Specific Guidelines for PIPELINE

CALL PIPELINE:
PharmaceutIcal Product dEveLopment from INnovativE academic research

Version 3, June 2024

Why academic pharmaceutical product development?

Treatment options remain unsatisfactory for many cancer types. Those patients that do not respond to current standard treatments face poor prognosis and suffer from severe side effects. The development of new, innovative pharmaceuticals that target unmet medical needs is needed to improve more patients' lives.

Rapid academic advancements in understanding molecular pathways and functioning of biological systems form the basis for the development of new pharmaceuticals (defined here as originator products manufactured for use as a medical product). Discoveries in the immuno-oncology field led to recent new breakthrough therapies such as checkpoint inhibitors and CAR-T cell therapy. New pharmaceuticals are typically brought to the market by industry after academic discovery. However, not all discoveries and innovations that target unmet medical needs are picked up by industry for clinical development because of market failure; products are considered non-commercially viable or too 'high-risk'. Innovations may be considered non-commercially viable by industry due to the rarity of the targeted disease or affected patient group, a highly personalized medicine approach, or weak Intellectual Property (IP) position. Complex production processes in a point-of-care setting may not fit well in the traditional pharmaceutical model of large-scale production and distribution. Venture capital and other private parties may hesitate to invest in innovations that are considered high-risk due to uncertainties.

When new pharmaceuticals are not, or not yet, commercially viable or interesting, academics are challenged to take on development themselves. However, the academic route for pharmaceutical product development has not fully matured. This ecosystem in which academic developers need to operate to develop new pharmaceuticals is full of bottlenecks. Ecosystem failures include social and operational reasons for early termination of product development, such as insufficient collaboration and a lack of resources. Furthermore, clinical trial conduct needs to be supported by strong business cases and regulatory strategies in order to reach marketing authorization and access in clinical practice. Academics face a wide range of bottlenecks along this development trajectory if they aim to reach clinical practice themselves. Efforts to transfer promising innovations to a commercial route through spin-offs, out-licensing or public-private collaboration may fail due to flaws in product design, regulatory strategy or business case, among others.

When market- or ecosystem failure arises for new academic innovations, academic efforts are needed to complete development trajectories and reach patients in need. Therefore, the Dutch Cancer Society (KWF) is organizing the call 'PIPELINE' to accelerate the development of academic innovations into new pharmaceuticals.

Aim

The PIPELINE call aims at the clinical development of new pharmaceuticals that originate from academic research and have the potential to substantially improve the treatment for cancer patients with unmet medical needs. Any type of pharmaceutical that is regulated as a medical product in the European Union is eligible.

Ambition

KWF sees an important role for academia in the development of new pharmaceuticals from academic research, when a commercial route is not, or not yet, viable. We aim to alleviate bottlenecks that academics face in pharmaceutical development by providing financial support, but also regulatory and business development support. KWF aims to anchor PIPELINE as a recurring call.

KWF collaborates with the Centre for Drug Development (CDD) in the United Kingdom, a charity-funded pharmaceutical development facility that is part of Cancer Research UK (CRUK). This collaboration is set up to alleviate bottlenecks and enable early clinical development for those academics that do not desire or cannot initiate trials themselves. However, if you apply to the call, engaging with the CDD is not mandatory. More information on the submission procedure and collaboration with the CDD is provided below.

We envision proposals on clinical trials that are supported by interdisciplinary teams (researchers, pharmacists, healthcare professionals), possibly in collaboration with centres in Europe, industry and/or service providers. Academics can aim to reach clinical practice with their innovations themselves. Other innovations could be de-risked for transfer to industry through the generation of clinical data. Public-private partnerships are another route for product development in this call.

Requirements and guidance

Project and applicants

Requirements		Guidance
Research type	Research project or consortia	- Projects that consist of 1 - 3 participating parties (research project) or 4 or more participating parties (consortia). - Project duration is between 4 and 8 years. - For consortia a project manager is mandatory.
Research phase	Clinical trials ranging from phase I to III.	- For the KWF route, phase I to III are eligible. For the CDD route, only phase I or I/II trials are eligible. - Confirmatory and/or 'pivotal' trials may be considered if they fit within the indicative budget. - The development and validation of GMP manufacturing can be part of a proposal for clinical trial conduct, if the duration from start of the project to start of patient inclusion does not exceed 2

