General Terms
CRYOSTEM Call for Projects 2019

These general terms (hereafter the "**General Terms**") aim in particular to present the terms and conditions governing the submission, selection and processing of academic or commercial research projects submitted to CRYOSTEM Scientific Committee.

INTRODUCTION :

CRYOSTEM is a project that is backed by the SFGM-TC (Francophone Society for Bone Marrow Transplantations and Cell Therapy (hereafter "**SFGM-TC**") and accepted by the French National Research Agency in relation to the "Cohorts" call for projects funded under the French government's "National Investment Programme" ("*Investissements d'avenir*") in June 2010.

Currently, CRYOSTEM is a network covering all the allo-transplantation centres in France and 27 related Biological Resource Centres (BRC).

Since 2012, CRYOSTEM has set up a collection of biological samples taken before and after allogeneic hematopoietic stem cell transplantation (HSCT) (hereafter the "**Collection**"), thus reaching its first objective.

Starting in April 2015, this Collection will be made available to scientists to enable high-level scientific projects to be performed focussing on the theme of Graft versus Host Disease (GvHD). The objective is to better understand the physiopathology of this little-known disease in humans, the predictive factors related to its occurrence, the response to immunosuppressive treatments and the long-term prognosis.

In 2016, CRYOSTEM obtained the authorization of the French Patient Protection Committee (CPP) to extend the collection thematic to the all HSCT complications, opening the fields of studies.

In relation to this availability, CRYOSTEM wishes to choose the most relevant scientific projects complying with the chosen scientific theme.

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PART I – GENERAL TERMS

I.1 – Purpose of the Call for Projects

The purpose of this Call for Projects (hereafter "**Call for Projects"**) is to open up the access to the Collection, established by CRYOSTEM, to all academic and/or commercial members as defined in article I.2 below, involved in research on all the Hematopoietic Stem Cell Transplantation (HSCT) Complications, and who wish to work on the scientific themes identified by CRYOSTEM.

The biological samples treated from blood samples and the derived aliquots, constituting the CRYOSTEM Collection, are named hereafter "**Biological Material**".

The Biological Material and the associated data are named hereafter the "**Biological Resources**".

The projects (hereafter "**Projects**") put forward by the academic and/or commercial members (hereafter "**Applicants**") in relation to this Call for Projects must abide by these General Terms and the Appendices.

The Applicants acknowledge that they have read and accepted these General Terms and the Appendices, by signing the act of commitment of the General Terms that will be sent to them before Biological Resources delivery.

For this Call for Projects, the CryoStem "**Scientific Committee**" has defined the content of this Call for Projects and is responsible for organizing the selection process and follow-up of the Projects. Its members are listed in Appendix 1.

I.2 – Conditions for submitting replies to the Call for Projects

The Applicants involved in this Call for Projects are as follows:

- Academic laboratories such as those registered by the Ministry for Higher Education and Research or under the supervision of this same Ministry, i.e. any laboratory of the following structures: healthcare centres, higher education and research establishments, public scientific establishments, public industrial and commercial establishments, public scientific and technological establishments, foundations, public interest groups, research organizations, regional delegations for research and technology (hereafter "**Academic Laboratories**"). The term "Academic Laboratories" in these General Terms includes consortiums and groups of laboratories of these same structures
- Commercial Applicants (hereafter "**Commercial Applicants**")
- Consortiums grouping together Academic Laboratories / Commercial Applicants

The Applicants may comprise separate legal entities, and a key contact for CRYOSTEM should be clearly identified by each Applicant (hereafter "**Project Initiator**").

For projects of equal scientific value, projects presented by research teams belonging to a French Academic Laboratory will be preferred.

The Academic Laboratories taking part in establishing the Collection are authorized to respond to this Call for Projects. In the case of a joint response between a Commercial

Applicant and an Academic Laboratory taking part in establishing the Collection, CRYOSTEM will be authorized to ask the parties to set forth in writing the motivations behind their desire to work together.

