EURORDIS Charter for Collaboration in Clinical Research in Rare Diseases

Preamble

EURORDIS-Rare Diseases Europe represents more than 830 rare disease organisations from 70 countries as of 2019, and has emerged as the voice of approximately 30 million patients affected by rare diseases in Europe. EURORDIS has contributed to the elaboration of the European Regulation on Orphan Drugs and has held seats on the Committee of Orphan Medicinal Products (COMP) at the EMA since its creation in 2000.

EURORDIS launched a process with a number of organisations involved in clinical research, initially within the Alliance Maladies Rares (France). This process highlighted the pressing need to define a common framework for collaboration between patients' organisations and sponsors of clinical research.

- *This Charter aims at responding to the expectations shared by both patients and sponsors: the rapid acquisition of quality scientific data and the development of effective and safe treatments and the subsequent access to them.*

- *This Charter also aims at focusing on the role of rare disease patient organisations in clinical research. For the purpose of this Charter, the term "patients" refers to both patients as well as patient representatives, families and carers. A Community Advisory Board (CAB) refers to a group of patients who offer their expertise to sponsors of clinical research and who advise several sponsors in their field. CABs are autonomous bodies, not related to the sponsor or chosen by them.*

General principles and context

Within the EU, the free movement of people and goods, as well as the single market, have given rise to a collective reflection on the practices of companies and the ensuing consequences for society, especially in the fields of environment, employment and health. This collective reflection has given rise to the concept of Corporate Social Responsibility. For the pharmaceutical industry, this concept refers primarily to the Public Health role and added-value of research-based pharmaceutical companies in their capacity to improve the human condition by developing medicines to treat diseases. For academic sponsors, this concept underlines the role and responsibility of scientific researchers towards society.

The Charter was conceived as a set of principles and rests on the voluntary commitment of a sponsor, whether a pharmaceutical company or an academic sponsor. The motivations of participants enrolling in a rare disease clinical research project go well beyond their legitimate individual short-term expectations of therapeutic benefit. Through their personal commitment, participants hope to contribute to therapeutic progress and improve life for all patients affected by the same rare disease. It is of primary importance that their contribution does indeed benefit the community of rare disease patients.

This is why it is important that all the information learned in a research project be shared with the entire patient and scientific communities. Having access to information on clinical research through their organisations is a fundamental element of trust for the participant. The need for validated information applies to all stages of the research: before consent, in order to make an informed choice, during the research project, in order to deal with the constraints and uncertainties calmly, and afterwards, in order to share the results, whatever they are.

The uniqueness of rare diseases

This Charter is for research projects performed in the field of rare diseases. For these diseases, the recruitment of patients is particularly challenging and represents an obstacle to research. In addition, due to the small number of patients, clinical research can rarely be carried out in a single country; they need to be multi-centre, and cross-border. The clinical research we refer to in this Charter is not limited to medicinal products, but includes any diagnosis, therapeutic method or device requiring a clinical evaluation.

Rare disease organisations

Due to their unique knowledge of the disease, patient associations can clearly be seen as the legitimate partners of clinical research sponsors.

Associations aim to promote the collection, production and dissemination of information on their disease. Their activities have already enabled progress in healthcare and social assistance provided to patients, the development of treatments, and have raised public awareness of rare diseases.

Sponsors are well aware of the representativeness and expertise of the patient organisations, and often call on them to facilitate the participation of patients in clinical research. Sometimes, organisations are consulted to validate documents designed for clinical research participants.

Unfortunately, this collaboration is frequently delayed and limited: sometimes organisations are approached only after the emergence of problems that might jeopardise the continuation of the clinical research project.

Collective expertise and legitimacy

CABs' and patient communities' expertise includes a full knowledge of patients' day-to-day life situations. CABs can therefore play a useful role by being involved at an early stage of protocol design.

This can facilitate everything from the choice of the most adequate endpoints, the assessment of the evaluation criteria, the quality of life or functional benefit in accordance with applicable guidelines...; it can also facilitate the evaluation of the acceptability of constraints during the research as well as information post-research and reporting of results (see Memorandum of Understanding).