		years and the total duration of the project does not exceed 6 years.
Trial design	Interventional, prospective, using the best-fitting trial design.	Best-fitting design for the trial phase, including single-arm and controlled designs. Consider regulatory requirements, and possibly HTA requirements and PASKWIL criteria for your design. Designs that make use of validated surrogate endpoints and real world data (for example as control arm) may be considered if these adhere to requirements and criteria mentioned above. Design should include the best suitable and most representative study population, with respect to the studied disease or patient subgroup.
Main applicant	Medical centre or research institute that must be located in the Netherlands.	Main applicants as well as public participating parties should fall within the following categories: Academic research groups (from universities or other higher education or research institutions); or Clinical/public health sector research groups (from hospitals/public health and/or other health care settings and health organizations).
Public participating parties	Medical centre or research institute that must be located in Europe.	A public participating party carries substantive and financial responsibility for a part of the project, the dissemination and/or exploitation of the results. A foreign participating party can perform parts of the work plan, when the project leader deems this necessary.
External inclusion centres	Medical centre or research institute that must be located in Europe.	- Centre outside the lead institute or participating organization(s) that only includes patients for clinical studies and has no active research role in the project. This centre has no right to the project results. An exception to this can be that an external inclusion centre retains the right on its own generated data, information, samples, knowledge and inventions. - External inclusion centres are not considered participating parties. A quotation for their services is obligatory.
Private participating parties	For-profit or industrial partners.	- Private participating parties are accepted if needed for the execution of the project, and as long as co-funding (in cash and/or in kind, see below 'Additional conditions') as well as appropriate agreements on intellectual property and fair pricing are in place (for full proposal). - Private participating parties cannot be the main applicant. - Both small- and medium enterprises and large industrial partners can

		participate in the project, yet the minimum required co-funding differs (see additional conditions).
Service providers	Department or organisation that provides a necessary service for the work plan.	- Internal service providers are departments of the lead institute or a participating organization that provides a necessary service for the work plan, such as data management or specific analyses. - External service providers are public or private organizations that provide a necessary service for the work plan, such as contract manufacturers, trial bureaus, and consultancy agencies. - Both internal and external service providers do not benefit from the project results and have no right to the project results. A quotation for their services is obligatory.
Patient participation	It is required to actively involve patients in the set up and execution of the trial.	Involvement of patients in the set up and execution of the trial is required. This may include, but not limited to, one or more of the following: letter of support from a patient organization, patient review of the Informed Consent Form, patient input on the protocol, dissemination of results to patients (including study participants), patient participation in steering committee. Information on patient participation is requested during the full-proposal.

Product

Requirements		**Guidance**
Intervention	New investigational pharmaceuticals (e.g. new chemical/biological entity, originator products)	Investigational pharmaceuticals intended to be used for treatment in humans (including but not limited to monotherapy, treatments in combination with standard treatment, (neo)adjuvant therapy, add-on therapy). These need to be new, originator products, meaning they have never been registered in any market before.
Product type	All types of experimental pharmaceuticals that fall under the EU definition of medicinal product (small molecules, biologicals, advanced therapy medicinal products).	Products are required to fall under the definition of medicinal product in the EU pharmaceutical legislation[1]. If it is unclear whether the product is a medicinal product, it may not be eligible.

[1] Article 1 of Directive 2001/83/EC.

Target Product Profile	A (preliminary) Target Product Profile (TPP) is mandatory.	- Key elements of a TPP are requested for the pre-application and pre-proposal. - A (preliminary) TPP is mandatory for the full proposal.
Indication	All cancer types, including rare- and paediatric cancers	- All cancer types can be targeted, including paediatric, orphan, and non-orphan cancer types. - The target patient population (currently or in the future) needs to be specified. - Patient stratification or inclusion for therapeutic intervention(s) based on defined biomarkers or targets, as part of an interventional trial with relevant endpoints is allowed.
Scientific rationale	(Pre)clinical research supports expected safety and/or efficacy outcomes.	- For the pre-application, please provide high level findings from most relevant preclinical efficacy/ pharmacology/pharmacokinetics/ toxicology and clinical data. - For the pre- and full proposal, detailed outcomes that support expected safety and efficacy outcomes are mandatory.
Added value	Product development addressing unmet medical needs, with added value to the patient with respect to clinical safety and/or efficacy compared to current standard treatment.	- Unmet medical need is defined as addressing a life threatening or severely debilitating disease, which is associated with a remaining high morbidity or mortality under current standard treatment. - Added value to the patient is defined as: 1) a significant reduction in severe side effects, and/or 2) a meaningful expected reduction in disease morbidity or mortality for the relevant patient population as a result of treatment with the experimental product, in comparison to current standard treatment. The threshold for 'meaningful' has been defined in the PASKWIL criteria. - Unmet medical need and added value to the patient need to be substantiated with argumentation of prognosis and (expected) clinical outcomes.
Development plan	Clear development trajectory with supporting regulatory strategy and business development.	- The planned development trajectory needs to extend to the end goal; to reach the patient in clinical practice. - It is not mandatory to have a regulatory strategy or business development plan for the pre-application, yet previous or planned regulatory and/or business