The appraisal and selection criteria of the Projects put forward by the Applicants will be submitted to international experts, thereby guaranteeing complete independence in the final choice of the Projects accepted.

PART II – TIMESCALE FOR THE CALL FOR PROJECTS

II.1 – Schedule for the Call for Projects

Projects submission to CRYOSTEM could be done at any moment of the year.

The application files and General Terms are available on demand (emilie.robert@cryostem.org) and can be downloaded from the CRYOSTEM website (www.cryostem.org).

Application files are studied during the Scientific Committee session following the Project submission. Four sessions of the Scientific Committee at least are organised during the year.

II.2 - Application submissions

Applications will be sent by e-mail to CRYOSTEM strategy & valorisation manager (emilie.robert@cryostem.org).

For further information, please contact him by phone (+334 91 22 34 37) or by e-mail (given above).

CRYOSTEM undertakes to take all appropriate measures in order to ensure the strictest confidentiality regarding the applications submitted. Applicants are however advised to perform all necessary procedures and take appropriate measures to protect the information that they provide within their response to the Call for Projects. Applicants should notify any possible conflicting interests and provide a list of the experts that they wish to challenge. CRYOSTEM undertakes to take this request into consideration where possible in order to guarantee the greatest possible fairness in the selection process.

II.3 - Description of the selection stages

First stage: Short-listing of Projects

This first stage aims to select the Projects that meet with the specific purposes set forth in the application.

With reference to the application, the following shall not be **accepted**:

- Incomplete applications;
- Applications written in French;
- Applications not signed by the person authorized to represent the Applicant.

At the end of this first stage, an unlimited number of Projects will be shortlisted by the Scientific Committee and examined in full as part of the second and third stages.

Applicants will be informed in writing of the result of this short-listing. Applicants could be invited to answer to remarks of the Scientific Committee of CRYOSTEM or to submit a revised proposal of the Project based on the recommended modifications.

No financial aid will be allocated to the Applicant on the basis of this first stage alone.

Second stage: Review by the international experts

Following the preselection by the Scientific Committee of CRYOSTEM, each project will be sent to three (3) international experts, in charge notably of the evaluation of the methodological and scientific quality of the Project.

The synthesis of the three reviews will be transmitted to the CRYOSTEM Scientific Committee.

No financial aid will be allocated to the Applicant at the end of this second stage.

Third stage: Final selection of Projects

The third stage is the final selection of the Projects. The final selection will be validated by the Scientific Committee and notified by the Steering Committee. The results of the Call for Projects will be notified to each Applicant by an official letter which will precise the logos to be included in any oral or written communication related to the use of the Biological Resources of the Collection (CRYOSTEM, SFGM-TC and the potential funders).

II.4 –Selection of Projects

Appraisal of the applications submitted by the Applicants will take place on the basis of criteria defined by CRYOSTEM. These criteria may be provided for information purposes and on request from the Applicant to CRYOSTEM.

PART III – CONDITIONS OF USE OF THE BIOLOGICAL RESOURCES MADE AVAILABLE TO THE CHOSEN APPLICANTS

III.1 – Conditions governing access to the Biological Resources

The Collection includes three types of Biological Material: viable cells in DMSO, dried cell pellets and plasma.

The Biological Resources made available by CRYOSTEM in relation to a Project accepted as part of the Call for Projects will be selected by CRYOSTEM in accordance with relevance criteria in relation to the Project.

The clinical data extracted from the PROMISe database, provided by the SFGM-TC, transmitted by CRYOSTEM, required for the Project to progress smoothly will be made

available with the Biological Resources. The accuracy of the clinical data extracted from the PROMISe database do not come under the responsibility of CRYOSTEM.

In the case of requirement of additional data for the Project, the Applicant will, on the one hand, precise them in the application file, and, on the other hand, ask for to CRYOSTEM strategy & valorisation manager before, to validate the feasibility and quantify the workload : an additional quotation will be provided for the obtain of these data.

Only the data asked for in the application file would be provided with the Biological Resources.

