**Work Package 7**

**Deliverable 7.2**

**Framework for patient involvement in ethical review of clinical trials**

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## Overarching principles for patient involvement throughout the medicines development cycle

The great majority of experts involved in the development and evaluation of medicines are scientists. There is an increasing need to draw on patient knowledge in order to understand what it is like to live with a specific condition, how care is administered and the day-to-day use of medicines to promote discovery of new effective drugs and improve their development and evaluation.

Structured interaction between patients, their representatives and other stakeholders is necessary and allows the exchange of information and constructive dialogue at national and European level where the views from users of medicines can and should be considered.

We recommend close cooperation and partnership between the various stakeholders including healthcare professionals’ organisations, patients’ and consumers’ organisations, academia, scientific and academic societies, regulatory authorities, health technology assessment (HTA) bodies, ethics committees, and the pharmaceutical industry. Experience to date demonstrates that close cooperation with patients has resulted in increased transparency, trust and mutual respect between them and other stakeholders. It is acknowledged that their contribution to the discovery, development and evaluation of medicines enriches the quality of the evidence and opinion available.[[1]](#footnote-1)

Existing codes of practice for patient involvement in medicines development do not cover the research and development (R&D) period. Where frameworks already exist, they have been written for use by a specific body (for example the European Medicines Agency, EMA) or a single profession (such as physicians). The EUPATI framework aims to support the development of patient involvement across the entire process of medicines development and evaluation.

The framework is presented as four separate guidance documents covering patient involvement in:

* pharmaceutical industry-led medicines R&D
* ethics committees
* regulatory authorities
* health technology assessment (HTA).

Each guidance suggests areas where at present there are opportunities for patient involvement. This guidance covers patient involvement in ethical review.

## Introduction to patient involvement in ethical review

2.1 To ensure optimal benefit for patients from a new medicine, and resulting commercial success, pharma companies focus the selection of compounds to develop and the definition of relevant research outcomes around the needs of patients with the respective disease. “Patient centricity” is a rapidly evolving and increasingly important element of pharma companies’ business models. It requires new strategies, new organisational structures, and culture change across the pharma sector. It requires partnership with patient experts who are capable of providing advice on the value of treatments and on what health outcomes are relevant to patients. However, the concept of patient centricity is also relevant for other stakeholders in the medicine development process, especially for research ethics committees who advocate for the protection of patients in clinical trials.

2.2 Before new medicines can be effectively and safely administered to patients they have first to be tested in animals and then in healthy volunteers, and finally in patients with the disease under study. These research phases are designed to investigate the desired and undesired effects of a new medicine on the body in general, and specifically on the disease in question. Research studies in humans, to test how effective and safe a new medicine is, are known as clinical trials. Good clinical trial design is both ethical and scientifically sound. Design decisions include whether the new medicine is to be compared to another medicine or a placebo and what kind of tests and assessments are to be made (and how often). The risk of potentially harmful side effects needs to be balanced against the potential benefits for the patients taking part, such as early access to a new medicine, more intense diagnostics and supervision, and the chance to contribute to the development of new treatments for other patients with the same disease. Patients’ judgements about such risks and benefits might be different to that of researchers: for instance, depending on the severity of the disease in question, they might be prepared to take a higher risk concerning potential side effects. In today’s practice, the involvement of patients in these decisions is not standard – neither in clinical trials initiated by pharmaceutical or biotechnology companies nor in those initiated by academic institutions.

2.3 Clinical trials are subject to a framework of very strict laws. Before a clinical trial can start it needs approval from the national competent authority which must ensure that all legal conditions are fulfilled, that the trial is scientifically sound, that the study medication is of good quality and safe and that there is a favourable balance between expected benefits and risks. In parallel to the review by the national competent authority, one or more multi-disciplinary research ethics committees review the study protocol and related documents in order to safeguard the study participants. They ensure that the information to patients is comprehensive and understandable. They assess the balance between benefits and risks, ensure that this balance is acceptable, and that the trial is scientifically relevant for patients with the disease in question. .

2.4 In most European countries patients, carers or patient representatives are only marginally or not at all involved in the ethical and scientific review of clinical trials. In the national legislation of most European countries as well as in the new Clinical Trial Regulation (Regulation (EU) 536/2014) the involvement of patients in the definition of the ethical conditions for clinical trials and in the review provided by ethics committees is not clearly defined. The regulation states: “When determining the appropriate body or bodies (i.e. ethics committees), involved in application assessments, Member States should ensure the involvement of laypersons, in particular patients or patients' organisations.”