		development activities are preferred (this is part of the selection criteria for pre-applications, see section 'pre-application' below). - The development plan needs to include a regulatory strategy and business development plan for the full proposal.

Out of scope

- Repurposing of registered pharmaceuticals for new indications.
- Combination therapy of registered pharmaceuticals only.
- Preclinical research cannot be part of the project.
- Private parties as a main applicant, or industry sponsored trials.
- (Early) diagnosis of (recurrent) disease and/or monitoring during therapeutic interventions and/or patient stratification for therapeutic interventions, without interventional and pharmaceutical development set-up (e.g., observational research).
- Investigational products with no or limited freedom to operate.

Additional conditions

If the for-profit private partner has an active role within the project, this party is considered a participating party and to this end must make a financial contribution: this is minimum 20% co-financing of the KWF requested budget (in cash and/or in kind). For partners with >250 FTE, co-financing must be at least 50% in cash. For small- and medium-sized enterprises (SME's) co-financing in cash is not mandatory, it may be contributed entirely in kind.

If the for-profit partner is involved on a fee-for-service basis, a contribution is not applicable. They are considered a service provider (see section on requirements).

There is a maximum hourly rate for payroll costs for service providers:
- Supportive (MBO) € 85,00
- Project Management (HBO) € 100,00
- Expert (WO) € 125,00

This is the maximum hourly rate excluding VAT and including all other costs (travel costs, parking costs, travel hours, etc.) as they should be applied. If institutes would like to apply a higher hourly rate for motivational reasons, this must always be agreed and approved in advance by KWF.

Pre-application

The call starts with a pre-application. It must be written in English and submitted by the main applicant by sending a pre-application form to pharmaceuticals@kwf.nl in a PDF file. The form must be signed by the project leader. KWF will evaluate whether the pre-application is eligible for the call and fits the ambition of the call. Upon favourable decision, the main applicant will receive an invitation to submit a pre-proposal.

The selection procedure starts with an eligibility check. Pre-applications need to adhere to the requirements and scope of the call (see above). Eligible pre-applications are subsequently scored to which extent they fit the ambition of the call. There are four criteria used to rank eligible pre-applicants; 1) addressing unmet medical need, 2) expected added

value to the patient compared to current standard treatment, 3) status of manufacturing, and 4) (proposed) development plan steps.

Applicants of pre-applications can submit a pre-proposal by invitation only. The outcome of the pre-application selection procedure was communicated to all applicants on December 21, 2023. There is an objection procedure in place for rejected pre-applications. Objection letters need to be sent to KWF no later than 11 January, 2024, preferably via pharmaceuticals@kwf.nl. The KWF regulations for objection procedures are available online.

Collaboration with Centre for Drug Development

KWF collaborates with the CDD for phase I or I/II trials in the PIPELINE call. In the pre-application phase, applicants indicated whether they prefer the CDD to be involved in their product development in the pre-application form. CDD involvement was not mandatory and selected preferences did not affect the pre-application selection procedure. Positive decision outcomes of the pre-application selection procedure included KWF advice on CDD involvement. Applicants can request informal meetings with KWF or CDD from January 2024 onwards to discuss the best way forward in the submission procedure. In the pre-proposal phase, the final decision on collaboration with the CDD is made by the applicants in the pre-proposal application form. The pre-proposal application form is the same for the CDD and KWF route.

KWF collaborates with the CDD to enable pharmaceutical product development that originates from academic research, which the academic party cannot or do not desire to undertake themselves. The CDD is a charity-funded drug development facility with preclinical and medical sciences, regulatory affairs, quality assurance, project management, legal, drug safety, clinical operations and data management capabilities. These capabilities are used to coordinate and monitor phase I or I/II conduct trials for promising new pharmaceuticals.

