


BMJ Open Investigating nanomotion-based technology (Resistell AST) for rapid antibiotic susceptibility testing among adult patients admitted to a tertiary-care hospital with Gram-negative bacteraemia: protocol for a prospective, observational, cross-sectional, single-arm study

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ABSTRACT

Introduction Effective treatment of bloodstream infections (BSIs) is relying on rapid identification of the causing pathogen and its antibiotic susceptibility. Still, most commercially available antibiotic susceptibility testing (AST) methods are based on monitoring bacterial growth, thus impacting the time to results. The Resistell AST is based on a new technology measuring the nanomotion caused by physiologically active bacterial cells and detecting the changes in nanomotion caused by the exposure to a drug.

Methods and analysis This is a single-centre, prospective, cross-sectional, single-arm diagnostic accuracy study to determine the agreement of the Resistell AST on Gram-negative bacteria isolated from blood cultures among patients admitted to a tertiary-care hospital with the reference method. Up to 300 patients will be recruited. Starting with a pilot phase, enrolling 10%–20% of the subjects and limited to *Escherichia coli* BSI tested for ceftriaxone susceptibility, the main phase will follow, extending the study to *Klebsiella pneumoniae* and ciprofloxacin.

Ethics and dissemination This study has received ethical approval from the Swiss Ethics Committees (swissethics, project 2020-01622). All the case report forms and clinical samples will be assigned a study code by the local investigators and stored anonymously at the reference centre (Lausanne University Hospital). The results will be broadly distributed through conference presentations and peer-reviewed publications.

Trial registration number ClinicalTrials.gov Registry (NCT05002413).

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Rapid antibiotic susceptibility testing recording fluctuations of metabolically active bacteria responding to drug exposure.
- ⇒ Outcome comparison with both clinical and diagnostic endpoints.
- ⇒ Real-life clinical data on a target hospital population.
- ⇒ Preliminary agreement data obtained in a preclinical phase.
- ⇒ Non-randomised observational clinical study.

INTRODUCTION

Background and rationale

Bloodstream infections (BSIs) represent the main cause of sepsis and septic shock, associated with high morbidity and mortality.^{1 2} Previous studies showed an incidence of BSIs up to 190 per 100 000 population, with increasing trends both in Europe and the USA.^{1 3–5} Effective treatment of BSI is relying on the ability to promptly identify the causing pathogen and its antibiotic susceptibility.^{6 7}

Timely antibiotic prescription and reduction of the antimicrobial spectrum are the cornerstones of antimicrobial stewardship programmes, as they reduce the selective pressure on bacteria limiting the spread of multidrug-resistant pathogens.⁸

Most commercially available antibiotic susceptibility testing (AST) methods are based on monitoring bacterial growth, representing the main limitation for the speed of



such tests.^{9 10} Other molecular technologies, including sequencing analysis (Sanger, pyrosequencing), are available but their use is mainly limited by the higher costs, for being determined by mutations or resistance-associated genes and due to changes in gene expression. Only few rapid phenotypical technologies have been developed (such as Accelerate Pheno, FASTinov AST) but not necessarily available in each country or not yet commercialised. The current gold standard are broth microdilution or disk diffusion test (Kirby-Bauer Test), which both take about 16–48 hours to yield results.¹¹ Automated systems, such as VITEK 2 (bioMérieux, France) and BD Phoenix (Becton Dickinson, USA), have the advantage of being directly connected to an advanced expert system software for interpretation of results and online data processing, therefore improving the turnaround time to 8–12 hours.¹²

The Resistell AST is a diagnostic tool based on a new nanomotion-based technology for rapid AST. It consists of a device (ie, Resistell Phenotech), single-use disposables, micro-electro-mechanical sensors—microcantilevers (ie, Phenotech Sensors), and software for data acquisition, processing and classification. Resistell AST characterises the bacterial reaction to a given drug by recording low-frequency fluctuations of microcantilevers.^{13–15} These fluctuations are caused by the nanomotion due to metabolically active bacteria and may change upon exposure to a drug. These changes in nanomotion as a response to a drug are growth independent and can be detected long before bacteria replicate.

