

**CHARTER OF THE
EUROPEAN RARE DISEASE THERAPEUTIC INITIATIVE (ERDITI),
A partnership between Academic Institutions
and Pharmaceutical Companies**

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1. OBJECTIVES AND STRUCTURE OF THE PARTNERSHIP

Background

- ◆ *Rare Diseases** (8000 different diseases, 10-20,000 patients each) are a significant public health problem in Europe.
- ◆ Research on rare diseases is done by multinational specialised networks, mostly of *Academic Teams*.
- ◆ *Rare Diseases* are not high R&D and commercial priorities for the pharmaceutical industry.
- ◆ Development of drugs for *Rare Diseases* benefits from Orphan Drug legislations. However, traditional pharmaceutical research such as screening and optimisation of molecules, complete preclinical development, clinical pharmacology in volunteers, cannot be economically justified.
- ◆ The availability of drugs which have been developed by pharmaceutical companies could allow to shortcut this traditional route and evaluate swiftly, and at minimal costs, drug candidates for the treatment of *Rare Diseases*.

Objectives

- ◆ Provide a user-friendly framework to foster the collaboration between academic research and pharmaceutical companies to develop drugs for the treatment of *Rare Diseases*.
- ◆ More specifically, the major objective is to facilitate the evaluation for the treatment of *Rare Diseases* of drugs that have been developed by pharmaceutical companies.
- ◆ Benefit for *Academic Teams* working on *Rare Diseases* : access to a large variety of drugs with known pharmacology which can be evaluated pre-clinically, and subsequently clinically, with minimal lead time and costs.
- ◆ Benefits for pharmaceutical companies :
 - Possible access to *Rare Diseases* which may be valuable "Proof of Concept" models for their R&D.
 - Public Relations perception of their contribution to research on *Rare Diseases*.
 - The option to commercialise drugs that would have been otherwise abandoned. This option can be exercised at three stages : by sponsoring a project from its preclinical evaluation stage, by taking responsibility for the clinical development of the drug or by walking-in at a later stage for registration/commercialisation.
 - Sale of the licence rights of drugs they do not intend to develop and/or commercialise themselves.
- ◆ Benefits for both parties : a streamlined facilitated process for what is usually a thorny exercise.

