Request for ballpark proposal for contracted clinical research services

INTRODUCTION

NanoSanguis S.A. is a med-tech company which has its origin in Warsaw University of Technology. The team of scientists working on technology of oxygen therapeutics for many years, in December 2015, founded NanoSanguis.

NanoSanguis mission is to develop safe red blood cell substitute for different clinical applications and recently we successfully performed experimental renal autotransplantation in pig - with the kidney perfused with our proprietary system NanOX composed of a prototype perfusion device and perfusion solution containing oxygen-carrying nanoparticles.

The NanOX system is still in the preclinical development phase but we plan to seek external funding to progress and we aim for a pilot clinical trial of the NanOX fluid in renal transplantation in 3 years, optimally.

Considering the requirements for the proposals being submitted in the public funding programs we need to understand at least a very rough estimate of the costs of services that we consider to subcontract for the preparation and conduct of the pilot clinical trial.

You are kindly invited to submit your proposal before October 20th, 2024.

Wherever possible, please construct your proposal showing costs according to instruction provided below in this document, in EUR (wherever needed please assume 1 EUR = 4,40 PLN exchange rate).

In addition to the costs estimation please include at least the following information in your proposal:

1) Experience in the area of nephrology and/or solid organ transplantation, and in medical devices trials. Feel free to add other experience highlights that you consider relevant.
2) Please estimate your operational capacity to provide such services in HQ4 2026 -Q4 2029 period.
3) Please share your initial considerations regarding the study design (remembering that the study will likely serve as a pivotal study for NaNox CE marking application as part of the clinical evidence or as complete clinical evidence) and expected challenges of such study.
4) If possible, please share short bios of your team members that you would delegate to this project (we understand that it may change before the project starts).
5) Please provide information on (key) systems/platforms/software that you intend to propose to use in this trial (e.g. for eCRT, eTMF, pharmacovigilance, etc.).

Important disclaimer:

At present we are collecting initial proposals/ballpark offers to understand the possible costs range and availability, and interest of potential service providers. Because of this we expect you to provide us with realistic valuation but without intention to compete by the costs at this stage.

The most critical from our end is the rough estimation of the budget – general data, then - more granular costs assumptions, and lastly - the presentation of your company, experience, interest and capacity. You are welcome to send us your proposals in parts if needed.

SCOPE OF SERVICES:

Please assume, that the Sponsor plans to contribute to a small extent only in the direct management of the trial and will mostly limit itself to the oversight of the CRO.

Therefore, for the purpose of this ballpark RFP the CRO should assume full-scope services, including but not limited to:

- Medical writing (in English), including drafting and finalizing the Clinical Investigation Plan (Study Protocol), IB, master ICF, CSR (study report)

- Study Feasibility (including legal)

- Regulatory – submissions pre and during the trial

- Study insurance

- Sites formal qualification

- Trainings for the sites

- Site Management during the study and study closure, including site monitoring visits 4/year

- Study monitoring including medical monitoring

- Contracting – sites and additional vendors

- set up of study systems including randomization of the assignment to the study arm

- eCRF design and electronic database setup

- Data Management

- Safety Management/Pharmacovigilance

- Project Management

- Biostatistics incl. development of SAP

- Study documentation management (eTMF)

- Support in set-up and work of DSMB (Data and Safety Management Board)

Instruction:

On top of the general budget estimate, please provide costs estimations for the following services **as separate** positions:

- Medical Writing 1 (including support in drafting the study synopsis, then drafting and finalizing the Clinical Investigation Plan (Study Protocol), writing two amendments to the protocol, IB, master ICF)
- Medical Writing 2 (CSR writing , please include ADDITIONAL interim study report after the interim analysis after 3 months of the last subject in)
- Medical Monitoring (full scope)
- Biostats including statistical assumptions for the study and SAP development
- Study feasibility assessment
- Study insurance
- Consulting support regarding the study design, including external consultations with a notified body in terms of study design preferred in view of future application for CE certification for the perfusion solution NanOX
- (Important!) Rental and provision to the sites of the renal graft hypothermic machine perfusion devices (for 3 and for 4 devices) for approximately 12-15 months
- Support for setup and management of the DSMB
- Sites qualification and contracting
- Roughly estimated pass through costs (including licences)
- Clinical laboratory assessments in local laboratories (including e.g. blood chemistry, hematology, typical immunological assessments for renal graft recipients)
- Imaging investigations (typical for renal transplantation)