CAB expertise is particularly important in the case of rare diseases, as sponsors can be often small themselves, often with limited experience of clinical aspects or of life with the disease; or larger enterprises usually more familiar with common pathologies.

Motivations and expected results

1. Sponsors

Research collaboration with patient organisations is typically the exception, not the rule, because sponsors often perceive this as a loss of time, a delaying factor for the research project. Examples reported by patient organisations show the opposite: the suitability of the protocol to the possibilities and expectations of patients improves recruitment, improves adherence to the study, and limits the risks of dropouts, among many other positive outcomes.

The research will be conducted in the best conditions if it is based on trust. To that effect, easy access to information concerning all aspects and any constraints of the research should be discussed with CABs transparently. They can play a useful role as information providers. It is important that the patient information document and informed consent form for the participants be as clear and understandable as possible.

Generally speaking, the lack of information on any aspect of the research project can cause reticence to enrol or lead to inadequate compliance and possible withdrawal, which are distinctly not in the interests of the research.

2. Investigators

The investigator does not always have sufficient time to spend with the participants to provide them with meaningful explanations, and reassurance that they may need before and during a study. Lack of time may be frustrating for the investigator, and the situation is more often than not distressing for the participant. Thanks to their expertise, CABs and/or patient organisations may prove extremely useful in providing participants with the necessary support when they feel the need for it.

3. Community Advisory Boards (CABs) and their added value

When patients and patients' representatives fully understand the research protocol, and more so, when CABs have been involved in the design of the research, ethics committees can rest assured that the research project is as patient-centric and patient-friendly as possible. In fact, while not the same patients, patients are also encouraged to be on ethics committees. This collaboration is time-saving and contributes to the elaboration of a patient-oriented project, taking into account the possible individual and collective risks and benefits.

The EURORDIS Charter for Collaboration in Clinical Research: A framework

A. Principles

1. This Charter is an expression of mutual intentions and aspirations
2. The Charter is not legally binding
3. The collaboration is based on respect and is not tokenistic
4. The CAB is recognized as an independent body and is not structurally dependent on the sponsor
5. The work and the structure are transparent
6. Agendas are cooperatively designed
7. The dialogue is meaningful and of high quality
8. Collaboration between the sponsors and the CAB is timely, where input can make a difference
9. Confidentiality is respected by both sides
10. The collaboration is based on trust
11. All interactions are considered non-promotional

The roles of EURORDIS and the sponsor

> This Charter constitutes an expression of mutual intentions and aspirations and does not constitute a legally-binding agreement between the parties.

As a set of general principles, this Charter proposed by EURORDIS can be embraced by any potential sponsor. By signing the Charter, a sponsor shows its determination to respect the Charter's principles of collaboration in clinical research.

EURORDIS will make public the list of sponsors that have signed this Charter and that it considers to be endorsing the principles contained herein, so their position can be known by the different parties involved: patients, their organisations, investigators, European and National authorities, and the public. EURORDIS commits to include in the list all those sponsors that it believes are endorsing these principles. In the event that a sponsor does not respect the Charter's principles during a research project, good faith discussions shall commence between EURORDIS and the sponsor to positively resolve the concern.

EURORDIS commits to working with the CAB on training, governance, and management/administration, according to the needs and capacities of each CAB. This Charter applies to all EUROCAB collaborations.

EURORDIS also commits to assist the sponsor in the search for organisations to implement a collaboration, whether the organisation is a member of EURORDIS or not.

> While this Charter is not legally binding, the value of signing this Charter is a demonstration of the firm intention to collaborate with patients in the research and development arena, respecting the principles of this Charter.

European dimension

Orphan medicinal products and other health technologies are developed at the European level. This Charter naturally fits within this EU framework and aims to share this level of patient involvement throughout the European Union.