2.5 While patient involvement in R&D is an accepted concept in the pharmaceutical and biotechnology industry, patient involvement in ethics committees is much disputed. Ethics committees are expert advisory groups providing advice on the ethical acceptability of research projects carried out in human beings. They have an obligation to the public to protect the research participants. To fulfil these obligations, ethics committee members need to be independent, neutral, objective and competent in scientific, ethical and methodological topics. The inclusion of a lay member is supposed to support this neutrality and to enlarge the scope of advice. Adding patient members to an ethics committee means a paradigm shift: the concerned party who will ultimately benefit from the research sits at the table. However, the considerations underlying the concept of “patient centricity” in R&D are likely to also apply here: the outcome can be improved if the concerned party can provide their expert input. There is a need for a generally accepted framework outlining the conditions for collaboration of ethics committees and patients in ethical review.

## Scope

3.1 This framework has been developed by the European Patient Academy on Therapeutic Innovation (EUPATI) for all stakeholders in medicines development involved in the ethical review of clinical research projects, with special emphasis on members of research ethics committees and patients/carers or patient representatives providing patient input. This covers patient involvement in advising on ethical aspects of the whole clinical trial – from definition of the research questions to protocol and informed consent preparation to ethical review and final reporting. See Appendix 1 (Roadmap).

3.2 This guidance is based on the discussions and conclusions from a multi-stakeholder roundtable discussion and a webinar on patient involvement organised by EUPATI, contributions from national ethics committees, consultation within the EUPATI consortium and an extended external consultation process.

## Defining “Patient”

“Patients” can be individual patients or their carers, or representatives from patient organisations with relevant expertise. To harmonise terminology for all possible types of interaction presented in this and the other EUPATI guidances, we further define patients as follows:

* “Patients” are patients with personal disease experience. If they have no or little experience in R&D methodology they are called “research-naïve patients”.
* “Carers” are people supporting the patients such as parents, carers and family members.
* “Patient representatives” are persons who have a particular diagnosis and are able to represent other patients with the disease in question, to play a central role in the management of a patient’s life and to minimise the impact of the disease in question.
* “Patient organisation representatives/patient advocates” are persons who do not necessarily have a particular diagnosis, but are mandated to represent patients with the disease in question.
* “Patient Experts” are patients or patient representatives with expertise in the disease in question and with some R&D experience. “EUPATI Fellows” are patients or patient representatives trained by EUPATI in the full spectrum of medicines R&D with experience of the disease in question.

## Current status of patient involvement in ethical review

5.1 Best practice examples (reference to EUPATI Case Studies) have shown that patient involvement in ethical considerations concerning clinical trials as early as in the trial design stage can be beneficial and enhance the ethics of the research. Involvement at this stage can ensure that the focus on the patient is maximised and the outcomes to be measured are relevant to patients. Guidance on this interaction is provided by the EUPATI “Guidance on patient involvement in industry-led medicines R&D” (reference…). Similarly, in clinical trials being driven by academia, patient experts could provide meaningful advice.

5.2 While participation of at least one lay person in ethics committees is longstanding practice and of undisputed value, the type and extent of patient involvement varies widely between - and even within - European member states. In countries like France or Austria participation of patient representatives is required by law and the conditions are clearly defined. In countries like Germany or Spain individual ethics committees are just beginning to develop patient involvement. In Italy the law leaves it to the ethics committee to decide if they will involve a lay person or a patient representative. Different practices exist for the following reasons:

* Although there is appreciation of the benefit of patient involvement there is no agreement on the role and most suitable patient profile: patient expert, patient organisation representative, naïve patient (without experience in ethical review and medicines development methodology).
* Finding patients willing to contribute to the ethical review is a challenge for ethics committees, and this is the case across Europe. There is no established match-making process..
* Involving patients with specific diseases can be logistically challenging, while involving patients who advise on all kinds of diseases requires a level of knowledge beyond their personal disease.
* There is disagreement about how far patients with a particular disease can be representative, and whether there is potential for bias because of their personal interests. The independence of representatives from patient organisations has been questioned on the grounds that their personal interests and financial support from the pharmaceutical industry might lead to conflicts of interest.
* Pan-European capacity of suitable patient experts is currently scarce

5.3 As of 2018, the approval and performance of clinical trials will be governed by the European Clinical Trial Regulation 536/2014. Involvement of patients in the ethical review process is not stipulated in this Regulation, although the legislation states that lay persons, in particular patients or patients’ organisations, should be involved in the assessment of the clinical trial authorisation application. The assessment process and the make-up of the assessing bodies (national competent authorities and ethics committees) are subject to national legislation so the involvement of patients in the ethical review process will continue to vary from country to country.