For the development of the AST, drug concentrations need to be predetermined and introduced in the algorithm, which will render susceptibility results. Categories will be classified into ‘susceptible, standard dose (S)’, ‘resistant (R)’ and ‘susceptible, increased exposure (I)’; Resistell classification into ‘I’ will depend on the number of drug concentrations tested and the reference outcome. In the absence of ‘I’ category for Resistell AST, samples resulting ‘I’ on the reference test will be classified as ‘S’ when compared with Resistell AST.

Resistell AST is expected to decrease the time to AST result to 2–4 hours, depending on the bacteria and antibiotic combination, thus, potentially reducing the time to results by 6–46 hours.

Preclinical development and validation

Before the start of the pilot phase, Resistell AST was developed for *Escherichia coli* and ceftriaxone. The method was optimised to work with bacterial pellets directly from positive blood cultures (PBCs) artificially inoculated (spike cultures) with clinical isolates from the Lausanne University Hospital as well as reference strains acquired from the American Type Culture Collection (ATCC), IHMA Europe Sàrl society, respectively. Direct attachment pellet preparation was used (see the Methods section for details of the procedure), with all experiments performed with 32 µg/mL ceftriaxone. The typical recording for a susceptible strain shows a stagnant or decreasing variance of the cantilever deflection over

time, while resistant strains exhibit an increase upon exposure to an antibiotic. The data can be fitted to an exponential equation resulting in the slope. Extremely susceptible or resistant strains can be differentiated based on a single feature such as the slope of the variance. However, in the clinical setting, we operate with strains of a wide minimum inhibitory concentration (MIC) spectrum and genetic diversity. To classify these strains, reliable classification algorithms sought out by machine learning are necessary as the slope is insufficient to deal with the various nanomotion curves resulting from the strain complexity in the clinic. To be able to classify antibiotic susceptible and resistant isolates, features or sets of features need to be extracted from the nanomotion signal. These features have a single mathematical value for each measured sample and a combination of them can be used to classify all the different susceptible and resistant isolates correctly. In one of the preclinical steps of developing the nanomotion-based AST, we required machine learning to calculate hundreds of thousands of features, select a few and validate these selected features in a procedure called 300 times repeated threefold cross-validation. In this validation (using spiked blood cultures), the dataset is repeatedly split in nanomotion recordings used for training and those used for validation (ratio 2:1). The resulting classification algorithm employs only a few general features and is further tested on a smaller set of anonymised PBCs from patients that were performed in replicates. This step is fast and comparable with the analysis applied in the clinical study.

The initial algorithm for *E. coli* and ceftriaxone was developed in the preclinical phase (concluded April 2021) and trained and validated on a batch of data comprising 706 experiments performed on spike cultures (step 1). This batch of data included two *E. coli* reference strains (‘S’: ATCC-25922 and ‘R’: BAA-2452) and 32 clinical isolates of *E. coli* with various MICs (‘S’: RN-01, RN-02, RN-03, RN-04, RN-08, RN-13, RN-15, RN-19, RN-23, RN-26, RN-27, RN-36, RN-37, RN-42, RN-43, RN-49, RN-52, RN-59, RN-61; and ‘R’: B1, B3, B4, B11, B12, B13, B14, B15, RN-28, RN-29, RN-35, RN-55, RN-64). Reference AST methods were Kirby-Bauer Test and Epsilon-meter Test (E-Test). The training and validation dataset was hence balanced among ‘S’ and ‘R’ isolates with 20 and 14 strains, respectively. Each strain was measured in replicates from the same spiked blood culture and repeatedly on different dates from a different culture. The method’s accuracy on the training dataset estimated using the 300 times repeated threefold cross-validation procedure amounted to 88%, with 89% sensitivity and 86% specificity.