After early clinical research is completed, the CDD aims to license successful products out to the pharmaceutical industry for further development and market authorisation, under strict socially responsible terms. The CDD uses a case-by-case approach how to license out in order to reach patient access. Throughout this process, there is ample room for dialogue between the academic party and the CDD. KWF aims to enable product development via a semi-commercial route with the CDD-KWF collaboration, while stimulating socially responsible terms.

Projects that are granted in collaboration with the CDD will be funded under separate terms and conditions (see below 'Terms and Conditions'). More details regarding the collaboration with the CDD and evaluation procedure can be found in section 'CDD route'.

Submission procedure

The call has a pre- and full proposal submission procedure. Both the pre- and full proposal must be written in English and submitted exclusively by the main applicant through the electronic submission system (Grant Management System - GMS). Please note that registration in GMS is required prior to submitting your application. It is recommended to register as soon as possible. If you are new in the system your registration must be approved by KWF. Please check at least six weeks before the pre-proposal deadline if your registration is approved. Instructions can be found in the KWF Guidelines 2024.

Pre-proposal

After the pre-application phase has ended, the submission procedure continues with a pre-proposal stage. The pre-proposals must be submitted no later than 12:00h on 19 March, 2024. Pre-proposals need to adhere to the requirements and scope of the call (see above). KWF will check the eligibility of all pre-proposals before evaluation starts. Pre-proposals that are not considered eligible are rejected without further review. Pre-proposals are accepted by invitation only. Applicants that did not receive an invitation to submit a pre-proposal based on their pre-application are considered non-eligible and will be rejected. The main applicants of non-eligible pre-proposals are informed accordingly and there will be no possibility to object to this decision.

There are two routes for evaluation of submitted pre-proposals; the CDD and KWF route (Figure 1). Applicants can choose to participate in the CDD or KWF route in the pre-proposal application form, which can be found in GMS. It is possible to schedule an informal meeting with the CDD to discuss their way of working and project specifics during the writing phase of the pre-proposal, for all applicants that consider the CDD route.

CDD route

To opt for the CDD route, applicants need to select the CDD route and provide permission to share the pre-proposal with the CDD in the pre-proposal application form. In the CDD route, eligible pre-proposals will be sent to the CDD to enter an evaluation procedure (Figure 2). The submitted pre-proposal application form will be the supporting document for stage one of the evaluation procedure.

All applicants in the CDD route are invited to an online meeting of 30 - 45 minutes with the CDD to discuss their pre-proposal. These meetings will be scheduled on 26 March 2024 and 2 April 2024. Applicants can prepare supporting visuals to illustrate and discuss data in these meetings, but it is not required to prepare a presentation. Projects that are not selected by the CDD in stage one review flow into the KWF route (see below).

If pre-proposals are selected in stage one review, they enter stage two review of the CDD evaluation procedure. In stage two, a confidential data pack needs to be shared with the CDD. Requirements are preclinical efficacy, pharmacology, pharmacokinetics and toxicology, biomarker strategy, clinical rationale, manufacturing status, IP and freedom to operate status, and competition.

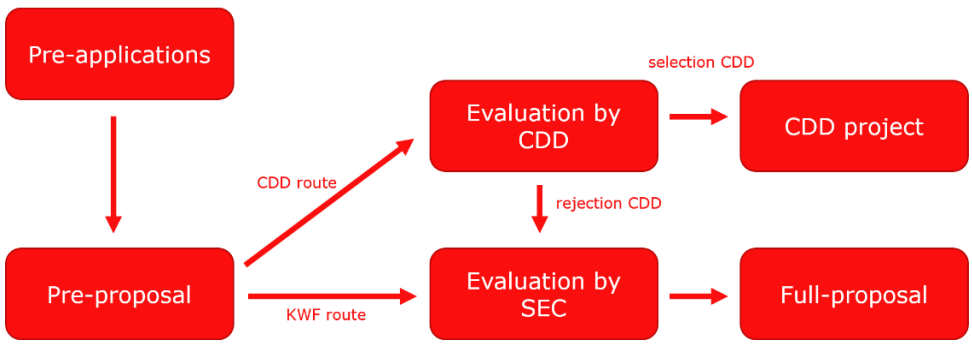

Figure 1: Evaluation routes (CDD and KWF). CDD = Centre for Drug Development, SEC = Scientific Evaluation Committee

Figure 2: CDD evaluation procedure.

