**Appendix: Clinical Validation**

 **RULES**

General context:

The health sector enjoys special attention within the Brussels-Capital Region, which is reflected at Innoviris through the implementation of the Health strategic priority presented in the *Regional Innovation Plan 2021-2027[[1]](#footnote-1)*.

In addition, *Health Technology Assessment* (HTA) type studies are essential for evaluating the safety and efficacy of a technology, medication or vaccine[[2]](#footnote-2). Such evaluations ensure the deployment of *evidence-based medicine* and consequently a sustainable, quality health system. In this respect, clinical validations play a key role because they scientifically evaluate and validate innovations in the health sector among real populations. They are a critical and essential step in the development of a new medicinal product or medical devices (whether computerised/mobile or not).

In this context, Innoviris is committed to the funding of clinical validations incorporated in industrial research or development projects. Indeed, such exploratory trials, which lead to a first *proof-of-concept* during the pre-commercial phases, still carry many risks and provide information capable of improving the product under development.

Legal framework and definitions:

This section contains all the definitions and concepts that determine the framework of the clinical validation as considered by Innoviris.

Medicinal products:

According to the definition in the **WHO** Drug Dictionary Enhanced and that of the **European Directive 2001/83/EC**, a medicinal product is *any substance or combination of substances presented for treating or preventing disease in human being.* Any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings is likewise considered a medicinal product.

Clinical trials for medicinal products - Legal framework:

Medicinal products are subject to clinical trials which are strictly regulated by legislation. Thus, the **Belgian Law of 7 May 2004** on experiments on humans defines clinical trials as being *any investigation conducted on humans, in order to*

* *determine or confirm the clinical, pharmacological and/or other pharmacodynamic effects of one or more experimental medicinal products*
* *and/or highlight any side effects of one or more experimental medicinal products*
* *and/or study the absorption, distribution, metabolism and elimination of one or more experimental medicinal products with the aim of ensuring their safety and/or efficacy.*

Clinical trials for medicinal products - Eligible phase:

In order to obtain reliable evidence of the safety and efficacy of its use in humans, the drug candidate is tested through successive trials, relating to different phases. Each phase is used to provide specific answers about the tested product.

The phase eligible for ‘clinical validation’ funding is the phase closest to the development of the product, namely Phase I. This phase is risky and the results obtained can be used to improve the development of the drug candidate.

Phase 1: Generally on 20-80 healthy subjects

Preliminary to the efficacy study of a drug candidate, this phase studies the kinetics and metabolism of the molecule and the tolerance and absence of side effects in healthy subjects. Phase 1 trials can also be offered to patients for whom [no further therapeutic options](http://fr.wikipedia.org/wiki/Impasse_th%C3%A9rapeutique) are available and for whom the prospective treatment is the only chance of survival.

Medical devices

Medical devices are defined by the **European Directive 98/79/EC** as being *any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:*

* *diagnosis, prevention, monitoring, treatment or alleviation of disease,*
* *diagnosis, monitoring, treatment, alleviation or compensation for an injury or handicap,*
* *investigation, replacement or modification of the anatomy or of a physiological process,*
* *control of conception,*

*and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.*

Today, mobile health products that generate health information are considered as medical devices and must be evaluated as such.

Clinical validation for medical devices:

Any medical device must demonstrate its compliance with the key requirements contained in the new European Regulation 2017/745 on medical devices[[3]](#footnote-3).

Furthermore, a clinical evaluation is compulsory for obtaining CE marking with the Federal Agency for Medicines and Health Products (FAMHP). These clinical evaluations aim to demonstrate the safety and performance for each indication claimed for the relevant device. They must also prove that the medical device satisfies the applicable standards.

It should also be noted that appendix VIII of Regulation 2017/745 classes medical devices in accordance with their associated risks:

* Class I: low risk (adhesive tape, corrective lenses)
* Class 2a: low to medium risk (tracheal cannulae, dental fillings)
* Class 2b: medium to high risk (radiography devices, bone plates and screws)
* Class 3: high risk (heart valves, breast implants and any active implantable medical device)

Clinical evaluation of medical devices is based on a critical analysis of the clinical data sourced from:

* 1. clinical investigations of the product concerned (sample generally less than 100 patients);
	2. clinical investigations or other studies reported in the scientific literature of a similar device for which equivalence to the device in question can be demonstrated;
	3. published and/or unpublished reports on other clinical experience of either the device in question or a similar device.

In the remainder of this document we will use the term ***clinical validation*** to refer to ***any study that evaluates the safety and efficacy of a medical device (computerised or otherwise) or drug candidate***.

Eligibility conditions:

In order to benefit from a financial intervention from the BCR, the clinical validation for a drug candidate or medical device must satisfy the following conditions:

* The subsidy allocated to the clinical validation cannot exceed €20,000 per patient and cannot exceed an upper limit of €500,000.
* In the case of clinical trials for drug candidates, only phase I is eligible.
* In the case of clinical validations for medical devices, the administrative costs related to certification and accreditation are not eligible.
* Clinical validation concerns products for which the field of application is human health.
* Compliance with the requirements set out by European Regulation 536/2014 on clinical trials on medicinal products for human use.