In the case of later demand of clinical data, the Applicant would be asked for additional financing equal to the cost related to data extraction specified in the Call for Projects pricing-list.

CRYOSTEM reserves the right to select the Biological Resources and restrict access to the Collection according to qualitative, quantitative and financial criteria. The selection criteria of the Biological Resources will be defined by CRYOSTEM strategy & valorisation manager and the selected applicants together.

The process for selecting the Biological Resources may be provided, for information purposes, to a selected Applicant upon submission to CRYOSTEM of a written request to this effect.

The access to CRYOSTEM Biological Resources and to the clinical data provided by the SFGM-TC needs to be subject to contract (convention, agreement…) signed by the representatives of the Applicant affiliation and those of CRYOSTEM. This document will precise the specific terms of the collaboration between the research team of the selected Applicant and CRYOSTEM.

III.1.1 Availability of the Biological Resources

CRYOSTEM will inform the Applicant of the availability and the planned date of availability of the Biological Resources.

In the case of a provision to an Applicant outside the French territory, a ministerial export authorization will be asked by CRYOSTEM. The provision will be done only at reception of the authorization ; the corresponding number provided by the French ministery will be provided to the Applicant.

The delivery of the Biological Material will be organized by CRYOSTEM, which reserves the right to choose the means of transport. The carriage costs of the Biological Material will be borne by the Applicant and billed at their actual cost. The Applicant may receive information about the amount of the applicable carriage costs, upon submission of a request to CRYOSTEM.

Once the Biological Material are received, the Applicant is responsible for inspecting their condition and setting forth any reservation or protest regarding their physical state, within a period of eight (8) days as of the date of receipt of the Biological Material.

The Applicant commits to return to the strategy & valorisation manager the provided Biological Material follow-up sheet, after any use.

III.1.2 Right to use the Biological Resources

The Biological Resources may be used for research purposes, respecting individual rights and the legal and ethical principles governing the status of the human body, its parts and its products, without any right to transfer them.

CRYOSTEM and the SFGM-TC will provide clinical data of interest for the Project in relation to the Biological Resources selected by CRYOSTEM.

III.1.3 Suspension – Return of the Biological Resources

Any use of the Biological Resources and of the clinical data other than that defined and authorized by CRYOSTEM is strictly prohibited.

Failure by an Applicant to abide by the conditions of use defined by CRYOSTEM upon selecting the Applicant may lead to the suspension of availability of the Biological Resources, and the return to CRYOSTEM of the Biological Resources already provided, at the Applicant's cost.

III.1.4 Financial Conditions

The Biological Resources and the clinical data made available to the Applicant will be accessible in accordance with the financial terms defined in Appendix 2.

These prices include the access to the Biological Resources and associated clinical data, the interventions of CRYOSTEM staff (project managers, transplant units and Biological Resources Centres staff) for the selection, the removal and the provision of the Biological Resources and the related clinical data.

The financial evaluation included in the application file is provided for information purposes only. Only the samples allocation quotation published following the final decision of the Scientific Committee and taking into account the availabilities according the demand, is financially valuable. It will be transmitted to the Applicant and must be sent back signed to the strategy & valorization manager for acceptance.

The Applicant will give information in the application file on the funding status (acquired or not, ongoing application) and on the source. The Applicant will precise if the funds are intended to compensate only the provision of the Biological Resources or the total achievement of the Project.

In the case of the Applicant would not be able to fund the provision of the Biological Resources or the Project in its totality, the Scientific Committee of CRYOSTEM could offer to the Applicant to include his Project into the "HTC Project" program, in order to get an entire or partial financial support, according the total cost of the Project and the available funds on the "HTC Project" endowment funds. The « HTC Project » is an international programme, created by CRYOSTEM, to promote the research in the field of HSCT complications.

In the case of the Applicant entirely funds on its own source the provision of the Biological Resources and the related clinical data, a 50% deposit will be asked for to the Applicant before the shipment.