## Timing and nature of patient involvement in ethical review

6.1 Patients can be involved in the ethical review of clinical trials at different time points (and see Appendix 1):

* Trial Concept Phase (handled by commercial or academic sponsor)
* Trial Design Phase (handled by commercial or academic sponsor)
* Ethical Review Phase (handled by ethics committee(s))
* After End of Trial (handled by commercial or academic sponsor)

6.2 In the Trial Concept Phase patient experts can advise on certain general aspects of the trial such as:

* Research questions, e.g. for specific indications, patient populations, etc.
* Defining the objectives of the trial to ensure its relevance for patients
* Acceptable/relevant endpoints
* The suitability of measurements and assessments, e.g. quality of life questionnaires
* Comparators (placebo or active comparator) and their acceptability for patients
* Acceptable risk levels: patients might have a specific opinion on the level of risk they are prepared to accept.

*We recommend that patient/carer experts should be involved in the trial concept phase whether a trial is being run by a company or academic centre, to optimise the value of the trial..*

6.3 In the Trial Design Phase the specifics of the clinical trial need to be defined in such a way that:

* a suitable number of patients can be recruited in an acceptable time frame,
* the benefits of trial participation outweigh the risks,
* the burden to patients is acceptable,
* administration of the trial medication is as easy and reliable as possible,
* measurements and assessments are practicable, acceptable to patients and reliable.

A typical area of patient involvement in this phase is the development of the informed consent process including the preparation of the patient information sheet and informed consent form. Input from the kind of patient that these documents are developed for can improve their readability, user-friendliness and completeness.

*We recommend that patient/carer experts should be involved in the trial design phase whether a trial is being run by a company or academic centre, to ensure that the conditions for participating patients are ethically acceptable.*

6.4 In the Ethical Review Phase, performed by one or more ethics committees, patients or patient organisation representatives can provide important input into the elements described above. In addition, patients can advise on local conditions for the trial such as:

* Suitability of patient liability coverage (insurance)
* Data protection measures
* Potential conflicts of interest
* Avoidance of inducement, for example ensuring that patient fees or travel expenses are appropriate
* How patient organisations can contribute to the patient information and recruitment processes.

*We recommend that patient/carer experts or patient representatives who are knowledgeable about living with the disease in question should be involved in the review of clinical trials provided by ethics committees, to ensure participating patients are properly protected.*

6.5 Sponsors sometimes involve patients in communication with participating patients After the End of the Trial, but this has been very limited in the past. Under the new Clinical Trial Regulation, however, the results of every clinical trial will have to be communicated in a lay summary, to ensure transparency and to recognise the patient community’s contribution to the trial. Patient input to lay summaries will be essential to ensure they are suitable and readable for patients.

*We recommend that commercial/academic sponsors involve patient/carer experts or patient representatives knowledgeable about living with the disease in question, in the development of lay summaries* *to ensure they are suitable and readable for patients.*

## Practical aspects of patient involvement in ethics committees

National legislation outlines the constitution, organisation and responsibilities of ethics committees, and reflects the roles of different types of ethics committees in the protection of trial participants and research integrity.

***Proposal from internal EUPATI consultation***:

*Different roles for patients in ethics committees can be considered:*

* *Full member of an ethics committee with equal rights and obligations as all other members*
* *External peer reviewer giving advice to the ethics committee members before their review meeting*

The specific process for selection of the members of an ethics committee varies between countries and are defined by national legislation, responsible professional bodies or the ethics committee’s own standard operating procedures.

**7.1 Patients’ level of expertise**

Ethics committees should consciously decide on the level of expertise they expect from their patient member(s):

7.1.1 “Research-naïve patients” with the disease in question, parents or carers of those patients, can provide valuable input to the patient information sheet and informed consent form and can comment on aspects of a trial that will affect quality of life and the burden for participants. However, after some months of experience they might not be naïve anymore and it is argued that this could affect the value of their input. It can be difficult for research-naive patients to take part in discussion of other ethical topics that involve scientific and/or methodological complexity. The contributions of naïve patients/carers without experience of the disease in question could be seen as comparable to those of lay persons.

7.1.2 “Patient representatives” have an in-depth knowledge of living with the disease from their own experience and might have a level of understanding of research and development for this disease. With each ethical review project they gain additional experience. The representativeness of their advice, however, might be limited by lack of in depth knowledge about cases beyond their own and perhaps a few other cases. Their contribution to ethical review of trials for other diseases will be limited to a general patient perspective.

7.1.3 “Patient organisation representatives/advocates” are either expert patients with the disease in question and/or actively engaged in a relevant patient organisation and are exposed to the disease experience of many individuals. They are knowledgeable about the needs, desires and opinions of this community and thus will be relatively representative. Since patient organisations exist to support their members and to lobby for their interests it is important to ensure that the patient representative in the ethics committee is aware of his/her obligation to provide neutral and objective advice. Their contribution to ethical review of trials for other diseases will be limited to a general patient organisation perspective.

7.1.4 “Patient experts” (e.g. EUPATI Fellows) have personal experience of living with the disease and/or the combined knowledge from working with members of their patient organisation. In addition, they have a comprehensive understanding of all aspects of the medicines development process, and can actively participate in all aspects of the ethical debate on the same level as the other ethics committee members. They are not joining the ethics committee in a representative role but have much exposure to other cases due to their activities in their patient organisation. Their contribution to ethical review of trials for other diseases could also be valuable because of their knowledge of R&D.