Nature of the collaboration for a given research project

For any research project, the CAB and the sponsor will endeavour to establish a collaboration in which the CAB brings its expertise on a rare disease to accelerate the production of quality data of scientific relevance and to optimise the process for the development of safe, effective, and accessible treatments. This collaboration shall be based on transparency on the part of both the sponsor and the CAB, and does not call into question their respective legal responsibilities.

Any collaboration within the framework of this Charter is specified for each research project in a Memorandum of Understanding between the CAB and the sponsor.

This collaboration shall be monitored by EURORDIS in order to overcome discrepancy by any party.

B. Areas of collaboration

The collaboration between CABs and the sponsor can cover the entire clinical research process, from design to dissemination of data and long-term follow-up. It can also include related aspects such as compassionate use and pricing strategy.

Terms of collaboration

Collaboration between the sponsor and the CAB for research projects will endeavour to optimise the elements as listed in the Memorandum of Understanding.
The elaboration of the patient information document and of the informed consent form for the research activity in partnership with the CAB will guarantee that the style and content of these documents are adapted to the expectations and understanding of participants, and can facilitate a better evaluation by Ethics Committees.
During the clinical research, the CAB may want or need to communicate with other patients on the status (recruitment status, publication delays…) of the study itself or other concerns. This information cannot relate to fields covered by a confidentiality agreement and cannot disclose other non-public details about the clinical research or the personal data of participants.

Data collected and results of the research

Two sets of results have to be considered:

- **Conclusions of the research**: adherence to this Charter implies that the results of the research will be communicated, to the participants as well as more broadly, whatever the results of the research are (positive or not), subject to applicable laws, following the norms outlined by EMA and FDA for pharmaceuticals. Accessibility to information is crucial in the case of rare diseases as it helps avoid duplication of clinical research in small populations. CAB members and/or research participants can follow the announcements of the results in scientific conferences if/when they are webcast.
- **Other data obtained during the research:** during clinical research, participants are closely monitored and are subject to numerous examinations (biological, functional tests, imagery, etc.). All these data, as well as the samples collected during the study, can contribute to the knowledge of the natural history of rare diseases and their physiopathology. They can also be valuable tools when preparing further clinical research. Data acquired as a result of a patient's participation in clinical research needs to be accessible to the scientific community, in order to respect the participants' original motivations for consent and commitment.

> EURORDIS will not have access to commercially-sensitive sponsor data unless the sponsor voluntarily consents to share it with EURORDIS.

When CABs are involved in the whole development process of a research project, they can cooperate in the elaboration of documents that the sponsor needs to seek scientific advice from Competent Authorities, to apply for marketing authorisation or for the evaluation of criteria relating to orphan status (e.g., significant benefit) as well as for the health technology assessment.

C. The EURORDIS CAB: the EUROCAB

Because of their role in the research process and in order to maximise transparency and mutual trust, the members of the CAB will have the same information as the sponsors, the investigators and the Competent Authorities.

In order to protect the interests of the sponsor, the members of the CAB can be asked to sign various documents - a declaration of interest, a confidentiality agreement, a statement on intellectual property, data collection and a document to prevent insider trading. PFMD, MPE/WECAN and PARADIGM will be designing and releasing documents that can be shared with all decision-makers. The fields covered by this commitment, as well as the list of members, will be specified in the MoU.

For training reasons, the CAB may look to the advice/expertise of external experts such as pharmacologists, statisticians, methodologists, etc. These experts will respect the same conflict of interest and confidentiality as the members of the CAB.
Companies do not select the CAB members.

The CAB members are chosen from an internal patient network process that EURORDIS will help with by supplying a Guidelines/Best Practices document to each CAB.

Each CAB will decide on the validity of any CAB member being a participant in the research project being discussed. At the end of the day, the composition of the CAB is decided on by the patient network itself. The CAB members help set the agenda, along with the sponsor. CAB members will be considered "patient investigators".

> These face-to-face meetings and all interactions that accompany them (including webinars, teleconferences, emails, phone calls, etc.) are not promotional and should not be considered as such.