to optimize PE opportunities throughout the entire asset lifecycle.
- **2021 – May** TAK-676-1003 Phase 1b trial goes live on CT.gov (NCT04879849)
- **2021 – July:** TAK-676-1003 Phase 1b trial expected to enrol its first patients

### Why were patients involved?

The Takeda GPT identified potential opportunities for PE in the protocol design and operational conduct of the Phase 1b trial TAK-676-1003. The team understood that first-hand knowledge would be instructive as it contemplated the design and implementation of the proposed trial in which radiation would be combined with two intravenously (i.v.) administered immune oncology agents; TAK-676 and pembrolizumab.

The GPT sought to understand patient and care partners’ unmet needs as well as to understand their impressions of the proposed clinical trial, especially regarding protocol design and the associated

(patient) burden. There was a strong desire to hear from patients and care partners experienced specifically with radiation combination therapy in the treatment of their advanced cancers.

### How was contact established with the patients?

The GPT worked together with Takeda PEO and their external vendor partner to determine top objectives for the advisory board meeting and the ideal composition of the patient and care partner advisor attendees. The external vendor conducted the recruitment of patient and care partner advisors on behalf of Takeda and through the connections with patient organizations, and regularly reviewed potential candidates with PEO and GPT.

The *Radiation Combination Cancer Therapy Patient and Care Partner Advisory Board* involved 9 advisors from diverse backgrounds. This group consisted of six individuals living with a cancer diagnosis relevant to the clinical trial and experienced with radiation combination cancer therapies as well as three care partners of whom two were the advisors' adult children and one was an advisor's spouse.

### Description of patient engagement activity

The patient and care partner advisory board meeting was organized in two separate 2-hour sessions, two days apart. On day 1, advisors shared their journey and challenges experienced and met and unmet needs, whereas on day 2 they reviewed the Ph1b protocol design. Patient and care partner advisors were involved in multiple ways prior and during the advisory board in order to support their preparedness to meaningfully engage in the advisory board meetings.

**Day 1 – Pre-work:** 30-minute 1x1 meetings were held individually for each patient and care partner advisor with the external vendor partner in preparation and to help advisors in set-up and usage of the online meeting technology as well as other online interactive platforms used during the meeting.

**Day 1 – Getting to know each other**, understanding challenges, expectations and unmet needs

- Two-hour virtual advisory board meeting
- The patients and care partners provided insights as to their individual journeys living with cancer and receiving treatment with specific emphasis on challenges experienced.

Patients and care partners then shared their top challenges and unmet needs both via discussion and through an online collaboration tool.

**Day 2 – Pre-work:** A video featuring the Takeda Global Clinical Development Lead (GCL) for TAK-676 was shared with advisors. The video describes the clinical trial rationale and the protocol design which would be the basis for the discussion on day 2.

**Day 2 – Reviewing the draft protocol design together:** Advisors were asked to reflect on the protocol with regards to the inclusion/exclusion criteria, the planned treatments, samplings/assessments and end of trial support. Learnings were captured on-screen live and discussed.

A short feedback survey was sent to all advisors after the conclusion of the advisory board meeting to ensure Takeda teams can continuously learn how to best engage patients in drug R&D. Five out of nine advisors responded, and all five provided very positive feedback on their experience, as well as the organization and content of the advisory board. In addition, all 5 advisors shared that they felt that their voices were heard during the PE experience. Assuring that advisors feel heard is a core value of the Takeda R&D PE office and is consistently assessed as a measure of success.

### Was the process adjusted to the patients' needs?

The meeting was originally planned as an in-person advisory board lasting 6-7 hours. Due to the global onset of COVID-19 pandemic, the meeting format was changed to virtual and split into two separate 2-hour virtual meetings. As online collaboration technology tools were used during the

meeting, technology training and pre-check meetings were conducted by the external vendor prior to the meetings with each advisor.

A "look book" was created and shared in advance of the meeting. This contained pictures and personal biographies for all individuals planning to participate in the advisory board meetings: patient advisors, Takeda, and the external vendor.

Pre-read information was shared in advance of meetings to help prepare patient advisors for the meeting, including:

- Slides explaining Takeda's commitment to PE with details about Takeda's PE philosophy, the Takeda PEO and expectations for the upcoming advisory board.
- A short video explaining the clinical trial and the protocol design that was to be discussed. The clinical trial was described using slides with illustrative graphics that explained the mechanism of action for TAK-676, the biological hypothesis behind combining TAK-676 with pembrolizumab and radiation therapies, and the details of the TAK-676-1003 clinical trial draft protocol. The advisors' responses to the video were overwhelmingly positive.