*We recommend that patient/carer experts or patient representatives knowledgeable about living with the disease in question should be involved in the work of research ethics committees, preferably as full members, to extend their input beyond development of the patient information sheet and informed consent form.*

**7.2 Finding supportive patients and interested ethics committees**

7.2.1 Ethics committees report that it is difficult to find patients willing to participate, and in particular to find patients with the expected level of expertise. Involvement of a “generic” patient representative reviewing trials for all kinds of diseases makes finding patient members easier but this has disadvantages as described above. Identifying patient members for specific diseases and bringing them to ethics committee meetings is a logistical challenge. However, patients can participate in ethics committee meetings via tele- or web-conference. Alternatively, patients can be asked to provide their written comments before the ethics committee meeting but this means that the impact of patients on the ethical debate during the meeting is missed.

7.2.2 There are a number of options for ethics committees to identify interested patients and for interested patients to join an ethics committee:

* Establishing collaboration with (umbrella-) patient organisations
* Advertisement
* Use of existing contacts
* Engagement of ethics committee members in local patient education in clinical trial ethics
* Unsolicited applications from patients
* Supporting the development of a national match-making platform jointly with academic and commercial sponsors to facilitate collaboration with interested patients with different diseases and different levels of expertise.

*We recommend that individual ethics committees develop a database of patients and we encourage ethics committees to join forces to establish a joint database.*

## Conditions for patient involvement in ethics committees

The conditions for patient involvement in the work of an ethics committee should be communicated to interested patients or patient representatives to ensure a smooth and efficient collaboration.

**8.1 Written agreement**

8.1.1 A written agreement should be signed by both parties containing a clear description of the role of the patient in the ethical review process. The agreement should make clear the legal and regulatory conditions, working procedures, ground rules and conflict resolution procedures, frequencies of interaction, mutual obligations including confidentiality, liability (insurance) protection, resource requirements and timelines as well as the mechanism for payment / reimbursement of expenses and any other benefits.

*To ensure clarity about the collaboration between ethics committees and patients we recommend signing a written agreement before the start of the collaboration.*

**8.2 Transparency**

8.2.1 As with all members of an ethics committee, patient members in ethics committees should ensure they are transparent about their own (and/or their patient organisation’s) professional interests and financial support.

*We recommend that patient members should sign the same Declaration of Interest as the other ethics committee members, to list potential conflicts of interest such as professional involvement and financial interests in other organisations and personal and professional (if the patient is a patient organisation representative) funding sources.*

**8.3 Representativeness**

8.3.1 Representativeness of the patient members’ advice is an important aspect for both the ethics committee and the patient community they are representing. Only a limited number of patient organisations have systematically compiled information relevant for the ethical review of a clinical trial in their area of indication and decided on a member interested and suitable to represent the organisation in an ethics committee.

*We recommend that patient organisations identify members interested in representing the organisation in an ethics committee and ensure that this member receives comprehensive information about the community’s treatment needs, quality of life deficiencies, and day-to-day life conditions.*

*We recommend that patient organisations implement a mechanism to exchange experiences which their members develop in ethics committees while respecting the patient members’ confidentiality obligations.*

**8.4 Appointment, introduction and training**

8.4.1 The appointment process and introduction of patient/patient representative members should follow the standard rules of the respective ethics committee.

8.4.2 Participating in the ethical review in an ethics committee is for many patients and patient representatives a new experience. Debating with experts in their field might be intimidating and can lead to a lack of contributions: it is important that the mere presence of a patient representative is not seen to endorse committee decisions. To support real engagement, the capacity of patients experienced to provide advice to ethics committees needs to be systematically increased. This should include a comprehensive introduction into the work of an ethics committee member and continuous professional development initiatives, even if his/her involvement is limited to contributions relevant to their disease area.

*We recommend that patient members receive a comprehensive introduction and appropriate continuous training independent of the frequency of their participation in ethical review.*

**8.5 Compensation**

8.5.1 Patients/patient representative members of ethics committees provide advice to the ethics committee like all other members and cannot be expected to do this without recompense. They provide their time and expertise and might have expenses for the meetings.

*We recommend that patient members should be paid for their engagement according to the same rules as all other ethics committee members. If no compensation for time is provided to the members of the ethics committee, patient/patient representative members should at least receive reimbursement of their travel expenses as they are not a member of the ethics committee’s institution.*

## Appendix 1 – Practical roadmap on patient involvement in ethical review

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1. Adapted from the EMA framework http://www.ema.europa.eu/docs/en\_GB/document\_library/Other/2009/12/WC500018013.pdf [↑](#footnote-ref-1)