Products that are selected in stage two review undergo a full scientific review by an independent review committee on novelty of the product and/or target, strength of supporting preclinical data, unmet medical need and feasibility of the project. The last stage is a data verification step by the CDD project team. Applicants that receive a positive outcome of the independent review and data verification are offered the possibility to collaborate with the CDD for the development of their investigational medicinal product. Please note that projects that are not selected by CDD in stage two review or beyond cannot participate in the KWF route of PIPELINE 2024 anymore due to conflicting timelines. For these projects, resubmissions in future PIPELINE calls will be possible. However, projects rejected in stage one review of the CDD remain eligible for the KWF route of PIPELINE 2024.

KWF route

To opt for the KWF route, applicants need to select the KWF route in the pre-proposal application form.

The pre-proposals in the KWF route are evaluated by the PIPELINE Scientific Evaluation Committee (SEC) with pharmaceutical development expertise. Pre-proposals are evaluated on scientific excellence, developmental potential and patient impact potential. See below for the evaluation criteria of the KWF route. Pre-proposals will not be evaluated by a Patient Advisory Committee (PACO).

The KWF evaluation procedure starts after the CDD evaluation procedure is finalized. These evaluations are performed in a consecutive order to allow KWF evaluation by the PIPELINE SEC for projects that are rejected in stage one review of the CDD route.

The PIPELINE SEC will also evaluate rejected CDD pre-proposals for the KWF full-proposal phase in a similar fashion as projects that entered the KWF route directly. In addition, the CDD evaluation will be shared with the PIPELINE SEC. This procedure is set up to ensure that good quality projects, which may be rejected due to too many applications for the capacity within the KWF/CDD collaboration, or strategic misfits with the CDD, remain in the running for funding.

The outcome of the evaluation procedure of the pre-proposal (KWF route) is communicated to all applicants in week 23 of 2024 (3-7 June, 2024).

Full-proposal

After the pre-proposal phase of the KWF route has ended, the submission procedure continues with a full-proposal phase. Full-proposals are accepted by invitation only. The full-proposals must be submitted no later than 12:00h on 10 September, 2024. KWF will check the eligibility of all full-proposals before evaluation starts. Applicants that did not receive an invitation to submit a pre-proposal based on their pre-application are considered non-eligible and will be rejected. The main applicant of the non-eligible pre-proposals is informed accordingly and there will be no possibility to object to this decision.

Please note that all participating parties, including medical centres, research institutes and private participating parties, that are not yet registered in KWF-GMS must submit a registration request via KWF-GMS no later than 6 weeks before closing date.

The information provided in the pre-proposal application is binding for the entire application process. Any substantial changes between the pre-proposal and the full-proposal, such as composition of the consortia or objectives of the project, must be communicated in advance of submission. KWF will determine whether the submission procedure can be continued with substantial changes. Yet, it is allowed to make improvements between the pre- and full-proposal following advice from the SEC, regulatory authorities or valorisation experts, or other insights. Such improvements and supporting argumentation need to be indicated in the full-proposal application form.

The full-proposals are again evaluated by the SEC on scientific excellence, developmental potential and patient impact potential (see below for evaluation criteria in KWF route). The full-proposals are also evaluated by external reviewers and a Patient Advisory Committee (PACO).

Pre-grant scientific advice and consultation for valorisation

KWF aims to alleviate bottlenecks that academics face in pharmaceutical development. Therefore, we offer the opportunity of 1) pre-grant scientific advice, and 2) a consultation for valorisation, to applicants during the full-proposal phase of writing. Costs are covered by KWF.

Pre-grant scientific advice entails a regulatory feasibility check on the project proposal and regulatory strategy based on the information provided in the pre-proposal, prior to the funding outcome of the full-proposal phase. This will be performed by Dutch regulatory authorities (College ter Beoordeling van Geneesmiddelen (CBG) and the Centrale Commissie Mensgebonden Onderzoek (CCMO)). Written feedback will be provided to full-proposal applicants that wish to receive pre-grant scientific advice.

Applicants that participate in pre-grant scientific advice need to give permission in the pre-proposal application form to share their pre-proposal with regulatory authorities. KWF will only share pre-proposals with regulatory authorities upon approval of the main applicant.

A consultation meeting with a valorisation expert from KWF will be available for all full-proposal applicants that wish to receive a valorisation consultation. Written feedback of the consultations will be provided to all full-proposal applicants. Applicants can request a consultation for valorisation at KWF once they receive an invitation to write a full-proposal.