* All words and phrases in italics are defined in Section 2

Structure

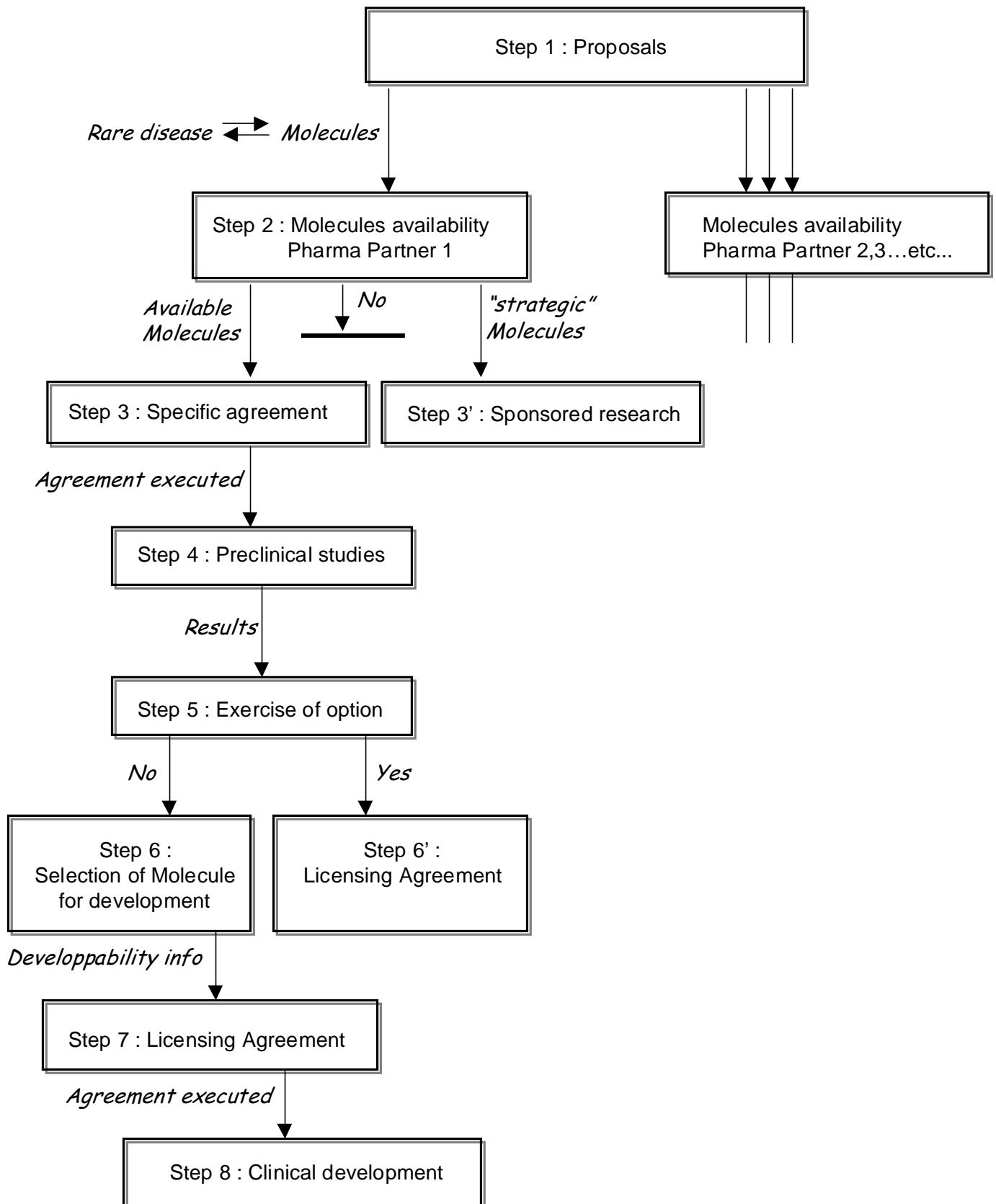
- ♦ All major non-profit research institutions from European countries will be invited to participate.
- ♦ Pharmaceutical companies identified as potential contributors of *Molecules* will be invited to participate.
- ♦ Participation into the *Partnership* implies that the *Partner* agrees to follow in good faith the working procedure and use the *Standard Agreement* as a framework for its contractual relationships with other *Partners*. *Partners* can withdraw from the *Partnership* at any time by informing the Co-Ordinator with a 3 months written notice.
- ♦ It is envisaged to create this *Partnership* under the sponsorship of relevant European Organisations such as the European Science Foundation (ESF).
- ♦ The *Partnership* will not incorporate as a legal entity but a light permanent structure (may be initially 1/2 or 1 FTE) will be necessary to assume the role of *Co-ordinator*. The *Co-ordinator(s)* will occasionally summon a Steering Committee of *Partners* to assess the (quantitative) results of the *Partnership* and amend its charter according to best practice.
- ♦ The *Scientific Advisory Board* will be composed of an equal number of experts nominated respectively by the *Public Partners* and the *Private Partners* by mutual agreement between each group of *Partners*. The composition of the *Scientific Advisory Board* (12 to 24 members total) should aim to a balance of pharmacological and therapeutic expertises.
- ♦ Each *Partner* will cover its "out of pocket" costs. It is anticipated that the central costs should remain small (*Co-ordinator* - Organisation of *Scientific Advisory Board*) and be covered by the sponsors and/or by European Community subventions.