**(**Patient and care partner advisors were not asked to disseminate any information before, during or after the advisory board.)

### Did the patients receive payment or compensation?

Patient and care partner advisors received compensation at the appropriate fair market value (FMV) rate. Advisors were paid hourly for their time spent advising Takeda. Paid time was inclusive of both participation in live meetings (4 hours) and any associated pre meeting activities (3 hours). In the event that in-person PE activities were conducted, Takeda would compensate for reasonable travel, lodging, and meals in addition to the above-mentioned compensation according to relevant policies and regulatory requirements.

### Did you discard any patient requests or recommendations and why?

The insights, findings and learnings from the advisory board meeting can be broadly categorized into five themes: 1/ Communication and education; 2/Psychological support, 3/Burden of trial participation; 4/Burden of biopsies, 5/Exclusion criteria.

All insights were noted and kept for possible future use through the lifecycle of the TAK-676 program. Importantly, several insights were actionable immediately and within the scope of the current Ph1b trial. Takeda will record the learnings and revisit with the GPT regularly as the program progresses to understand how these learnings might impact the TAK-676 program going forward as well as Takeda R&D more broadly. Where applicable, the insights gathered might also be used as part of *Patient Experience Data* in the regulatory review/discussions/submissions.

### Impact

The learnings from the advisory board meeting helped the Takeda GPT to understand the potential patient and care partner burden the trial might cause and to improve the trial design in ways that could help alleviate that burden. Below is a summary of actions taken by the team as a result of the insights and learnings gathered from the advisory board:

*1. and 2. To improve communication and education and provide ongoing support:*

The team created an optional online patient portal for study participants. The portal provides information to help support participants during the clinical trial. The portal features welcome and thank you notes, contains educational videos explaining the trial and protocol, outlines the schedule of visits and "what to expect", explains the rationale for needed samples and biopsies and provides links to patient support organizations.

As an add-on to the portal, the team created several dedicated resources for study participants and their care partners. These include a visit guide, a study fact sheet, and a patient brochure which is also provided in print. Furthermore, the team created two educational videos featuring a clinical scientist and medical oncologist from the GPT explaining the TAK-676-1003 trial in specific detail.

All patient facing materials undergo Takeda legal review and approval as well as ethics review and approval as per the clinical trial Institutional Review Board (IRB) before dissemination to study participants.

Finally, to increase emphasis on the value that site-based psychological support brings to patients, the team added a question to their clinical site feasibility questionnaire to specifically understand psychological support offerings. It is hoped that this question will build up Takeda's line of sight and knowledge-set around our site offerings and might eventually help inform preferred site selection.

*3. and 4. To reduce the burden of trial participation:*

The team reassessed the number of visits, consolidated the treatments and procedures where possible, and reconsidered the necessity of biopsies since these factors clearly contributed to what advisors perceive as risks or burdens of the trial. For example, study participants who would have had a recent biopsy taken may not need to do a repeat biopsy upon entering the trial. Also, on-treatment biopsies would only be sought from trial participants who have received a dose of TAK-676 which is known to activate the immune system.

The Takeda team will offer study participants reimbursement for some travel and accommodation expenses incurred during study participation and has contracted with an external partner to facilitate this. This includes discounted and reimbursed hotel stays during the necessary visits, especially given that the clinical sites for this Phase 1b trial are primarily medical institutions located in larger cities rather than local centers where participants may access their more routine treatment.

*5. Regarding the exclusion criteria and the advisors' emphasis on having the opportunity to participate:*

Advisors shared general concerns regarding clinical trial exclusion criteria and emphasized giving a greater percentage of cancer patients the opportunity to participate in trials. The TAK-676 team reassessed the exclusion criteria for their trial and built-in flexibility to have discussions between investigator clinicians and patients regarding their enrolment. One specific example shared by patient advisors was the desire to not broadly exclude from eligibility patients who have history of metastatic disease in the brain. The exclusion criteria related to brain metastases now reads "*History of brain metastasis unless: Clinically stable, (that is, treatment completed >=4 weeks prior) following prior surgery, whole-brain radiation, or stereotactic radiosurgery, AND Off corticosteroids.*"



## Conclusion

Continuous PE is important to making a meaningful shift from developing medicines FOR patients to developing medicines WITH patients at Takeda, and this case study showcases the benefits PE brings to R&D. Importantly, the PEO partners with R&D to support the creation and implementation of comprehensive and longitudinal Patient Engagement Plans (PEPs) to help ensure that patient perspectives are continually and appropriately attained as the R&D strategy evolves. Furthermore, as the value of patient experience data is increasingly recognized by regulatory bodies, including FDA, the Takeda R&D PEO integration of patient and care partner insights throughout the drug development process can be a component of the totality of evidence that regulators can evaluate during their decision making. The Takeda PEO is committed to comprehensive and longitudinal patient engagement in support of Takeda's broader mission to address healthcare needs and to improve health outcomes of patients worldwide.