It is strongly recommended to obtain pre-grant scientific advice and a valorisation consultation. Advice from both parties will be provided in the beginning of the full-proposal writing period, which allows to improve the full-proposal. Please note that the advice from regulatory authorities and valorisation experts will be shared with the SEC during the final evaluation of the full-proposals.

Interview

The SEC will convene in the week of 11 – 15 November, 2024 for the full-proposal Board Meeting. For each full-proposal, an oral interview will be scheduled for explanation and clarification of certain aspects of the full-proposal as part of the evaluation procedure. Full-proposal applicants will receive an invitation well in advance before the Board Meeting. The scheduled date and time cannot be changed. It is the responsibility of the project leader and team members that will join to be available at the scheduled date and time. Applicants will not have access to evaluation reports prior to the interview.

Decision on full-proposals

The outcome of the evaluation procedure of the full-proposal is communicated to all applicants in week 50 of 2024 (9-13 December, 2024).

Evaluation criteria in KWF route

Scientific Evaluation Committee (SEC)

In both the pre- and full-proposal evaluation, the SEC will use the following criteria to evaluate proposals:

1. Scientific excellence
    a) Scientific quality: including sound trial design (i.e. statistics, methodology) and scientific background, previous research and evidence supporting the objective of the trial (i.e. state of the art).
    b) Feasibility: including feasible workplan and recruitment plan, good quality project team or consortium, project management.
    c) Proven safety and anti-tumour effect, or a strong rational in favour of safety and an proposed anti-tumour effect (available data showing safety and efficacy for the investigational medical product in relevant preclinical research and/or the targeted patient population).

2. Developmental potential
Depending on the presence (if any)* and quality of:
    a. Proposed development trajectory and Target Product Profile.
    b. Regulatory strategy up to market authorisation.
    c. Business development plan and go-to-market and implementation strategy (either academic or commercial).

*It is not obliged to have all these criteria completed at time of the pre-proposal; applicants may describe the current status and future plans on these topics. However, the better elaborated and the further in progress, the higher the developmental potential.

3. Patient Impact potential
Which may be impacted by:
    a) Close-to-patient/clinical implementation innovations.
    b) Targeting an unmet medical need.

c) Added clinical benefit, with respect to clinical safety and/or efficacy compared to current standard treatment.

Available input from the CDD, external reviewers, pre-grant scientific advice, and business development consultations, are all external sources for the SEC committee members in their evaluation.

Patient Advisory Committee (PACO)

The full-proposals only (not pre-proposals) are evaluated by the PACO. The PACO consists of members that are current or former cancer patients with a variety of indications and stages of the disease. PACO members use the Dutch summary to review the project proposal from the patient perspective on relevance, feasibility and patient involvement using the following criteria:

1. Relevance:
   a) does the objective of the project proposal match the needs/wishes of cancer patients or the general public?
   b) does the envisaged result offer sufficient added value compared to the current status quo?

2. Feasibility:
   a) Is the burden placed upon participants in the study acceptable, considering the envisaged results?
   b) Has sufficient consideration been given to ethical aspects, the implementation of the results, or the realization of any necessary follow-up action?
   c) Will (enough) patients be willing to participate in this study?

3. Patient involvement:
   a) To which extent are patients involved in the design of the project proposal, the execution of the study and the dissemination of results?
   b) Have patients, patient organizations or patient representatives actively been participating in the design and execution of the study?
   c) How have their efforts been incorporated in the study?

The advice issued by the PACO will be included in the review of the project full-proposal along with the other review reports. Members of the PACO will attend the board review meeting. A PACO member will also be present at the interview.

<u>Terms and Conditions</u>

Granted KWF projects will be funded under the current Funding Terms and Conditions. Additional project specific conditions may be applied.

Projects that are granted in collaboration with the CDD will be funded under separate terms and conditions. For each granted project, a product specific Project Agreement will entail all agreed terms and conditions between applicants and the CDD. In this process, there is ample opportunity for discussion between applicants and the CDD, on both the execution of the trial and the future development trajectory. KWF will oversee adherence to KWF goals and standards in projects funded within the KWF-CDD collaboration, including adherence to socially responsible terms.

Timelines

Pre-applications opens:	September 19, 2023
Pre-applications closes:	November 30, 2023
Pre-proposal opens:	January 9, 2024
Pre-proposal closes:	March 19, 2024
Full-proposal opens:	June 4, 2024
Full-proposal closes:	September 10, 2024
Funding decision:	December 12, 2024

Indicative budget:

The indicative total budget is 5 - 8 million euro. The budget indication per proposal is 1 – 4 million euro.