2. DEFINITIONS

- ◆ **Academic Team(s)** : a team of biologists and/or physicians affiliated to a *Public Partner* and carrying research on the treatment of *Rare Diseases*.
- ◆ **Clinical Study** : an investigation in humans of the potential of a *Molecule* to treat a *Rare Disease*.
- ◆ **Co-Ordinator** : an organisation which facilitates the implementation of the *Partnership*. More specifically, the co-ordinator organises the *Scientific Advisory Board* and ensures the liaison between *Academic Teams*, *Public Partners* and *Pharma Partners* (see working procedure).
- ◆ **Developer** : a for-profit company or non-profit institution (not necessarily a *Partner*) who, under necessary license rights, undertakes the *Clinical Studies*, and possibly registration and commercialisation of a *Molecule* for the treatment of a *Rare Disease*.
- ◆ **Field** : treatment of a *Rare Disease*.
- ◆ **IPR Agreement** : agreement signed by the *Public Partners* for a specific *Research*. A standard template is provided in Part 5 of this document.
- ◆ **Lead Partner** : one of the *Public Partners* of a *Specific Agreement*. The *Lead Partner* acts on behalf of others *Public Partners* of a given *Specific Agreement* to secure intellectual property rights on the results of the *Research* and negotiate the exploitation rights of the relevant *Molecule(s)*.
- ◆ **Molecule(s)** : a chemical compound or class(es) of chemical compound(s) owned by a *Pharma Partner*.
- ◆ **Partners** : *Public Partners*, *Pharma Partners* and *Co-ordinators*.
- ◆ **Partnership** : collaborations on the treatment of *Rare Disease* carried out according to the present charter.
- ◆ **Pharma Partner** : a pharmaceutical company member of this *Partnership*.
- ◆ **Preclinical Study** : an investigation, in vitro or in animals, to test the therapeutic potential of a *Molecule* in a *Rare Disease*.
- ◆ **Public Partner** : non profit research institution from an European Union or European Economic Area country, or Switzerland, member of the *Partnership*.
- ◆ **Rare Disease** : a disease, with a prevalence under 1/2000 (worldwide), eligible for the *Partnership*. Eligibility will be endorsed by a *Scientific Advisory Board*.
- ◆ **Relevant Public Partner** : the *Public Partner* to which an *Academic Team* is affiliated.
- ◆ **Research** : all *Preclinical Studies* or *Clinical Studies* on a *Rare Disease* performed with a *Molecule* under a *Specific Agreement*.

- ♦ **Scientific Advisory Board** : a board of clinical and pharmacology experts meeting to select *Rare Diseases* and *Molecules* to be tested in the *Partnership* and examine results. *Public Partners* and *Pharma Partners* will nominate experts who will serve as unpaid consultants.
- ♦ **Specific Agreement** : the agreement between a small number of *Public Partners* and a *Pharma Partner* to cover *Research* on specific *Molecules* in a *Rare Disease*. *Specific Agreements* are "customisations" of the *Standard Agreement template*.
- ♦ **Sponsored Research** : the agreement between the *Pharma Partner*, the *Academic Teams* and the *Relevant Public Partners* entered into in Step 3' when a *Pharma Partner* is willing to sponsor a collaboration with the *Academic Team* submitting a request with regards to a *Molecule/Rare Disease* of high strategic interest for this *Pharma Partner*.
- ♦ **Standard Agreement** : Part 4 of the present charter, which covers the provision of *Molecules* to *Academic Teams* for *Preclinical Studies*.

3. WORKING PROCEDURE FOR THE PARTNERSHIP



Working procedure for each step (see logical flow chart).

Step 1 : proposals

A *Co-ordinator* calls upon the scientific community to identify *Academic Teams* working on *Rare Diseases* where physiopathological basis for treatment may be considered. The *Co-ordinator* organises a *Scientific Advisory Board* to study proposals from *Academic Teams*. The composition, meetings and mode of operation of Scientific Advisory Boards will be determined in consultation with the *Partners*. The Board will assess the pertinence of submitted proposals and provide advice regarding the choice of *Molecules* to be tested. For example, proposals for the treatment of rare cancers are unlikely to be retained since, in many cases, the same mechanisms and *Molecules* may be applicable to more common cancers. It is also not in the spirit of the Partnerships to sponsor the random screening of large numbers of *Molecules*, eg. as anti-infective agents. Provision of *Molecules* that are under active development for other indications will be at the discretion of *Pharma Partners*.

Step 2 : checking molecules availabilities

The *Academic Teams* submit to the *Co-ordinator* a protocol for the specific evaluation of chosen *Molecules* in vitro and in animal models. The *Co-ordinator*, using a predefined template (Appendix 1), interrogates several *Pharma Partners* on the availability of those *Molecules* identified from literature as belonging to the *Pharma Partner*, and more generally on undefined *Molecules* belonging to pharmacological classes of interest.