## Contact details

Ameet Pawar, Associate Director, Global Patient Safety Evaluation (GPSE)

# G. Patient activism to counter AIDS denialism and improve access to HIV medicines in South Africa

## Purpose/objective of the case study

To understand how AIDs patients in South Africa successfully campaigned to overcome state-supported AIDS denialism and government resistance to evidence-based responses and the prohibitive price of the drugs which made them unaffordable for the majority of South Africans with AIDS.

Although the objectives of activism do not fall squarely within the scope of this report, the methods and tactics described hold important lessons for patient involvement in the development, regulation and safe use of medicines. Lessons from this South African activism also apply to the SARS-CoV-2 pandemic (see Conclusions, below).

## Indication/disease treated

HIV damages cells in the immune system and weakens the body's ability to fight infection and disease. Left untreated, it can develop into AIDS – potentially life-threatening infections and illnesses which occur when HIV has damaged the immune system.

In the 1980s, the average life-expectancy after an AIDS diagnosis was about one year. Now, with early diagnosis and effective treatment, most people with HIV do not develop AIDS and can have normal life-expectancy.

## Pharmacology

Antiretroviral (ARV) medicines are used to treat HIV. They prevent the virus from replicating and allow the immune system to repair itself. They are available mainly in the form of tablets that need to be taken daily; treatment is continued indefinitely.

## Stage of the drug development life cycle

In 1996, an effective combination of medicines known as highly effective ARV treatment (HAART) was proven effective against AIDS. Despite this compelling evidence, the South African government questioned the efficacy of the medicines and did not make them available for patients with HIV.

Founded in 1998, the Treatment Action Campaign (TAC) became South Africa's largest and most prominent AIDS activist movement. It engaged patients in its campaigns and successfully campaigned for ARV treatment to become available to AIDS patients in South Africa.

Led by the TAC, patients engaged in grassroots education programmes to disseminate information about ARVs and organised civil disobedience campaigns to petition the government to make HAART accessible for all.

## Why were patients involved?

Between 2000 and 2004, the South African state's response to AIDS was dominated by denialism. Treatments were proven to be effective but they were unaffordable and inaccessible to the majority of the South Africans. After fighting for access to affordable generic medicines in South Africa, activists turned their attention to the South African government which still refused to make them available to all.

The TAC educated patients on HIV science, discrediting AIDS denialism. Eventually, public pressure forced a change in the state's stance.

### How was contact established with the patients?

The TAC used various approaches to establish patient contact in South Africa.

- An effective, organised national campaign made good use of the media and courts.
- Strong relationships were fostered with the media. Interviews between journalists and TAC members, workshops to explain HIV science and detailed explanations of court cases and civil disobedience campaigns all increased patient understanding.
- An education programme developed treatment literacy among patients in clinics – these programmes were delivered to patients by patients who were living proof of the effectiveness of the treatments. Their stories were repeated throughout the townships and inspired others to get tested.

### What did the patients do?

1998 – The TAC launched its first campaign calling for the use of zidovudine for pregnant HIV-positive mothers for the prevention of mother-to-child transmission (PMTCT). They urged the government to plan affordable treatment to HIV-positive South Africans.

1999 – The TAC marched on one of the largest hospitals in South Africa and staged a lie-in at the hospital gate calling for the introduction of PMTCT services.

2000 – The non-governmental organisation (NGO), Médecins Sans Frontières (MSF) illegally imported generic medicines into South Africa and demonstrated their success in treating AIDS. Many recovering patients become supporters and activists. Having witnessed the successful use of ARVs in Brazil, patients-turned-activists promoted ARVs in a press conference organised by the TAC, MSF, OXFAM (another NGO) and the Congress of South African Trade Unions.

2003 – The TAC launched its civil disobedience campaign demanding the South African government make ARV treatment available to all HIV-positive patients.

### Was the process adjusted to the patients' needs?

The treatment literacy programme was developed with the help of British and American activists as well as local doctors and nurses. Some 300 treatment literacy practitioners were employed to train full-time. Teaching was delivered to patients in waiting rooms. Many practitioners were placed in clinics where they explained the importance of HIV testing and treatment to patients in crowded waiting rooms. There they recruited practitioners, many of whom had HIV and had survived as a result of ARVs.