Procedure submission of the appendix form: ‘clinical validation’ work package

Within the work programme developed within the industrial project, clinical validation must be subject to a **specific work package** for which all the specific features are set out in the appendix form: **‘Clinical validation’ work package**

It is crucial that the information provided in this form is complete, detailed and supported at this time. A meeting to present the clinical validation may also be requested by Innoviris.

Innoviris reserves the right to consult with external experts in order to evaluate the quality of the clinical validation submitted. This consultation is also the opportunity to advise the project leaders whether this is necessary. The experts responsible for evaluating the clinical validation are subject to a duty of confidentiality, through a confidentiality agreement that can be consulted on request to Innoviris.

**APPENDIX FORM:**

**CLINICAL VALIDATION WORK PACKAGE**

In order to benefit from funding for the clinical evaluation of a drug candidate or medical device, this appendix form must be duly completed. It must be **attached to the funding application form for RDI projects in two paper copies with an electronic version sent to** **funding-request@innoviris.brussels**

This form is based on the form developed by KCE as part of the ‘Pragmatic Clinical Trials’.

The information in green in the text must be removed before the project is submitted.

**Company name**

*"Project title"*

|  |  |
| --- | --- |
| **Start date of the clinical validation** | *DD/MM/YYYY* |
| **Duration of the clinical validation** | *XX* **months** |
| **Amount of total budget for the clinical validation** | **€***XXXX* |

* 1. Health problem targeted by the solution:

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| --- |
| *Describe in a maximum of 500 words:**- The health problem to which the solution in development relates**- Its incidence and prevalence* |

* 1. Patients targeted by the solution:

|  |
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| *Describe in a maximum of 500 words:**- Description of the patient group targeted by the solution. How would you define the individuals or group of people affected by the problem, state or particular characteristic?* |

1. Tested solution in development:

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| --- |
| *Describe in a maximum of 750 words:**- The solution (molecule, medical device) to be validated**- The solution's development stage at the start of the clinical validation**- To which category does the solution belong: molecule, medical device?**- In the case of a mobile health product, justify why it is a medical device**- For medical devices, indicate to which risk classification it belongs* |

1. Justification of the implementation of the clinical validation:

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| --- |
| *Describe in a maximum of 500 words:**- The research question (which will be validated)**- Why a clinical validation phase is necessary**- The key stages of the planned validation* |

1. Patients included in the clinical validation:

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| *Describe in a maximum of 500 words:**- What are the main eligibility criteria for taking part in the clinical validation?* |

1. Comparator:

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| --- |
| *Describe in a maximum of 500 words:**- Describe the control treatment/solution (absence of treatment or placebo) or alternative treatment/solution (current or other treatment which is normally the best or most used treatment).*  |

1. Results: Outcome/Evaluation criteria

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| *Describe in a maximum of 500 words:**- The main parameters measured and their justification**- What are the solution's expected effects on the patient* |

1. Recruitment of patients:

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| *Describe in a maximum of 750 words:**- If it was the case, how were patients and the public involved in the design of the clinical validation?* *- What are the initiatives used to facilitate the recruitment of patients?* *- What are the initiatives used to increase the patients’ involvement in the clinical validation?**- Where and how will the patient recruitment process take place?**- Provide a schedule or time line estimating the number of patients recruited over time during the recruitment phase and presenting the key stages (be sure to stay realistic):**- 1st visit to the 1st patient: (month/year)**- 1st visit to the last patient: (month/year)**- last visit to the 1st patient: (month/year)**- last visit to the last patient: (month/year)* |

1. Design of the clinical validation protocol:

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| --- |
| *Describe in a maximum of 1000 words:**- Describe and justify as clearly as possible the design of the validation protocol Including the sample size, the schedule of visits, the monitoring of patients.* *- In the appendix, include a* ***flowchart*** *page*  |

1. Analysis of the clinical validation results:

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| --- |
| *Maximum 500 words for this section of statistical considerations:**- Provide sufficient detail on the calculation of the sample size and justify it**- Provide information which is as comprehensive as possible about the statistical analysis (the variables, the planned statistical tests)*  |

1. Key bibliographic references:

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| --- |
| *List of a maximum of 10 key bibliographic references illustrating the latest developments, the planned experimental design, the justification of the solution developed.* |

1. Addendum

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| *In a maximum of 500 words:**Any other information or comments that you wish to add.**This may also include the obstacles that you already see for the clinical validation* |

Appendices:

* + - 1. If necessary, a letter signed by the Clinical Trial Unit (CTU) which will take part in the clinical validation
			2. A flowchart page and/or a page with a schedule of visits
			3. The necessary authorisations to conduct a clinical validation (European Regulation 536/2014)

1. http://www.innoviris.be/en/rdi-policy/regional-innovation-plan?set\_language=en [↑](#footnote-ref-1)
2. KCE (https://kce.fgov.be/en/health-technology-assessment) [↑](#footnote-ref-2)
3. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745&from=EN [↑](#footnote-ref-3)