The *Pharma Partner* replies to the *Co-ordinator* within two months. The transactions with each *Pharma Partner* are dealt with separately and in confidentiality. The decision to supply a *Molecule* shall be at the sole discretion of the *Pharma Partner*. Nothing herein will require or oblige the *Pharma Partner* to supply any particular *Molecule* or class of *Molecules* or provide a reason for refusal to supply.

A positive answer leads to Step 3, a negative answer terminates the process. No answer shall be considered as a negative answer.

Another option for the *Pharma Partner* is to sponsor *Research* independently of the present working procedure → Step 3' : Sponsored Research

Step 3 : negotiation of a Specific Agreement

The *Co-ordinator* facilitates the interaction between the *Pharma Partner*, the *Academic Team(s)* and the *Relevant Public Partner(s)* to customise the *Standard Agreement* into a *Specific Agreement*. If there are several *Relevant Public Partners*, a *Lead Partner* is identified and an *IPR Agreement* made between the *Relevant Public Partners* to cover intellectual property rights and exploitation of the results of the *Research*. If there are several *Pharma Partners* interested in entering a *Specific Agreement*, each *Pharma Partner* will negotiate a separate *Specific Agreement*.

Step 3' : Sponsored Research

A small number of *Molecules/Rare Diseases* may be of high strategic interest to the *Pharma Partner* so that he will be willing to sponsor a collaboration with the *Academic Teams* submitting a request. In this case, the *Standard Agreement* is not applicable and *Sponsored Research* should be negotiated directly between the *Pharma Partner*, the *Academic Teams* and the *Relevant Public Partners* outside the framework of this working procedure.

Step 4 : Preclinical Studies

This process described below is based on the assumption that relatively large numbers of *Molecules* (may be 10's) from several *Pharma Partners* will be screened in vitro and a very small number will be selected for further in vivo evaluation. The step can be simplified in other situations (few *Molecules*, no in vitro screen, etc...).

As part of the *Specific Agreement*, the *Pharma Partner* will agree to provide to the *Academic Teams* the reasonable quantities of *Molecules* required for in vitro studies. It is understood that the quantity of *Molecules* may be limited. The *Pharma Partners* has no obligation to synthesise further quantities of the *Molecules* or to provide its complete stock of any particular *Molecule*. The *Pharma Partners* shall however permit *Academic Team* to synthesise or have synthesised the *Molecules*, if required to conduct the *Research*. The *Pharma Partner* will also provide such other information in its possession which, according to the *Pharma Partner*, is strictly necessary for conduct of the studies or otherwise required by law in the supply of the *Molecule*. The *Academic Team(s)* perform(s) the *Research* and reports back all data and results of *Research* to the *Pharma Partner*.

Based on the results, the *Academic Team* selects a shortlist of *Molecules* for in vivo testing. A dialogue, facilitated by the *Co-ordinator* if necessary, takes place between *Academic Teams* and scientists from the *Pharma Partner* to ensure that the in vivo studies will be meaningful (route, regimen, dose, formulation, known side effects, etc...). Subject to available supplies, further quantities of *Molecules* may be requested and provided by the *Pharma Partner*. The *Pharma Partners* has no obligation to synthesise further quantities of the *Molecules*. The *Pharma Partners* shall however permit *Academic Team* to synthesise or have synthesised the *Molecules*, if required to conduct the *Research*.

The *Academic Team(s)* perform(s) the in vivo studies and reports to *Pharma Partners* (and the *Co-ordinator*) all the data and results of *Research* carried out with their *Molecules*.

Step 5 : Exercise of option

The *Lead Partner*, in agreement with the *IPR Agreement*, may file a patent application (e.g. for the use of the *Molecules* in the *Rare Disease*). The *Lead Partner* must ensure that the results of *Research* are not publicly disclosed before such filing (see Article 2 of the *Specific Agreement*).

The *Lead Partner* interrogates the *Pharma Partner* on the exercise of his option rights on the results of the *Research*. A negative answer of the *Pharma Partner* leads to Step 6. A positive answer to Step 6'.