Training at TAC branches allowed the organisation to reach a critical mass of people and showed that HIV is treatable.

Clinical nurses in some clinics spoke Xhosa which helped them to work closely with communities, bridging the cultural divide between white doctors and their patients.

Songs were also used to promote community learning. For example, one included the lyrics:

> We know AZT protects children from HIV globally
> MTCT Prevention
> We know neviraprine protects children from HIV, globally
> We want Biozole
> We want nevaprine from you, Thabo Mbeki
> Thabo Mbeki, what is our debt?
> What is our sin? Is it AIDS?

### How patients disseminated information

Many patients receiving ARV treatment became health literacy practitioners, educating others about the disease and treatment. Patients also joined campaigns to pass on information and knowledge through face-to-face meetings and also through interaction with the media, press conferences and civil disobedience events.

### Did you discard any patient requests or recommendations and why?

Patient demands were to follow scientific advice in line with international guidelines. They did, however, go against the recommendations of the State.

### Conclusions

**Outcomes**

2002 – South African courts ruled that the government must provide the ARV nevirapine to pregnant HIV-positive women to prevent their children contracting HIV.

2004 – as a result of mounting pressure from patients, scientists and prominent national and international figures, the South African government began the rollout of ARV treatment for all HIV-positive patients.

**Lessons**

Many of the following lessons can be applied to the SARS-CoV-2 pandemic to help local communities understand information about the disease, vaccination programmes, and other ways to prevent spread of the disease.

- Institute treatment literacy programmes – they were highly successful in educating patients and giving them agency. Patients who were given the tools to inform and educate others helped build strong community networks.
- Encourage national and international organisations to work independently of the government to inform patients and share knowledge.
- Draw in and work collaboratively with healthcare professionals and with partners in other countries.
- Recruit treated patients as campaign champions – they can inform and educate patients as well as participate in interactions with the media and government agencies.
- Respect local traditions and communities – passing on messages through song and speaking with patient in their dialect can encourage patients to engage with the campaign.
- Celebrate successes and build on them.

### Supporting quotes

> 'I visited Khayelitsha because everyone I spoke to in the Treatment Action Campaign and at the UN in South Africa said that Khayelitsha was the model on which an eventual rollout of ARVs would be based. They realised that Khayelitsha was thumbing its nose at the government – and taking the government on. Their stance was not only that this was an excellent example of a principled stand in the face of a curmudgeonly and denialist government, but that it was also a fascinating glimpse at the way ARVs could transform the situation of people living with AIDS.'
>
> Stephen Lewis – UN Secretary-General's Special Envoy for HIV/AIDS in South Africa 2001–2006

> 'We called for a people's fund that would strive to see that everyone, regardless of class, creed or colour, could access the treatment they needed to stay alive. The idea of a global mechanism to support people living in poverty to access treatment seemed unthinkable. Some people even doubted whether

people living in Africa had sufficient literacy to adhere to treatment. But we marched on. That push led to political action and the creation of the Global Fund to Fight AIDS, Tuberculosis and Malaria – a people's fund with a governance structure that would involve civil society, communities and people affected by diseases.'

Vuyiseka Dubula – HIV/AIDS activist and director of the South African centre for AIDS management at Stellenbosch University

## More details available from:

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Dubula V. I thought that HIV meant death but it led me to fight to save millions of lives. The Guardian; 5 July 2021. (Webpage, accessed 22 February 2022)

Geffen N. Debunking Delusions – The TAC campaign against AIDS denialism. Auckland Park (South Africa): Jacana Media Ltd; 2010.

# APPENDIX 3:
# CIOMS Working Group XI statement

COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES

ESTABLISHED UNDER THE AUSPICES OF THE WORLD HEALTH ORGANIZATION AND UNESCO

CIOMS

CONSEIL DES ORGANISATIONS INTERNATIONALES DES SCIENCES MEDICALES

FONDE SOUS LES AUSPICES DE L'ORGANISATION MONDIALE DE LA SANTE ET DE L'UNESCO

7 December 2020

Statement[1] of Council for International Organizations of Medical Sciences (CIOMS) International Expert Working Group XI:

## Patient contribution to the development and safe use of medicines during the Covid-19 pandemic[2]

The threat of another infectious disease pandemic has loomed over the world since the 1918 influenza pandemic caused by the H1N1 influenza A virus ("Spanish flu.[1] The brief and limited outbreaks related to coronaviruses,[2] SARS and MERS, were preludes to the future, which has now arrived with a novel coronavirus that has impacted every country in the world.

