Publishable Summary for 18HLT03 SEPTIMET

Metrology to enable rapid and accurate clinical measurements in acute management of sepsis

Overview

The overall aim of SEPTIMET is to improve the speed, accuracy and reproducibility of diagnostic tests for the identification and treatment of sepsis. Sepsis is a life-threatening condition where time to diagnosis is critical to patient outcome. This clinically driven project will develop and characterise reference systems to support confident application of existing tests and investigate metrological support required by new, innovative approaches that offer the next generation of diagnostic solutions. Moreover, the outcomes of the project will also support IVD manufacturers in meeting developments in EU diagnostic regulation.

Need

Today's physicians do not have sufficiently fast or accurate diagnostic tools to identify and manage septic patients. Sepsis must be treated within hours to avoid potentially high mortality or morbidity. Yet today's diagnostic deficit is a major contributor to the devastating impact of sepsis, resulting in ~700,000 European deaths a year. Faster and more accurate tests are needed to diagnose and guide treatment of sepsis Metrological support is needed to improve the performance of existing methods and enable the efficient translation of new near patient solutions.

Biomarkers exist that could diagnose sepsis, but uncertainty over accuracy has led to variable uptake. Reference measurement procedures to support the traceability of fast biomarker tests, alone and in combination do not exist (objective 1), and the possibility of applying machine learning algorithms to identify solutions for sepsis management requires further investigation. The main method for guiding treatment, culture, is too slow to realistically help sepsis patients. Therefore, a metrological framework is required, which currently does not exist, to support faster laboratory tests to guide treatment (objective 2). Reference measurement procedures are also needed to support rapid near patient test manufacturers in meeting the new Regulation 2017/746 (objective 3). In addition, the accuracy and metrological requirements of new and innovative 'omics' methods that could deliver more sensitive and specific tests to aid sepsis patient survival needs to be assessed (objective 4).

SEPTIMET will ensure that metrological principles will contribute to a solution to this global health issue that affects 30 million people a year leading to 6 million deaths. The clinically focussed consortium will achieve this by developing the underpinning metrological concepts to facilitate the development and application of the rapid, accurate tests desperately needed to improve sepsis survival.

Objectives

The overall goal of the project is to support traceable measurement of established and new biomarkers to rapidly diagnose and guide treatment 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 will include the development of validated methods with target improvements to measurement uncertainties of <20 % 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 cause of sepsis. This will 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 to reduce uncertainties to <30 % and enhance reproducibility of rapid near patient (point of care) testing for sepsis (diagnosis and to guide treatment). 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. transcriptomics) and treatment guidance (e.g. 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, SoGAT), and end users (e.g. ESCMID, ESICM, IFCC).

Progress beyond the state of the art and results

Improving the traceability and accuracy of measurements of established biomarkers

To date, identification of sepsis relies on well-established but non-specific measurements like temperature. Several studies have suggested procalcitonin (PCT) is a more specific marker for differentiating between infectious and non-infectious causes, but despite this hospital uptake is variable. A possible reason for this is poor calibration leading to reproducibility problems. A previous EMPIR project (15HLT07 AntiMicroResist) introduced the first initiative to construct an internationally agreed reference system for PCT. SEPTIMET will build on this by developing a primary reference measurement procedure to implement SI traceable measurement for PCT. SEPTIMET will also investigate the accuracy of panels of multiplexed biomarkers and use of uncertainty in the wider application of data science to develop algorithms using diagnostic data to better manage sepsis.

Development of a metrological and quality assurance framework for current methods used to confirm the microbiological aetiology of sepsis

Microbiological culture, the gold standard for identifying the cause of most bacterial infections takes more than 24 hours, which is too slow to guide treatment for most sepsis patients. A number of automated solutions have been developed that have fast turnaround times and can confirm microbiological cause with culture or directly from patient samples. However, the support for the development and application of these approaches (such as quantitative reference materials) is in its infancy. SEPTIMET will develop a metrological quality assurance framework to support the routine application of these methodologies.

Development of improved reference methods for rapid near patient (point of care) testing for sepsis

Near patient testing is routinely used in many clinical scenarios in hospitals and the community. However, poor reproducibility and sensitivity currently limits their use in sepsis. SEPTIMET will develop reference methods to enhance the application of such approaches for sepsis testing. This will support confident application of established tests. SEPTIMET will also develop sensitive analytical methods to conduct high accuracy measurements in the patient, providing IVD manufacturers with the results needed to design new tests.

Development and qualification of a metrological framework underpinning new and innovative methods

SEPTIMET will focus on developing the underpinning metrology in three areas of innovation for sepsis management:

1) Frequently sepsis involves bacterial endotoxins released into the blood stream. SEPTIMET will develop direct measurements of endotoxin in patient blood using a novel biosensor platform based on surface plasmon resonance.
2) Direct metagenomics analysis has the potential to provide detailed information on the causative pathogen and its resistance to antibiotics. However, standard approaches are too slow for sepsis. SEPTIMET will evaluate the likely metrological support needed for rapid sequencing technologies (e.g. the Oxford Nanopore MinION) that potentially provide direct results in less than four hours.

3) Characteristic changes of cell concentrations (e.g. leukocytes, endothelial cells) and cellular response to systemic infection (e.g. changes in antigens, RNA or neutrophil extracellular traps induced by endotoxins) are among the potential cell-based sepsis markers. SEPTIMET will explore the possibility to measure these cells using advanced flow cytometry, microscopy and transcriptomic strategies.

