Working with European MedTech Industry to create a novel medical device: experiences form the European Nightingale Precommercial Procurement Project (727534)

A Guide for prospective users of the European Commission's **Precommercial Procurement** funding scheme to stimulate healthcare innovation

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For The Nightingale Project Steering Committee:

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Content

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Introduction

Several years ago, the European Commission started a new project to stimulate European Technological innovation by allowing the prospective users of novel technological solutions to societal problems to direct European innovation subsidies to competing industries (start-ups, SMEs and larger corporations), and work closely with these - competing - industrial partners to develop solutions that best meet the societal need. The envisioned prospective end-users are typically large public bodies or not-for-profit organizations, for example in the Nightingale project: a consortium of five large European University Medical Centres.

A hallmark of the Precommercial Procurement is that the prospective users have a clear and well-defined but *unmet need* for a solution to a relevant societal problem. The novel solution to that problem should be realizable within a time span of several years, but it cannot be already available on the market. The buyers group thus needs to demonstrate that they have thoroughly searched the market and were unable to find any solution that conforms to their specifications. Yet, at the same time, it is not advisable to 'ask for the moon', by requesting solution that is highly unlikely to materialize within a time span of 3 to 4 years. In this way, the future users and the developers of the new solution interact during the entire development cycle, and the likelihood of achieving a good match between the users' needs and the new solution is increased.

The four phases of a typical Precommercial Procurement project

Phase 0 – a precommercial project starts with a period of intense communication between the procurers (the 'buyers group') and potentially interested industries, companies or public-private consortia, during a so-called 'Open Market Consultation'. This takes the form of joint meetings, digital communications (website, email, social media, webinars) and face-to-face interaction to clarify the need for the requested solution and its scope. This process should help the buyers group to refine its final Call for Tender for a better match with what industry believes is realizable with current cutting-edge technologies and solution and – importantly – within the allotted time span for the project. A key focus is to understand and describe the challenges and unmet need at hand – not the solutions. The Open Market Consultation Process and preparation of the final Call for Tender can take up to one year in total. The last stage is to officially publish the Call for Tender on the EU TED (Tender Electronic Daily) website (https://ted.europa.eu) and advertise the call as widely as possible to reach any potentially interested and capable industrial partner in Europe.

Phase 1 – After the time to submit proposals in response to the Call for Tender has passed, the buyers group selects from all applications a number of the most appealing proposals to develop these into a detailed Technical Plan, Business Plan, including Plans for commercialization. In the case of *Nightingale,* the challenge to industry was to develop a user-friendly wireless wearable personal patient monitoring system combined with an intelligent clinical decision support system. To properly evaluate the tenderers' proposals – and during the later stages their

prototype solutions – the *Nightingale* buyers group decided to form an evaluation committee in each of their five participating academic hospitals, which independently evaluated every tender proposal. In each local evaluation committee, with a cross competence representation; we invited at least one patient, a nurse, a doctor, a medical technology expert, a business expert and an IT specialist. By combining the scores from evaluations in each of the five hospitals, we selected from 26 original submissions (16 valid applications) 9 proposals for further development. Each tenderer received a limited amount of funding for 3 months to develop a detailed outline for their project, as explained above.

Phase 2 - The next stage in PCP is to select a number of tenderers and offer them a contract to actually develop a prototype solution, that can be evaluated by the buyers group. In case of the Nightingale project, there was a projected budget available to fund 7-9 tenderers to develop a detailed project plan within a time span of three months during Phase 1. Based on the offers from the tenderers, we selected 9 tenderers to enter Phase 1. Each of these 9 project plans was then evaluated by the same committees in each of the 5 academic hospitals.
Four tenders were clear favourites in each hospital; each of these tenders proposed to develop a unique novel *reusable* wearable with extended functionality and develop the software for clinical decision support. Prospective tenderers knowledgeable in the field of AI had warned us that developing valid clinical decision support systems requires a very large amount of well-curated well-organized clinical data. As there are currently no such data sets available from wearable sensors in either hospital or home settings, we had to accept that the initial iterations of the clinical decision support systems were to be based on heuristic methods and extensive input from knowledgeable clinicians. Before the Phase 2 prototypes were delivered to the buyers group, the Nightingale consortium had already jointly developed extensive test protocols, both for the initial studies in healthy human volunteers (we recruited former hospital patients), consisting both of accuracy measurements against a clinically used ICU monitor as reference standard, and we performed extended 5-day usability tests with the volunteers wearing the device 24/7 in their home settings during their daily activities.