In the second step, the algorithm was tested on a blind batch of data, using bacterial pellets isolated directly from PBCs originating predominantly from the Lausanne University Hospital’s emergency room. The test dataset included 23 pellets of PBC samples from different patients directly measured in technical triplicates or quadruplicates, resulting in 90 Resistell AST experiments.

Twenty of these samples were confirmed as ‘S’ and three as ‘R’ for ceftriaxone using the standard AST methods Kirby-Bauer Test and E-Test, with no strains in the ‘I’ category. For the 90 experiments, the performances were 94.4% category agreement (CA), 1.1% very major errors (VMEs, resistant pathogen classified as susceptible) and 4.4% major errors (MEs, susceptible pathogen classified as resistant) rate, corresponding to 94.4% accuracy, 94.9% sensitivity and 90.9% specificity. However, after implementation of a majority-based voting system between replicates (in case of a tie between replicates, the sample was classified ‘R’), the performance for the 23 PBC samples increased to 95.7% accuracy, 95% sensitivity (95% CI 75.1% to 99.9%) and 100% specificity (95% CI 29.2% to 100%), corresponding to a CA of 95.7% with 0% VME and 4.3% ME.

In this preclinical period, the algorithm has been further improved to cope with additional strains and species/antibiotic combinations that will be addressed in the main phase of the study. Adding more strains in this process of machine learning will result in a more comprehensive and general classification algorithm.

Objectives

This study aims to clinically evaluate the performance of the Resistell AST compared with the reference. The primary endpoint is the correct classification of susceptible samples: ME/sensitivity. For this purpose and to also reach the secondary endpoints, CA, VME rate, mE (minor error, pathogen with an intermediate MIC classified as susceptible or resistant) and turnaround time of the Resistell AST will be evaluated on prospectively collected clinical routine PBC samples by comparison with reference methods. We hypothesise (1) a CA rate $\geq 95\%$, with a VME rate $\leq 3\%$, an ME rate $\leq 5\%$ and an mE rate $< 10\%$ compared with the reference method; (2) a gain in time to result of at least 6 hours (from blood culture positivity for Gram-negative bacteria to obtainment of susceptibility results) compared with the reference method (VITEK 2).

The performance will be based on the comparison with standard comparators, such as Kirby-Bauer and VITEK 2. In addition to ME (which, in absence of ‘I’ category reflects the test ‘sensitivity’) and for a better comparison with other AST methods approved by EUCAST and CLSI, we will also report CA (reflecting the overall ‘accuracy’) and VME (which, in absence of I category, reflects the test ‘specificity’). Using Resistell AST, we anticipate a gain in time to result (TTR, from blood culture positivity to AST results) of at least 6 hours compared with VITEK 2. Hence, we expect a more rapid and narrowed-down effective antibiotic spectrum with the Resistell AST that will potentially aid patient treatment and curb the spread of antimicrobial resistance.

Primary objective

The primary goal of this study is the assessment of ME/sensitivity of the Resistell AST on prospectively collected



Figure 1 The red arrow points to the measurement head, visible and accessible for the operator. The measurement head and chamber are covered with a removable lid (blue arrow).

clinical routine PBC samples by comparison with the reference methods.

Secondary objectives

We will also assess: (1) CA/accuracy, VME/specificity and mE of the Resistell AST on prospectively collected clinical routine PBC samples by comparison with the AST reference methods; and (2) evaluate the differences in TTR with these methods. This last endpoint is further defined in: (a) time from blood culture positivity to Resistell AST results, (b) time from MALDI-TOF MS strain identification to Resistell AST results, (c) time from start to return of Resistell AST results.

MATERIALS, METHODS AND ANALYSIS

Investigational device and materials

The Resistell Phenotech system comprises: (1) a measurement head with a measurement chamber holding the Phenotech Sensor; (2) a stand for the measurement head and a vibration damping/isolation set-up; (3) a light source with a driver; (4) data acquisition system; and (5) a laptop with control software and access to data archiving server (figure 1).