The costs for remaining services and activities should be presented in a way allowing for at least general understanding of the costs of the key components, like project management, PV, DM and eCRF set-up, Trainings, study start-up , study monitoring, study closure, regulatory.

Please provide your budgets in 2 scenarios – as explained below in the section "Draft study design".

(INITIAL) DRAFT STUDY DESIGN

At this moment we have only very initial plan regarding the trial design, so the assumptions provided underneath need to be understood only as our initial concept which will be subject to critical review and adjustment going forward.

Study location: Poland

Number of sites: 3 (this is the number of sites in which the transplant surgery will be performed, but the renal grafts will be collected at an undefined number of hospitals in Poland which will not be contracted, and will not be formally involved in the study). The Sponsor has already pre-identified 3 sites, so there is currently no need to plan search of new sites by the CRO (and no need to allocate budget on such task).

Number of study participants with the kidney (treated or control) transplanted:

(Note: "treated" means kidney perfused with NanOx solution before transplantation, "control/SoC" means standard of care – simple hypothermia for regular kidneys, and machine perfusion for extended criteria donor's kidneys)

Scenario #1: 30* (15 treated + 15 control/SoC)

Scenario #2: 50* (25 treated, 25 control group)

*Early drop-outs, i.e. within first three months post transplantation, will be replaced, so in the Scenario #1 maximum 40 kidneys should be planned as enrolled, and in the Scenario #2 maximum 65 kidneys should be planned to be enrolled.

***Note**: at this stage we assume that the study participants (graft recipients) will be transplanted with one kidney per patient, and that from each organ retrieval, one kidney will be allocated to the treated group and one to the control/SoC group, unless it is not feasible.*

Intervention: perfusion of kidneys collected from DBD donors (potentially also from DCD donors, but you do not need to consider such option at present) with experimental perfusion solution NanOX (classified as medical device).

Important non-study procedure involved:

the renal grafts (either perfused with NanOx or treated in a SoC way) will be transplanted to graft recipients (patients with renal insufficiency) according to their qualification, availability, agreement to participate in the trial, and taking into account the national waiting list. The transplantation surgery, follow-up clinical treatment and monitoring will be performed as part of normal standard healthcare procedure with trial-specific assessments added on top of the SoC.

Randomization and blinding

The allocation to the treated group/NanOx or to the control/SoC graft perfusion **will be randomized** and the **arm assignment will be unblinded for the site staff and study team but blinded for the study participants**. We consider partial blinding of the site staff, i.e. blinded clinical evaluator/ Sub-Investigator, but this is yet to be discussed.

Timelines:

1. *Kidney graft collection and processing (in total approx. up to 18 hours from organ retrieval)*

The process flow:

Kidneys retrieved from the donor at an external hospital* – > kidneys stored in simple hypothermia for up to 4 hours and transported from the external hospital to a study site -> kidneys storage/perfusion with NanOx or in SoC for approximately 12 hours (TBD) at a study site -> kidneys transplanted to the patients recruited/consented to the trial.