Phase3 – consists of the further development towards a marketable product. In the case of Nightingale, phase 3 also consisted of pre-planned initial clinical tests in real high-risk patients on medical and surgical hospital wards. To be able to compare performance and accuracy against a clinically used reference standard, some centres also measured patient vital signs during their postoperative stay in a high-dependency unit such as the Intensive Care or Post-Anaesthesia Care unit. The Nightingale consortium initially had kept open the possibility of allowing three tenderers to enter Phase 3, depending on the test results and the willingness of tenderers to stay within the project longer at a reduced EU subsidy amount.
The Phase 2 tests had previously revealed that each wearable had remaining technological issues that needed to be satisfactorily addressed before the start of the clinical testing in real patients, but two solutions were clearly superior, both in terms of functionality and test results (Emfit and Checkpoint Cardio).
The two contracts for Phase 3 were awarded in November 2019, with the express provision that remaining data communication issues needed to be resolved. We demanded that both communication from sensor to smartphone or dedicated relay device (all tenderers used

Bluetooth LE as transmission protocol) and also from the smartphone/relay device to the server (via 3G/4G and WiFi) should be robust. In the summer of 2020, after Europe had already dealt with Covid-19 for 6 months, one of the tenderers (Emfit) informed us that – due to personnel shortages and unanticipated technical issues - they were unable to resolve all remaining issues in time for the planned clinical tests in high-risk hospital patients, scheduled to start in October 2020. Because the consortium had made an express declaration to each tenderer that we would not subject consenting patients to wearing sensor devices that are not yet developed far enough for clinical testing, we could only allow the Checkpoint Cardio Nightingale solution to enter the clinical test phase in the five participating hospitals. Each hospital collected extensive data from 25 of their high-risk patients for up to 14 days, for a total of 125 patients and thousands of hours with continuous vital signs registration.

The results of the clinical tests with the Checkpoint Cardio system are presented in more detail in the Nightingale public final report. Briefly, the Checkpoint Cardio Nightingale system was able to accurately track heart rate, ECG, respiratory rate and temperature. Oxygen saturation and blood pressure availability and accuracy was dependent on the presence of a valid continuous pulse plethysmogram waveform (PPG) derived from a sensor worn on the ear. In several cases, the CPC system was able to detect deterioration events hours before the event was noted clinically. In case of new onset atrial fibrillation (a high irregular heart rate), this was often missed by current routine nursing vital signs checks. This is an important observation, because in high-risk surgical patients new onset of atrial fibrillation is a strong predictor of serious surgical complications. There were several usability issues with the CPC ear sensor that made it less suitable for continuous use in active patients. In response to the usability feedback from the Nightingale hospitals, the company has started an intensive program to develop a novel PPG sensor that can be worn on the chest and does not hinder the patient. We found that the presence of a wire connecting the ear sensor to the chest-worn CPC device was an obvious cause for sensor displacement of and motion artefact, as vigorous head movement could easily result in sensor dislodgment. We found that these initial observations on accuracy and patient usability are extremely important. Such essential data that could never have been obtained, had the sensor only be tested for short time periods in healthy volunteers. We believe that this should have implications for future standardized test protocols for medical wearables, as many devices on the market today have been insufficiently tested for accuracy and usability, especially when they are to be used over longer time periods in sick patients.

Lessons learned from performing a Precommercial Procurement project

Based on our experiences within the Nightingale Project over the last five years, we believe that PCP is a potentially very useful and novel means that allows industry to collaborate and innovate with health care in a productive way, while preserving competition - by not tying one single company to a group of hospitals. It allowed doctors and nurses from the participating hospitals to freely share ideas with industry without having to declare a conflict of interest (the advice was available to all tenderers and publicly shared).

As an example of such open sharing of ideas and concepts, during Open Market Consultation, we suggested to all interested parties to consider using information from an embedded accelerometer motion sensor to flag potential signal artefacts in ECG or PPG waveforms. In addition, we told industry that – if battery life would become a prohibitive issue for continuous oximetry – we would accept intermittent blood oxygen saturation updates rather continuous measurements. We intensively discussed critical issues with battery life and the need for frail patients to be able to change batteries or sensors themselves. Originally, we insisted that each device would need to be able to function for at least 5 days. However, it must be acknowledged that this demand was based on the *disposable* patch sensors available at the time, that guaranteed a 5 day battery life and then needed to be discarded. During the project it became clear that a daily battery change - provided that it was very easy to do, even for elderly patients – was completely acceptable and allowed better signal quality and continuous transmission of real-time available waveform data (a highly useful feature of the Checkpoint Cardio system that allows ECG and PPG waveform observation and arrythmia detection by dedicated personnel in a nursing station, or a remote medical observation centre).

Considerations for healthcare procurers

Some points to consider for healthcare procurers when embarking on Precommercial Procurement to stimulate the development of a novel medical device.

Developing a medical device within a (competitive) PCP allows healthcare personnel to collaborate with industry while limiting conflict of interest

Innovations in drugs and medical devices for diagnostic and therapeutic applications are often driven by doctors and other users with an *inventors' streak* or by industry, but most often successful collaboration between the two is the critical factor. Unfortunately, once a doctor collaborates closely with industry, *conflict of interest* (COI) can threaten the validity of scientific research. The owner of the intellectual property rights typically benefits from future sales. If this person also performs clinical validation studies, bias can creep into the research or influence future purchasing decisions. PCP is a unique mechanism that allows doctors and nurses to collaborate with industry without a priori committing to a single product and/or company. Because PCP takes pains to assure fair competition and the doctor is in the role of procurer rather than that of producer, COI is minimized.