Step 6 : Selection of Molecule for Clinical Development

If the *Pharma Partner* declines the option to exploit the results of the *Preclinical Studies*, the *Academic Teams* (optionally with the advice of the *Scientific Advisory Board*) can select potential *Molecule(s)* for clinical investigation.

The *Pharma Partner* is still bound by the built-in clause of the *Standard Agreement* to grant necessary license rights and provide any strictly necessary proprietary information exclusively for the development and commercialisation of the *Molecule(s)* in the *Rare Disease*.

The supply of further information relating to the *Molecules* shall only be disclosed to those parties under suitable conditions of confidentiality and to the degree necessary for such parties to make an appropriate evaluation for the onward development of the *Molecule*.

Based on responses, the *Academic Teams*, with the help of the *Co-Ordinator* (and possibly consulting the *Scientific Advisory Board* experts) select the preferred *Molecule* for *Clinical Studies*.

Step 6' : Licensing Agreement Optback

If the *Pharma Partner* decides to exercise the option, the *Pharma Partner* and the *Lead Partner* negotiate in good faith a license agreement for the *Pharma Partner* to exploit the results of *Research* and associated IP rights. By this contract the *Pharma Partner* will undertake to develop one of the *Molecules* in the treatment of the *Rare Disease*.

The terms of the license agreement shall reflect the commercial and sales potential of the *Molecule* in question taking into account other relevant matters such as the potential scope of patent protection and the likely development cost and the financial and scientific contributions. Unless otherwise agreed, the parties shall submit to mediation in accordance with International Arbitration Rules of the International Court of Arbitration any dispute relating to the negotiation of the licence agreement foreseen under this Charter. The place of mediation shall be the International Chamber of Commerce, Paris, France. Should such mediation not lead to an agreement with X months, proceed to Step 7.

Step 7 : Licensing Agreement

The *Lead Partner* identifies a *Developer* to carry out the clinical development plan of the selected *Molecule*.

The *Lead Partner*, the *Developer* and the *Pharma Partner*, negotiate a *Licensing Agreement*, to cover the provision of license rights, proprietary information (and possibly drug substance) to enable the *Clinical Studies* and to define future exploitation rights of the *Molecule* in the treatment of the *Rare Disease*. There are too many variables to propose a template for the licensing agreement. One of the provisions may be that the *Pharma Partner* retains a buy back option or first refusal on commercialisation rights, should the *Developer* not wish to commercialise by himself the *Molecule* world-wide.

The terms of the license agreement shall reflect the commercial and sales potential of the *Molecule* in question taking into account other relevant matters such as the potential scope of patent protection and the likely development cost and the financial and scientific contributions. Unless otherwise agreed, the parties shall submit to mediation in accordance with the International Arbitration Rules of the International Court of Arbitration any dispute relating to the negotiation of the licence agreement foreseen under this Charter. The place of mediation shall be the International Chamber of Commerce, Paris, France.

APPENDIX 1

REQUEST FOR MOLECULES AVAILABILITY

Rare disease (*brief description if necessary*)

Proposed studies

Academic Team/Public Partner	Brief description of study (full protocol available on request)

Requested Molecules

Name	Activity	Availability
<i>Eg. xy1234</i>	<i>Inhibitor of enzyme ABC</i>	
<i>Eg. any available</i>	<i>YZ1 receptor antagonists</i>	

Academic Teams

Pharma Partner

Date and signature

Date and signature

APPENDIX 2

DOCUMENTATION TO SELECT POTENTIAL CLINICAL CANDIDATES

At this stage (Step 6), summary information only is necessary, and documentation prepared for regulatory purpose (Clinical Investigator Brochure, IND or CTX filing) is suitable. Full documentation will be required only at Step 7 (due diligence before execution).

This may only be disclosed to such parties who are under suitable obligations of confidentiality to the relevant Pharma Partner.

Provided by Academic Teams	Provided by Pharma Partner
<ul style="list-style-type: none">- Description of Rare Disease- Preclinical evidence for selection of Molecule- Proposed clinical study	<ul style="list-style-type: none">- Chemical- Pharmacy- Existing supplies, expiry dates, rework possibilities- Preclinical Pharmacology- Toxicology- DMPK- Clinical Pharmacology- Regulatory situation- Intellectual Property situation