

## **Title: Metrology to enable rapid and accurate clinical measurements in acute management of sepsis**

### **Abstract**

Sepsis affects approximately 30 million people a year and is the cause of 6 million deaths worldwide, (more than the number of deaths associated with bowel, breast and prostate cancer combined). It represents a clinical emergency where the speed and accuracy of diagnosis directly and substantially reduces mortality. However, there is currently a lack of rapid and accurate tests to diagnose sepsis. While attempts have been made to tackle this diagnostic shortfall, the uptake has been slow. This has been exacerbated by the absence of a metrological framework for ensuring clinical test accuracy and reproducibility. Therefore, metrology for such rapid and accurate clinical measurements is needed to support the identification of sepsis and to improve sepsis patient survival.

### **Keywords**

Infection, sepsis, biomarker, antimicrobial resistance, diagnosis, point of care

### **Background to the Metrological Challenges**

In 2017, the World Health Assembly and the World Health Organisation (WHO) made sepsis a global health priority, by adopting a resolution to improve, prevent, diagnose, and manage sepsis. Sepsis is a life-threatening condition that arises when a dysregulated response to infection results in multi-organ dysfunction or failure. Sepsis accounts for approximately 50 % of intensive care bed days and has a mortality rate of >30 %. Time to diagnosis is the critical factor in managing sepsis: the window for initiating appropriate treatment is > 6 hours. Survival is also linearly correlated with time to antibiotic treatment, and each hour delay increases the chance of mortality by 7.6 % making fast and accurate diagnosis essential. However, sepsis is easily confused with other conditions, a fact exacerbated by a lack of accurate and rapid diagnostic tests for it.

To address this, new WHO guidelines urge member states to promote research aimed at diagnosing and treating sepsis and this has led to several initiatives such as the International Sepsis Forum and The European Sepsis Academy.

Early diagnosis of sepsis depends on the identification of a range of non-specific symptoms that are easily confused with a variety of other common conditions. Existing diagnostic guidelines, combine symptoms and signs to estimate the likelihood of sepsis and guide the choice of treatment. Currently, these methods aim to stabilise patients while also treating them with broad-spectrum antibiotics based on the assumption that there is a bacterial cause. Crucially, if a patient is to survive, then such clinical interventions must be rapid, however the current state of the art means that this must be done without knowledge of the microbial aetiology.

In more challenging clinical situations, such as intensive care, diagnosis can be further complicated by a patient's existing conditions, which may render them susceptible to a much wider range of bacterial, viral and fungal pathogens. Further to this, antimicrobial resistance can hinder the treatment of sepsis as current tests cannot detect resistance fast enough. Pathogenic cause and antimicrobial resistance should be considered during sepsis treatment, however current diagnostic tests do not support this. Instead these tests can be subdivided into those that (i) biomarker aid sepsis diagnosis and (ii) directly identify the underlying microbiological aetiology. Therefore, advancing the state-of-the-art depends on concomitantly improving existing sepsis test accuracy and speed whilst also developing the next generation of biomarker and microbiological tests.

## Objectives

Proposers should address the objectives stated below, which are based on the PRT submissions. Proposers may identify amendments to the objectives or choose to address a subset of them in order to maximise the overall impact, or address budgetary or scientific / technical constraints, but the reasons for this should be clearly stated in the protocol.

The JRP shall focus on the development of traceable and reproducible measurements for the acute management of sepsis.

The specific objectives are

1. To improve the traceability and accuracy of measurements of established biomarkers, (e.g. C- Reactive Protein and Procalcitonin), used for sepsis diagnosis. This should include the development of validated methods and traceable materials for single and simultaneous, multiple sepsis biomarker measurements, as well as the definition of reference ranges of biomarkers in patients who are at risk of sepsis.
2. To develop a metrological and quality assurance framework for current methods used to confirm the microbiological aetiology of sepsis. This should include an evaluation of the accuracy and reproducibility of current methods and the quantification of target levels of accuracy and reproducibility required for quality assurance.
3. To develop improved reference methods (e.g. lower uncertainties and better reproducibility for methods such as haematological, biochemical, microbiological or immune assessment) for rapid near patient (point of care) testing for sepsis. Such methods must be suitable for accreditation and meet EU Directive 98/79/EC regulations. In addition, to develop an associated proficiency scheme for the point of care testing platforms, specifically for non-specialist users (e.g. healthcare workers without laboratory training).
4. To develop and qualify a metrological framework underpinning new and innovative methods for early sepsis diagnosis (e.g. metabolomics and metagenomics). This should include an evaluation of their accuracy and reproducibility and the identification of target levels of both, for each method.
5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain (Clinical Laboratories, Hospitals), standards developing organisations (ISO/TC 212, CCQM Working Groups on Nucleic Acid Analysis (NAWG), Protein Analysis (PAWG), and Cell Analysis (CAWG), National Institute for Biological Standards and Control (NIBSC) Standardisation of Genome Amplification Techniques and Serology/Standardisation of Infection Diagnostics (SoGATS/SID), and end users (e.g. the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), European Society of Intensive Medicine (ESICM), and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC).

These objectives will require large-scale approaches that are beyond the capabilities of single National Metrology Institutes and Designated Institutes, and it is expected that multidisciplinary teams will be required. To enhance the impact of the research, the involvement of the appropriate user community such as medical practitioners, hospitals and industry is strongly recommended, both prior to and during methodology development.

Proposers should establish the current state of the art, and explain how their proposed project goes beyond this.

EURAMET expects the average EU Contribution for the selected JRPs in this TP to be 1.8 M€, and has defined an upper limit of 2.1 M€ for this project.

EURAMET also expects the EU Contribution to the external funded partners to not exceed 35 % of the total EU Contribution across all selected projects in this TP.

## Potential Impact

Proposals must demonstrate adequate and appropriate participation/links to the “end user” community, describing how the project partners will engage with relevant communities during the project to facilitate knowledge transfer and accelerate the uptake of project outputs. Evidence of support from the “end user” community (e.g. letters of support) is also encouraged.

You should detail how your JRP results are going to:

- Address the SRT objectives and deliver solutions to the documented needs,
- Feed into the development of urgent documentary standards through appropriate standards bodies,
- Transfer knowledge to the medical and health sector.

You should detail other impacts of your proposed JRP as specified in the document “Guide 4: Writing Joint Research Projects (JRPs)”

You should also detail how your approach to realising the objectives will further the aim of EMPIR to develop a coherent approach at the European level in the field of metrology and include the best available contributions from across the metrology community. Specifically, the opportunities for:

- improvement of the efficiency of use of available resources to better meet metrological needs and to assure the traceability of national standards
- the metrology capacity of EURAMET Member States whose metrology programmes are at an early stage of development to be increased
- organisations other than NMIs and DIs to be involved in the work

### **Time-scale**

The project should be of up to 3 years duration.