The measurement head holds the measurement chamber in which the Phenotech Sensor, measuring microbial nanomotion, is located. The Resistell Phenotech head works similarly to measurement heads used in atomic-force microscopy (AFM). However, it is inverted compared with standard AFM set-ups, which allows (1) a better sensor and liquid handling during experiments without affecting the optical set-up, and (2) the investigation of the sensor from the top using an optical microscope. The light beam generated by a superluminescent light-emitting diode enters the measurement chamber through a sealed window. The beam is then reflected by the Phenotech Sensor’s microcantilever towards the

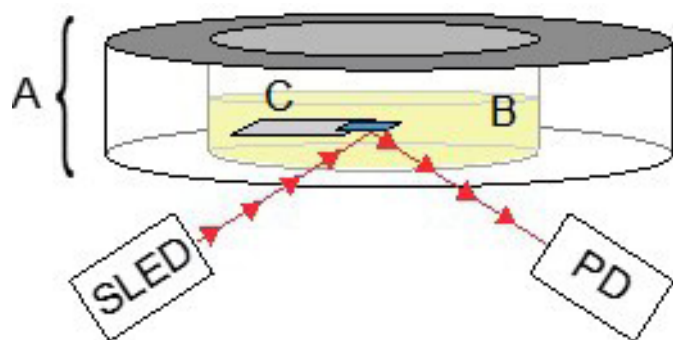


Figure 2 Schematic of the components in the measurement head of the Resistell Phenotech device, with the removable measurement chamber (A) forming a 2 mL reservoir for liquid culture media (B) in which the Phenotech sensor (C) with the cantilever (in blue) is placed. Though the measurement chamber is made of stainless steel, it contains light-permissive windows in its bottom, allowing the light beam emitted by the superluminescent light-emitting diode (SLED) to enter and the beam reflected from the cantilever to exit, measured by the photodetector (PD).

position-sensitive photodetector (figure 2). The Phenotech Sensor is fully submerged in a culture medium that may or may not contain drugs. Microcantilever vibrations induced by attached cells are transformed into electrical signals recorded by a data acquisition system and further processed by dedicated software.

Procedures

Bacterial pellets are obtained from PBCs as follows: (1) for the direct attachment protocol, 1 mL of anaerobic (ANH) or aerobic (AEH) PBC is filtered using a 5 µm or 1.2 µm membrane filter, respectively (to separate bacteria from blood cells and debris), subsequently centrifuged for 3 min at 2000 g. (2) Alternatively, the MBT Sepsityper IVD Kit (Bruker, USA) can be used, according to the manufacturer's protocol, to obtain pellet for ANH and AEH PBCs. Briefly, 1 mL of blood culture is mixed with 200 µL of Lysis buffer and centrifuged at 12 000 g for 2 min. Supernatant is discarded and pellet is resuspended in 1 mL Washing buffer, centrifuged again at 12 000 g for 1 min. For both methods, the obtained pellet is resuspended in 200 µL of Thickening buffer A. This cell suspension is then used for cell immobilisation on a Phenotech Sensor (figure 3) pretreated with the Functionalizing Buffer A for 45 s at room temperature. After aspiration of the suspension and a short wash with phosphate buffered saline (PBS), the sensor can be placed into the Phenotech device and the nanomotion recording be commenced.

Study design

This is a prospective, observational, cross-sectional, single-arm study investigating nanomotion-based technology (Resistell AST) for rapid AST by comparison with one of the following reference methods: (1) disk diffusion (Kirby-Bauer Test), (2) VITEK 2 or (3) BD Phoenix system.

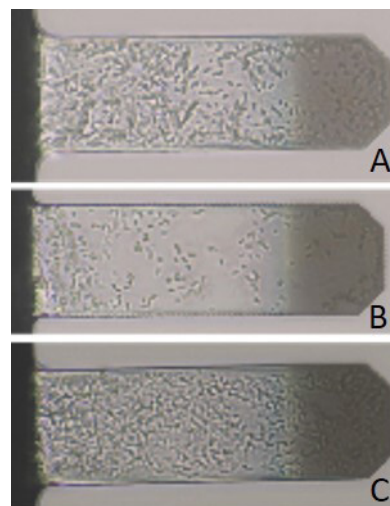


Figure 3 (A–C) Phase contrast images (40× objective) of *Escherichia coli* isolated from a positive blood culture and attached on a microcantilever using the Resistell Attachment Kit after a 45-second incubation at room temperature. The dimension of the cantilever is 130×40×0.75 µm and made of silicon-like material. The tip is coated with a reflective material for a better signal-to-noise ratio in the optical measurement system.