The availability of the Biological Resources is part of an operation that is not subject to value-added tax in accordance with the terms of article 256 of the French Tax Code and the Official Bulletin of the French Tax Authorities BOI-IS-CHAMP-10-50-10-20.

III.2 – Obligations

III.2.1 CRYOSTEM's Obligations

CRYOSTEM is bound by an obligation of means as regards making the Biological Material available to the Applicant. CRYOSTEM is also bound by an ISO 9001 : 2015 certification process including the surveillance of the BRCs for the management of the Collection in accordance with the requirements of standard NF S 96-900. The Biological Material included in the Collection have therefore been prepared in accordance with a standardized procedure defined by CRYOSTEM. This procedure is applied by all members of CRYOSTEM in accordance with good laboratory methods.

CRYOSTEM regularly inspects that these methods are respected and performs random quality tests on the Collection at least once per year, the results of which may be provided to the chosen Applicant, upon submission to CRYOSTEM of a written request to this effect.

CRYOSTEM commit to providing to the Applicant a protocol of thawing when viable cells in DMSO are provided.

Some Biological Material, by their very nature, may not present all of the characteristics required, which is specifically acknowledged by the Applicant. The Applicant undertakes not to claim that CRYOSTEM replaces the Biological Material which does not meet its expectations.

CRYOSTEM guarantees, to the exclusion of any other guarantee, that the Biological Material has been prepared in accordance with the "standardized procedures regarding samples and data" drawn up by CRYOSTEM.

In particular, CRYOSTEM may not be held liable for any damage to the Biological Material in the Applicant's premises, or for their mishandling by the Applicant, as the latter bears exclusive responsibility for Biological Material storage.

III.2.2 Applicant's Obligations

Before the use of the Biological Resources, the Applicant must have taken the required steps regarding the regulatory and legal framework for his Project and bring the evidence to CRYOSTEM.

The chosen Applicant undertakes to inform CRYOSTEM regularly concerning the progress of the Project, and to provide a progress report, at the latest eighteen (18) months after the last provision of the Biological Resources by CRYOSTEM, along with a final report at the end of the Project. However, the chosen Applicant might be asked for intermediary reports on demand of the Scientific Committee or the potential sponsors or for communication actions. The chosen Applicant undertakes to inform CRYOSTEM of the end of the Project within three (3) months following the end of the Project.

The chosen Applicant undertakes to inform CRYOSTEM strategy & valorisation manager of any relevant information related to the Biological Material quality in link with their use in a reasonable delay following the cession.

The chosen Applicant undertakes to destroy the Biological Resources and the related clinical data extracted from PROMISe or any additional data within a period of thirty-six (36) months from the time when the research programme approved by CRYOSTEM is completed. A destruction certificate of the Biological Resources and the related data must be sent to CRYOSTEM upon expiry of this period.

However, the Applicant benefiting from CRYOSTEM's Biological Resources may, within this period of thirty-six (36) months following the end of the Project, ask for authorization from CRYOSTEM to use the Biological Resources for another research project.

This Project must be submitted beforehand to CRYOSTEM Scientific Committee. The Scientific Committee undertakes to examine the said Project involving the Biological Resources already provided and to provide its decision within a period of two (2) months. CRYOSTEM will communicate the Scientific Committee decision to the Applicant which undertakes to abide by it.

The chosen Applicant is explicitly prohibited from performing research on the Biological Resources provided by CRYOSTEM outside of the scope of the Project for which CRYOSTEM has given its approval. This ban includes all clinical data provided by CRYOSTEM and the SFGM-TC in relation to the Biological Resources provided by CRYOSTEM as part of the Project.
The chosen Applicant commits not to put back together or to identify in any case the subjects from whom the anonymised data would be transmitted by CRYOSTEM, whatever the way used, notably by avoiding to match them, or trying to match them, with other sources of data or Biological Resources provided regarding the Project or that would be accessible for him.

III.3 – Intellectual Property

The Applicants undertake to declare the intellectual property rights that they own in relation to the Project that they are submitting as part of the Call for Projects.