*Note: surgical team from a study site will travel to the external hospital to perform the surgery – kidneys retrieval from the donor, then they will come back to the study site with the organs maintained in a classic cold storage; it is not sure if the Sponsor will need to cover the costs of the travel, surgery, and cold storage transportation, or they will be considered as SoC and will be covered by a public payer (that seems to be a more likely scenario). **If you consider that it is likely that the Sponsor will need to reimburse the costs of the surgical retrieval of kidneys, and their transportation to the study site, please estimate the costs of such procedure as separate position.**

2. Study participants:

a) Screening period (duration– up to 24 hours) (Day: -1):

Identification of eligible potential recipients from the national waiting list within the reach of the study sites -> pre-qualification to the transplantation as per national procedures/SoC -> offering the initially qualified recipients option to participate in the trial (this step will be repeated until a patient consenting to join the trial is found) or remaining on the national waiting list

b) Kidney transplant surgery performed at one of the study sites – Day 0

As indicated earlier, the plan is to transplant at approximately the same time one kidney (treated with NanOx) to one recipient and the second kidney (SoC) to the second recipient – both recipients having consented to the trial.

c) Study visits (note: per SoC in-patient for at least 2 weeks post-surgery, then per SoC visits in the hospital every 1-2 weeks initially)

Day 1, Day 2, Day 3, Day 5, Day 7, Day 10, Day 14, Day 21, Day 28/Week4 (visit with optional biopsy), Week 6, Week 8, Week 10 (phone visit), Week 12 (Month 3, visit with per protocol biopsy), Month 4-5, Month 6, Month 7-8 (phone visit), Month 9, Month 10-11 (phone visit), Month 12 (visit with per protocol biopsy)

Up to 2 ad-hoc study visits e.g. required due to safety issues, should be planned in the budget.

No hospitalization is required due to study procedures so no hospitalization costs should be expected except for those required due to adverse events.

Costs of hospitalization days due to logistics* and/or social reasons should be planned as optional PTC costs.

Reimbursement of travel and hotel costs should be taken into account with assumption that 80% of patients will need to travel 100-300km, and 50% of patients will require one-night hotel stay for visits from Day 21 (included) onwards.

*Note: it is expected that qualified graft recipients may live in distant parts of Poland, in some cases even requiring travelling by plane to the study site for the study visits.

Two interim analyzes planned:

Simplified Interim Analysis (1) planned after the last participant completes Month 1

Interim Analysis (2) planned after the last participant completes Month 3

Independent Data and Safety Management Board is planned (3 members) to monitor the trial.

Assessments and clinical investigations:

A. Kidney before transplantation:

- Ultrasound before organ retrieval (unless done as part of SoC), organ biopsy after organ retrieval but before start of the organ perfusion or SoC storage, additional biomarkers TBD

- organ biopsy after the perfusion/SoC storage but before its transplantation

B. Study participants:

Before transplant surgery:

- routine laboratory analyzes

- additional blood samples collected for trial -specific testing (TBD)

- routine (as per SoC) pre-surgery imaging diagnostics, at least abdominal and pelvic ultrasound

- ECG

After the transplantation:

- routine lab and imaging investigations as per SoC

- additional blood samples collected for trial -specific testing (TBD)

- ad-hoc additional diagnostics in case of complications, as per SoC, including e.g. ultrasound +/- with contrast, CT +/- with contrast, doppler ultrasound)

- As indicated earlier: at Day –1, Day 0, M3 and M12 per protocol kidney biopsy + transplanted kidney ultrasound, on Day 0, M1, M3, M12.

At M1 optional kidney biopsy.

Central laboratory for clinical assessments is NOT planned (local labs and imaging will be used).

Centralized pathology assessment is planned of the organ biopsy material. Please take into account the cost of 2+1 pathologists performing the assessment including consensus meeting**. It is assumed that 2 pathologists will be from Poland and the third one can be either Polish or an international (preferably European) kidney transplant pathology expert.**

Other important study procedures:

It is planned that the kidney perfusion with NanOX will be performed with a machine perfusion device (capable of hypothermic perfusion). CRO should assume that the CRO will be expected to provide the study sites with such device for the duration of the recruitment phase. **Therefore the ballpark should preferentially include separate position for the cost of such equipment (rental).**

Study calendar (TBC):

First patient in (first transplanted kidney) – Q3 2027

Last patient in – June 2028

Last patient Out- July 2029

FINAL REMARKS

Please provide you proposal to:

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