The study is divided into a pilot phase and the main study. In the pilot, only prospectively collected routine *E. coli* PBCs will be analysed and tested for ceftriaxone susceptibility using Resistell AST. *E. coli* was prioritised, representing the most frequently isolated pathogen in BSIs¹⁶ and considering the continued increase in third and fourth-generation cephalosporin resistance in Switzerland from 0.9% in 2004 to 11.4% in 2019.^{17–19}

About 10%–20% of all the required samples need to be analysed (30–60 samples). The recruitment rate and proportion of resistant strains will be assessed after the pilot. If at least 10% samples could be analysed, with at least 10% resistant, an interim analysis will be performed. However, if major amendments are required, the recruitment will be temporarily stopped.

Moreover, if after 3 months 10% recruitment has not been achieved (such as in case of high proportion of consent refusal, low prevalence of resistance or, overall, of *E. coli* BSIs, patients' transfer, patients' death), further samples will be analysed until 10% of the required samples (n=30) are reached.

In the main phase of the study, nanomotion-based Resistell AST of *E. coli* and *Klebsiella* spp (most common *Enterobacteriaceae* isolated from blood cultures¹⁶) will be analysed for ceftriaxone and ciprofloxacin. Single or multiple antibiotic concentrations will be experimentally determined for other antibiotic molecules (such as cefotaxime, ceftazidime, piperacillin–tazobactam, meropenem, gentamicin, amikacin and cefepime), as well as for other Gram-negative bacteria (such as *Enterobacteriaceae* and *Pseudomonas aeruginosa*) in a further multi-centre international study, which will include centres

with a higher rate of resistance according to the country epidemiology.

To control for selection bias, we planned, (1) a main 'per-protocol' analysis (included patients) and (2) an 'intention-to-test analysis', with all patients, including those initially excluded for reasons such as technical problems (eg, (1) bent/damaged Phenotech Sensor, (2) extensive cell elongation after drug exposure, (3) technical problem during recording, in particular loss of signal).

CA between Resistell AST method and reference method will be interpreted according to ISO 20776-2:2007 guidelines.²⁰

Study setting

The study is conducted at Lausanne University Hospital, a tertiary care centre with over 1500 beds and over 50 000 patients every year. The microbiology laboratory receives about 50 000 blood culture samples every year, out of which about 3% are true positives. Of these, *E. coli* constitutes about 28%, and all Gram-negative about 62%.

Sampling

All PBC samples will be treated according to the microbiology laboratory procedure in place. Each PBC containing Gram-negative bacteria (identified by MALDI-TOF MS) will be screened for eligibility.

Recruitment

If the sample passes the eligibility screening, a written informed consent form (ICF) is gathered from the patients or from next in kin/legal representative (if the patient cannot sign). Alternatively, a signature from an independent physician is obtained and an a posteriori ICF will be submitted to the patient once they regain the ability to sign (see the Informed consent and participant withdrawals section).

More than one specimen may be collected for AST. In such case, the absolute number of specimens analysed will be considered within the scope of this study, but only one consent will be obtained per patient per hospitalisation.

Inclusion criteria

Patients meeting all the following criteria can be recruited in the study: (1) patients over the age of 18 years, or their legal representatives, who sign the ICF; (2) patients with *E. coli* or *Klebsiella* spp bacteraemia; (3) patients hospitalised at Lausanne University Hospital at the time of blood culture inoculation; (4) patients whose PBCs were not older than 24 hours at time of AST start.