Timelines: developing truly innovative healthcare solutions cannot always adhere to rigid PCP project timelines

The Nightingale consortium partners were well aware that they were asking a lot from the tenderers when allowing only three years to develop a fully-fledged hardware/software system for remote wireless wearable patient monitoring that incorporated novel sensor modalities (such as continuous mobile oxygen saturation and cuffless non-invasive blood pressure) as well as the ability to monitor these signals remotely in the home setting. Nonetheless, we have now learnt that such short timelines may disadvantage innovative companies, especially if they have to start from scratch. As we have seen, unanticipated personnel problems (Covid-19) or unanticipated hardware issues with early prototypes can set back a company many months. On the other hand, the buyers group needs to stay within the pre-agreed project timelines and start its clinical testing no later than a fixed date. As a result, these PCP

timelines do not allow the buyers group to grant extensions to the companies involved. We suggest it may be advisable to consider allowing longer project timelines for riskier complex 'high-stakes' PCP projects.

Start-ups versus MedTech giants; 'anti-shelving' clauses
An unresolved issue is whether large multinational companies should be allowed to enter PCP projects. During the Open Market Consultations, several multinationals conveyed to us that they really considered the amount of PCP funding extremely small, and their main incentive to join the PCP was to have access to the combined clinical experience within the buyers group. In contrast, PCP funding was essential for most start-ups and SMEs. For them, being able to obtain the maximum amount PCP funding (obtaining a contract for Phase 1, Phase 2 and Phase 3) meant the difference between being able to realize their vision for the solution - by hiring the necessary extra personnel - or not even being able to start working on the problem. Some multinational companies objected to a number of standard clauses in the model PCP contract, such as the 'anti-shelving' clauses that demand a company tries hard to bring the product – developed jointly during the PCP – actually to the market. The penalty for not attempting to commercialize the solution is that any IP generated during the project will fall to the buyers group, if, 5 years after the end of the project, no visible commercialization efforts have been made. This was unacceptable to a number of multinational companies, as they feared it could jeopardize any valuable prior background IP that – according to them – would inevitably be incorporated in the solution. In contrast, none of the start-ups and SMEs objected to any clauses in the model PCP contract.

Considerations for MedTech companies

Some points to consider for MedTech companies procurers when embarking on Precommercial Procurement with health care organisations to development of a novel medical device.

Create your own connections with clinicians in a hospital close by
Unlike large MedTech companies that have extensive networks that they developed over many years, start-up companies and SMEs often have only limited collaborative connections to healthcare institutions and access to clinicians, nurses and hospital technicians. During the last stage of a PCP, when there are no longer any competitive bidding processes for contracts, it is easier to share insights freely, but during the first two phases, the buyers group must be extremely careful to treat every prospective tenderer equally, which includes equal provision of information. It is therefore advisable to create a working relationship with a nearby hospital or care organization, to perform prototype testing and to gain better insight into the clinical and technological challenges. During Nightingale, we found that companies with such connections and existing collaborations were more agile and could respond faster to requests and suggestions from the Nightingale consortium partners.

Medical device regulation: when developing a medical device under PCP you should take into account the time needed to comply with European and national regulatory processes (as of May, 2021: the EU Medical Device Regulation)
When seeking permission from national agencies in the Netherlands and UK to perform initial validation of four different sensor prototypes in human volunteers (Phase 2 evaluation), the Nightingale partners and their tenderers ran into unanticipated delays due to the regulatory

processes in the two countries where the initial volunteer tests were to be performed (the Netherlands and United Kingdom). In short: producing a complete full Investigational Medical Device Dossier (MDD), obtaining the necessary insurance certificates and regulatory approval was completely new and complex for three out of the four Phase 2 tenderers, and the process took many months to complete.

It is important to realize that for national regulatory authorities, it is not really relevant whether the devices are considered extremely low risk or will not be tested on patients in a clinical situation. As a result of these regulatory delays and tenderers trying to catch up – sometimes by hiring experts in medical device regulation – the Nightingale project incurred a delay of several months and the consortium partners decided to apply for a 6-month extension to the project in the fall of 2019 (please note this was before Covid-19).

Interfacing your product with Hospital Electronic Medical records

When a medical device consists (mainly) of software, for example, a clinical decision support system, it is critical that this product can both accept data from and write data to the hospital EMR. This is no trivial matter, as there are many different vendors with very different systems. Although many EMRs – at least in theory - allow such bidirectional communication using standard interfaces such as HL-7 and FHIR, in reality this will often be only possible by creating time-consuming costly bespoke software solutions. This seriously hampers the integration of innovative software solutions from start-ups and SMEs with EMRs. Moreover, for many reasons - including security and efficiency - it is not desirable to transfer very large amounts of patient data out of the EMR, making it necessary for third-party software systems to work within the hospital EMR environment as 'plugins', either working directly with EMR data, or processing data that has been routinely copied into a health system 'data lake'.

Finally, having 'parallel' systems, where care workers must separately enter patient data into each system (once in the EMR and once into the system from a third-party vendor) are unacceptable. Nurses and doctors are already overwhelmed with data entry tasks. They will simply not accept the extra work resulting from such redundant data entry.