CRYOSTEM co-owns the results obtained with the Biological Resources from the Collection.

The conditions governing the use of the results obtained with the Biological Resources from the Collection are specified in articles III.3.1 and III.3.2 below.

III.3.1 Special terms for "Academic Laboratory" Applicants

"Academic Laboratory" Applicants are prohibited from making further direct use of the results from the research programme authorized by CRYOSTEM.

In the case of patentable or useable results, or results involved in a partnership between the "Academic Laboratory" Applicant and a Commercial Applicant, CRYOSTEM may grant a non-exclusive co-development right subject to joint use with CRYOSTEM.

The minimum financial conditions and the imperative obligations will be discussed mutually between CRYOSTEM and the "Academic Laboratory" Applicant, prior to the undertaking by

the said Applicant of the initial negotiations, and will be set forth in a “development delegation letter” drawn up by CRYOSTEM in favour of the said Applicant.

The minimum conditions will be set forth lastly by CRYOSTEM. However, should a dispute arise, the “Academic Laboratory” Applicant may, at its cost, appoint a financial appraiser registered on the list of court experts.

The expert’s assignment will include the encounter between CRYOSTEM and the “Academic Laboratory” Applicant in order to gather their respective arguments for setting the minimum financial conditions proposed by both parties, and the drafting of a report proposing a range of minimum values, and the grounds for the said range.

If the value proposed by CRYOSTEM is included in the said range, this value will be accepted.

If the value proposed by CRYOSTEM differs by more than 10% from the nearest outer limit of the range set forth by the expert, the value accepted will be that of the nearest outer limit.

If the value proposed by CRYOSTEM differs by more than 50% from the nearest outer limit of the range set forth by the expert, the value accepted will be that of the nearest outer limit and CRYOSTEM will also reimburse the appraisal costs up to a maximum amount of €5,000 excluding VAT per appraisal.

III.3.2. Special terms for “Commercial Applicants”

CRYOSTEM and the chosen “Commercial Applicant” will be co-owners of the results obtained with the Biological Resources made available as part of this Call for Projects. The parties shall meet immediately and in any event prior to publication or disclosure of the results, in order to decide on the possibilities for patenting the said results.

If it is deemed appropriate to patent the results, the parties will file a patent application in both names, of which the ownership and each party’s rights and obligations will be governed by the terms of the standard co-ownership agreement available on request to the strategy & valorisation manager.

For each new invention to be patented, CRYOSTEM and the applicant will sign a co-ownership agreement that complies with the standard agreement.

In the case of specific clauses related to therapeutic drugs discovery or others, that will be asked for to be motivated, an amendment to the present General Terms could be edited between CRYOSTEM and the Applicant in order to define more precisely the intellectual properties terms.

III.4 – Right to publication

The chosen Applicant undertakes to refer to CRYOSTEM and the SFGM-TC in any publication in relation to the Project in accordance with the following conditions:

- By quoting CRYOSTEM Consortium in the list of authors and by listing in the appendix the institutions members of the Plenary Committee (complete list to be obtained from CRYOSTEM)

- By noting the origin of the Biological Resources in the "Materials and Methods" section in the following format *"The samples annotated have been provided by the CRYOSTEM Consortium and SFGM-TC."*
- By quoting the Digital Object Identifier (DOI) assigned to the CRYOSTEM Collection and provided by the strategy & valorisation manager.

The Applicant undertakes to include CRYOSTEM and SFGM-TC logo, provided to him, in any oral and written communication, and those of the potential funders.

Any quotation of CRYOSTEM Biological Resources used by the chosen Applicant will follow the CoBRA guideline for the citation of biological resources.

The Applicant undertakes to submit the draft publication to the Scientific Committee at least one (1) month prior to publication, for its opinion, so that CRYOSTEM can check its accuracy.

CRYOSTEM will inform the Applicant of its decision within a maximum period of fifteen (15) days from when the Project is sent. Should no response be received within this period, CRYOSTEM's consent will be deemed to have been provided.