Exclusion criteria

Patients meeting any of the following criteria will be excluded: (1) patients with polymicrobial bacteraemia; (2) samples undergoing technical errors during the Resistell AST analysis (eg, bent or damaged Phenotech Sensor; extensive cell 'elongation' after drug exposure; technical problem with a device during recording, in

particular loss of signal); (3) patients refusing to sign the ICF.

If the maximum capacity of the Resistell AST is reached, no more ICFs will be obtained for that day.

Interventions

Fraction of the pellets is analysed for AST with Resistell AST and the reference methods: (1) VITEK 2, (2) BD Phoenix system and/or (3) Kirby-Bauer Test. In case of a discrepancy between the Kirby-Bauer Test and VITEK 2/BD Phoenix system, an E-Test will be performed. Only AST results obtained with the reference method will be used for patients' care.

Outcome measures

CA is considered as the number of bacterial isolates with the same AST category as the reference method category result.²⁰ VME is defined when classifying the test method as 'S' and the reference method being 'R'; ME is defined as when classifying the test method as 'R' and the reference method being 'S'; and mE represents the test in which either method is reported as 'I' while the other being 'S' or 'R'.²⁰

Summary statistics for the duration of tests (mean, SD and 95% CI) will be calculated for the TTR, collected in minutes as continuous variables. The difference of TTR between Resistell AST, VITEK 2/BD Phoenix systems and Kirby-Bauer Test will be assessed by one-way analysis of variance with Tukey's HSD post hoc comparison. Continuous variables will be compared using the Student's t-test and Mann-Whitney U test for normally and non-normally distributed variables, respectively. The χ^2 test or Fisher's exact test will be used to compare categorical variables.

Other assessments

Summary statistics on data gathered from clinical charts (if available) will be performed, along with 95% CI. In addition, the following variables will be collected: age, gender, site of infection, height, body mass index, drug allergies and antibiotic history.

Timeline schedule

After the first site initiation visit on 25 May 2021, the first patient for the pilot study was enrolled on 7 June 2021, and recruitment was stopped in December 2021 (figure 4). Six months from the recruitment of the first patient, the recruitment rate and proportion of resistant strains were assessed and further samples were collected up to 10% of the required samples were reached. An interim analysis is ongoing to assess potential problems, confounders or critical factors to adjust before the main study. The main study will start after this evaluation and will continue until the optimal sample size calculated is reached (or the study stopped for other reasons).

Sample size calculation and statistical methods

Based on the preclinical validation, the Resistell AST is expected to be at least 95% accurate.

Study Timelines



Figure 4 The study started in June 2021 with the pilot phase, which was completed in December 2021. RMV performed by the external CRO for quality assessment. RMV, routine monitoring visit. FPFV = first patient first visit. CRO = contract research organization, i.e a company that provides clinical trial management services for biotech industries.

To this aim, a total sample size of 240 (with anticipated 209 susceptible samples) achieves 90% power to detect a change in sensitivity from 0.97 of the ‘gold standard’ to 0.8 of Resistell AST using a two-sided binomial test, with target significance level at 0.05. The actual significance level achieved by the sensitivity test is 0.0377. About 87% of the PBCs analysed with Gram-negative bacteria at Lausanne University Hospital are susceptible to antibiotics. Therefore, the sample size was rounded to 300 to account for withdrawals, with an inflation of about 20%. The sample size was calculated using PASS 2019, V.19.0.5 (NCSS, Kaysville, Utah, USA).

Data storage and retention

A unique anonymised identifier will be used to track patients, samples and their clinical data. A list will be maintained at the investigational site with this unique identifier, along with the patient’s hospital number and the sample identification code; only the investigators and the study nurse will have access to it. Another list will be included in the electronic case report forms (eCRFs) with the patient’s unique identifier and medical record only accessible to investigators, study nurse and the contracted research organisation (see the Roles and responsibilities section). All records will be stored on a secured electronic data capture platform (www.Smart-Trial.com).