This new pandemic coronavirus, designated as SARS-CoV-2 ("COVID-19"), has catapulted the issue of the patient voice in healthcare and healthcare policy to the front of the global agenda. In this context, we are all patients or potential patients, which includes all members of the public, healthcare professionals, patients with pre-existing conditions and so forth, and we will use the term "Patient" to designate this. The world population has been affected with varying government-required risk mitigation measures including social distancing, national, regional and local "lockdown" quarantines,[3] and the wearing of masks along with diligent handwashing. Clearly, not all of these measures are possible in every country due to a lack of resources and healthcare infrastructure, and it will surely be Patients who will suffer the most as a result. This issue must be dealt with responsibly on the local level by all countries and Patients cooperating with and supporting overwhelmed healthcare systems and aiding the planned implementation of mitigation measures. **If not, pockets of SARS-CoV-2 will remain in these regions with continuous suffering of their populations.[4] This is critical as we still do not fully understand the clinical, pathological and epidemiological attributes of SARS-CoV-2; the longer it stays embedded and circulating, the possibility of mutation into a deadlier virus remains along with further waves of epidemics.[5]**

Unanswered questions surrounding prevention and treatment for SARS-CoV-2, including the urgency of vaccines, hygiene, clinical trials, "emergency use authorizations", compassionate use, testing and convalescent plasma, have arisen and the world has moved beyond general issues to another crucial one: the role of the Patient voice in partnering with scientists and governments. The Patient voice can help answer the crucial questions resulting from the evolving clinical and epidemiological behaviour of



1 Disclaimer. The views and opinions expressed in the statement above are the consolidated views of the participants of the CIOMS Working Group and should not be attributed to any individual expert in those or any organization with which these individuals are employed or affiliated.

2 CIOMS Working Group WG XI: Patient involvement in the development and safe use of medicines. For more information about the Working Group and its members, please visit: https://cioms.ch/working-groups/working-group-xi-patient-involvement/

a potentially devastating virus through informed and active participation in the scientific and medical quest for solutions. This is not "a nice to have" but rather a requirement in view of this pandemic.

Communication that is jointly developed with Patient partners, and which is timely, reliable and factual, must be disseminated in plain language. Patients are already organizing in such a way as to exchange experiences regarding signs and symptoms of SARS-CoV-2, and on the consequences to their health due to the lockdown and the interruption of planned care,[6] and as such, a clearer clinical picture of the infection is potentially developing. This is an opportunity for researchers (who are also Patients!) to apply methodologies to the exchange of information.

Our armamentarium of medical weapons to fight SARS-CoV-2 (swifter and more accurate testing, re-purposed existing therapeutics and experimental medicines, expedited vaccine development) have received the most attention. But within the context of a pandemic, the active participation of the general global population is needed to help "flatten the curve."[7] The pandemic has resulted in an evolution of healthcare rhetoric. In general, from a healthcare policy perspective, some have been discussing "the patient voice" in a passive manner. An important lesson from this ongoing pandemic is that we must now shift to a more comprehensive understanding of "Patient actions" and how these can be incorporated into the search for solutions in defeating this virus. Patients wish to participate in research on the physio-pathology of the disease and in clinical trials testing experimental treatments within scientific protocols.[8] Outside such protocols, all Patients could potentially contribute with their data collected in medical records and/or databases.

As with any ecosystem, the component parts of global healthcare systems are not necessarily equal, but they are requirements for success.[9] The Patient voice must be recognized and be integral to the scientific march in defeating this virus. **This requires that all ethical, patient consent, scientific and public health processes that were in place prior to the pandemic, must involve Patients and adhere to robust methodologies and responsible peer review in order to avoid decisions that could bring about dangerous public health consequences.** This requirement will maximize the safest route forward until effective and safe therapies are identified and implemented, which will be an enormous endeavor in view of the billions of people affected.

The struggle against SARS-CoV-2 is truly a battle in which we are all called upon to unite to find global solutions. As Patients, we are all affected and we can have a powerful and active voice. We will learn from this pandemic, and we will apply these lessons and thereby be better prepared for the next pandemic that emerges from whatever infectious agent.

The CIOMS WG XI, focusing on patient involvement in the development and safe use of medicines, has been working diligently with patient organisations, academia, pharmaceutical industry, and health authorities to help address the questions raised in this Statement and other issues. The CIOMS WG XI report is expected to be published in 2021.

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8 https://covid19studies.org/

9 https://www.pnhp.org/single_payer_resources/health_care_systems_four_basic_models.php

# APPENDIX 4:
# CIOMS Working Group membership and meetings

(To follow)

# APPENDIX 5:
# List of commentators

(To follow)