Impact

This project inherently responds to the needs of healthcare sectors, where its impact will be strongest. Although different sectors can benefit from the project results, the fast diagnosis to guide rapid treatment of sepsis and therefore improved sepsis survival remains the main focus for impact where this coordinated metrological programme will have major long-term contributions.

Impact on industrial and other user communities

SEPTIMET will develop new biochemical, molecular and cellular/immunological National Measurement Institute (NMI) measurement capabilities and reference systems that will directly assist IVD manufacturers and clinical end users. Early impact and fitness for purpose will be ensured through the direct involvement of the four hospitals as externally funded partners. Routes to impact will be ensured via a project stakeholder network

and wider partner involvement in organisations and learned societies within the countries and specialisms they represent.

This project will also assist IVD manufacturers to transfer technology to the clinic (including near patient tests). Industrial stakeholders in the IVD domain will benefit from the development of SI traceable reference measurement procedures for biomarkers to identify sepsis patients and guide their treatment. IVD manufacturers will be able to use project findings to support demonstration of test development and routine performance and meet regulatory requirements. In addition, manufacturers and providers of external quality assurance / proficiency testing schemes will also be able to leverage such new metrological frameworks.

Impact on the metrology and scientific communities

As a result of SEPTIMET the metrological community will expand its remit into clinical diagnostics of infectious diseases, especially with respect to biomarkers and point of care instrumentation; many of the faster methods currently used in the management of sepsis have unclear reproducibility as metrological concepts are generally not applied. The higher order methods developed in this project will have a significant impact on advancing the SI system for biological measurements in general e.g. in developing molecular methods for bacterial identification to support rapid near patient testing. This project brings together European NMIs, each contributing in their own area of expertise to complement a critical body of inputs guaranteeing the delivery and further development of the objectives through an improved system of metrology.

This project will develop reference methods specifically targeted at clinical samples. These higher order measurements will define the accuracy of a variety of analytes speculated to be used in sepsis management. The route to impact will be via presentations, workshops, webinars and open access publications and guidance documents. This will ensure findings are directed at and integrated with the stakeholder research priorities. Metrological findings will also be incorporated into medical microbiology masters programmes ensuring the next generation of scientists are prepared for future diagnostic challenges.

Impact on relevant standards

SEPTIMET is expected to have a direct positive effect on the effective implementation of EU IVD regulations both in meeting currently requirements under Directive 98/79/EC and in assisting the transition process to the new regulation, Regulation (EU) 2017/746, currently under way and due to be in place by spring 2022. An example is the need for traceability of the values assigned to IVD calibrators to reference materials and/or reference methods of higher order which are not currently available for many tests used in sepsis management.

Partners hold committee membership and/or Working Group convenor status in a range of relevant international organisations that are active in the area of enhancing the comparability of laboratory medicine including IFCC and JCTLM as well as sitting on ISO TC212 (Clinical laboratory testing and IVD test systems), with WG2 on reference systems for Protein Biomarkers and WP3 on molecular microbiology. WP4 will also address standards for newer technologies such as next generation sequencing for which guidelines are currently being drafted (e.g. ISO/WD 20397). Partners are also involved in driving the development of specific working groups to address issues associated with sepsis (e.g. IFCC WG-PCT and CM-MD).

Longer-term economic and social impacts

The potential economic impact of improving sepsis outcomes in healthcare terms is stark. Sepsis accounts for ~50 % of intensive care unit (ICU) bed days, which costs ~1700 € per day, each sepsis patient in the ICU costs almost 30,000 € to treat. Sepsis is estimated to cost Europe and estimated 18 billion € a year. More accurate application of existing diagnostic methods as well as efficient development of innovative cutting-edge solutions

will identify sepsis patients earlier, reducing treatment costs and those associated with prolonged hospital stay. Sepsis is usually treatable if accurate timely diagnosis is available. Yet incorrect treatment often administered in the absence of such tests reduces the patient's chances of survival while also increasing the risk of antimicrobial resistance.

In addition to the economic benefits from the improved healthcare of the population, commercial benefits linked to IVD companies wishing to develop newer fast diagnostic assays for sepsis (and other medical emergencies such as meningitis) will benefit from improved validation frameworks and RMs developed within the project. This will empower both existing European commercial providers of centralised laboratory tests but also the growing number of providers of near patient point of care methods. Given the growing market size in the overall Med Tech sector, the lack of metrological concepts to de risk pre-clinical research, and support translation and application of rapid diagnostic tests represents a significant bottle neck. The outputs of this project will aid in reducing the associated risks by implementing the required reference measurement systems. This project aims to address this gap while providing a sufficiently large-scale European effort that will be able to support major downstream economic impact.

As well as patients, long-term beneficiaries from this project include doctors, nurses and other healthcare professionals who will benefit from improved outcomes of their clinical decisions and better health service performance. Epidemiologists and public health laboratories will benefit from improved diagnostic accuracy of patient identification due to better accuracy and comparability of the surveillance data across Europe.

The current incidence of sepsis in Europe is 3.4 million people a year. Better management of these patients, enabled by high accuracy measurements, underpinned by the metrological concepts developed by SEPTIMET, could reduce the devastating mortality and morbidity they currently face.

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<tr><td colspan="2">Project start date and duration: September 2019</td><td>36 months</td></tr>
<tr><td colspan="3">Coordinator: Jim Huggett, LGC Tel: +44 (0) 208 943 7655 E-mail: Jim.Huggett@lgcgroup.com
Project website address: https://www.lgcgroup.com/our-programmes/empir-septimet/</td></tr>
<tr><td>Internal Funded Partners:
1. LGC, United Kingdom
2. LNE, France
3. METAS, Switzerland
4. NIB, Slovenia
5. NPL, United Kingdom
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