Traceability

During the clinical investigation, traceability of the Resistell AST will be achieved according to Resistell quality management, that is, each device is identified by a unique serial number, while nanomotion sensors are identified by lot numbers. All device service activities are kept in a ‘Revision Track’ online system. The model name and serial number of the device are displayed on the device label. Full traceability is established using unique device serial numbers, delivery notes, incoming inspection, installation and calibration.

Roles and responsibilities

The manufacturer of the investigational device (Resistell AG, Switzerland) is the sponsor of the study, who is responsible to competent/health authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of data recorded in the eCRF. The sponsor contributed to the study’s design, together with the investigators, and will take part in the report for publication. The ultimate authority over the decision to submit the work for publication and samples’ collection, study management, analyses, interpretation of data and writing the report is reserved to the investigators. The sponsor reserves the right to discontinue the study at any time for any reason.

The coordinating centre (Lausanne University Hospital) is composed of the coordinating investigator, two subinvestigators, two study nurses/coordinators and two operators. The investigators will allow inspections of the study documentation and maintain patient confidentiality during all audits and inspections from the sponsor, the sponsor representative, the ethical committee (EC), external auditors or representatives of the regulatory authorities. Furthermore, they will ensure that the investigational device and the study documentation are stored in a secure area under recommended storage conditions and in accordance with applicable regulatory requirements. Investigators are also responsible for safety reporting to their local EC, following its reporting requirements and timelines.

An external contract research organization (CRO) has been commissioned to help the investigators and the sponsor maintaining a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial. It will be part of the steering committee, which participates in endpoint adjudication. It will have access, at any time, to the source documents, signed consent

Table 1 Categories of adverse events

Adverse events	Non-device related	Device related	
In the scope of this study, the device may cause direct harm to the user or another person; as the study is performed on previously collected samples and is non-interventional, no harm is anticipated to the patients.			
Non-serious	Adverse event	Adverse device effect	
Serious	Serious adverse event	Serious adverse device effect	
		Anticipated	Unanticipated
		Anticipated serious adverse device effect	Unanticipated serious adverse device effect

forms and all other study-related documents. The external monitoring team will perform routine monitor visits monthly and will be responsible for reporting the reportable events (severe adverse events (SAEs), device deficiencies that might have led to SAEs and new findings/updates linked to already reported events) to the competent authority completing appropriate adverse events (AEs) forms.

An independent Data Monitoring Committee (DMC) will monitor the safety of the study and advise the sponsor. The DMC will be formed and composed of three medical doctors; the members of the DMC are otherwise not actively involved in the trial. The primary responsibilities of the DMC are the following: (1) to assess results of the pilot phase in the interim analysis, (2) to periodically review and evaluate the accumulated study data for effectiveness, (3) to make recommendations concerning the continuation, modification or termination of the study. In addition, the DMC considers study-specific data and relevant background knowledge about the disease, test agent or subject population under study.

Safety reporting

AEs will be summarised by severity and by relationship to the study device. All safety events will be coded according to Annex G of ISO EN 20916:2019.

All applicable AEs will be routinely monitored by the DMC and reported in interim and final study reports. The applicable categories are described in [table 1](#).

Both investigator and Resistell/CRO will make a causality assessment of the event for the Resistell AST. Device deficiencies that might have led to an SAE are always related to the device. All AEs judged by either the reporting investigator or the sponsor as having at least a 'possible' causal relationship to the study device qualify as an adverse reaction or as an adverse device effect (or both). All SAEs will be evaluated, regardless of whether they are related to the investigational medical device or anticipated.

Informed consent and participant withdrawals

The lead researchers or a delegated member will obtain informed consent at the start of the study visit directly from the patient or from next of kin/legal representative (online supplemental files 1–3). Alternatively, a signature from an independent physician (treating the patient)

will be obtained (online supplemental file 4). A further a posteriori ICF will be submitted to the patient when again able to sign it (online supplemental file 5). The investigators will explain the nature of the study, its purpose, the procedures involved, the expected duration, potential risks and benefits and any discomfort it may entail. All those obtaining consent will have received informed consent training as well as Good Clinical Practice training. Participants have the right to withdraw from the study at any time, without giving a reason and without affecting their future care. If withdrawn from the study, all gathered information will be destroyed.