Consequently, CRYOSTEM may make any amendment or suspend the draft publication if any information due for publication presents omissions or inaccuracies.

Publication fees will be the charge of the Applicant.

Patients of the CRYOSTEM cohort, partners of the CRYOSTEM network, potential funders, could be informed about some information coming from the selected Projects (title, authors, affiliations, description, key words, Layman's summary…) and the results, notably via the CRYOSTEM website (www.cryostem.org).

PART IV – FINAL TERMS

IV.1 – Dispute settlement

The parties shall endeavour to settle their disputes on an out-of-court basis or via a mediator.

Otherwise, the parties will settle their dispute before the *Tribunal de Grande Instance* in Paris.

IV.2 – Applicable law

These General Terms are governed by French law. In the case of their translation into a foreign language, only the French text will be binding.

IV.3- Acceptance of the General Terms

The submission of an application by an Applicant implies the latter's specific and unreserved acceptance of all of these General Terms.

- Qualified members in Stem Cell Transplantations and / or Hematology:
  - Pr Gérard Socié, head of Hematology Units, Saint Louis hospital, Paris
  - Dr Eolia Brissot, MCU-PH in Clinical Hematology and Cell Therapy, Saint Antoine hospital, Paris
  - Pr Marie-Thérèse Rubio, PU-PH Clinical Hematology, head of the transplantation programm, Nancy
  - Pr Frédéric Baron, PU-PH Clinical Hematology, head of the transplantation programm, Liège
  - Dr Maud D'Aveni-Piney, PH Clinical Hematology, Nancy
  - Dr Edouard Forcade, doctor in Hematology, Haut-Lévêque hospital, Bordeaux

- The chairman of the SFGM-TC Scientific Committee or a representative

- Members of Steering Committee:
  - Pr Régis Peffault de Latour, project coordinator, PU-PH Saint-Louis hospital, Paris
  - Pr Jean-Hugues Dalle, PU-PH Paediatric Hematology, Robert Debré hospital, Paris
  - Dr Boris Calmels, BRC coordinator, PH in Cell Therapy Centre of « Institut Paoli-Calmettes » Marseille
  - Mrs. Claire Fontenille, regulatory & operational manager
  - Mrs. Emilie Robert, strategy & valorisation manager

Pricing list covering the provision of samples from the CRYOSTEM Collection

A : Academic project initiator and member of the CRYOSTEM consortium
B : Academic project initiator unaffiliated with the CRYOSTEM consortium
C : Non-academic / private / commercial project initiator

Samples provision	**A**	**B**	**C**
mononuclear cells in DMSO*	**13.60 €**	**17.00 €**	**47.60 €**
dry precipitate*	**10.60 €**	**13.25 €**	**37.10 €**
plasma*	**9.60 €**	**12.00 €**	**33.60 €**
selection, removal from storage and unpacking (flat rate)*[1]	**9.00 €**	**11.25 €**	**31.50 €**
blood sample (flat rate)**	**8.80 €**	**11.13 €**	**30.80 €**

** cost to be applied per aliquot*

*** cost to be applied per period and per patient*

Patients data provision	**A**	**B**	**C**
extraction of clinical data via PROMISe database (flat rate)	**280.00 €**	**350.00 €**	**700.00 €**
extraction of additional data (i.e. blood count, enzymes…)[2]	**on quotation**		

Administrative management	**A**	**B**	**C**
shipment (applicable rate provided as a guide for the shipment in dried ice of a cryobox containing from 1 to 100 aliquots on a national scale)[3]	**215.00 €**	**215.00 €**	**215.00 €**
centralization and control on receipt before sending to the PI (flat rate)***[4]	**23.00 €**	**28.75 €**	**80.50 €**

**** cost to be applied per group of 100 aliquots*

[1] corresponds to the aliquots removal from nitrogen tanks and to the database updating

[2] data availability would be checked before with the project managers

[3] to be applied per number of shippings given by the project managers

[4] aliquots tranport from CRYOSTEM network BRCs to the CRYOSTEM platform for checking before provision