Study-related procedures and documentation should end on the day of the patient's study termination. However, SAEs directly related to the investigational device, which are not resolved on the date of the patient's study termination, will be followed until termination of the study, if not resolved before. In addition, any harm to the user arising due to the device or the investigation will be followed up until the conclusion.

Subjects will receive standard medical care arising from SAEs after completion of the investigation.

Patient and public involvement

No formal patient advisory committee was established, and there was no patient or public involvement in the design and planning of the study.

Ethics and dissemination

The study will be conducted according to the ethics and regulatory principles. All local regulatory requirements will be adhered to. Before initiating the study, the investigators obtained a written and dated favourable opinion from the national ethics committee (swissethics, project 2020-01622). All the CRFs and clinical samples will be assigned a study code by the local investigators and stored anonymously at the reference centre. The results will be broadly distributed through conference presentations and peer-reviewed publications.

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Contributors GG conceived the idea and devised the project and its main conceptual ideas assisted by GC, AK, DC, MPV, AS, JD, ED and AL. GC and GG supervised the clinical study. GC also wrote the manuscript, assisted by AL, ED, AS, DC and GG. AK, AV, AS, GJ and JD provided editorial input. AV, AL and ED had hands-on conduct of the experiments. GC, assisted by AK, performed patients' inclusion and supervised the patients' clinical data collection. SK supervised the ethical, scientific, technical and regulatory quality aspects.

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Competing interests GG is medical advisor for Resistell. AV, AL, ED, AS, DC and GJ are employed by Resistell. GC, AK, SK and JD have no conflict of interest.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

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NANO-RAST : Nanomotion-based Resistell AST to determine the antibiotic susceptibility of Gram-negative bacteria causing bacteremia and/or sepsis.

This research project is organized by Resistell AG, Hofackerstrasse 40B, 4132 Muttenz

Dear Madam, Sir,

We would like to ask you whether you would be willing to participate in our research project.

Your participation is voluntary. All data collected in this project are subject to strict data protection regulations.

In a conversation we will explain the most important points to you and answer your questions. So that you can read about and understand the project, you can find a brief description below. This is followed by further, detailed information.

Please do not hesitate to ask further questions if there is anything you do not understand or would like further clarification on.

1. Aim of the study

In this project, we want to investigate how accurate a new device is at predicting whether a particular medicine will work against certain bacterial infections in patients that are currently at the Lausanne University Hospital – Centre Hospitalier Universitaire Vaudois (CHUV) due to these infections. The new device is called Resistell AST.

2. Resistell AST

When bacteria develop the ability to defeat the drugs (antibiotics) designed to eradicate them, this results in the drug becoming ineffective and the bacteria continue to grow — this phenomenon is called antibiotic resistance. Infections caused by such bacteria can be life-threatening and very difficult to treat and may require alternative antibiotic medicines.

In such situations, it is very important to know early during an infection whether a drug will work against a bacterial infection or not. Currently, several tests exist that can assess this. These tests are called antibiotic susceptibility tests (ASTs). However, the time to result can range from 8 to 48 hours, depending on the test.

Resistell AST is a rapid test that could significantly reduce the time needed to obtain a result by a minimum of 6 hours to a maximum of 46 hours, giving an approximate time to result of about 2 hours. This time is crucial in life threatening situations and starting patients on the right treatment is important to improve survival rates.

3. Who can participate?

Participation is open to all people who are admitted at CHUV due to certain bacterial infections that can be detected in the blood of the patient. This condition is called bacteremia. However, due to logistical restraints we can only enroll patients whose blood tests positive for the bacteria before 12:00 (noon) on weekdays.

If you had more than one kind of bacteria in your blood, you cannot take part in this study.

If your blood showed the presence of the following bacteria that we are interested in: *Escherichia coli*, *Klebsiella* spp., other Enterobacteriaceae, *Pseudomonas aeruginosa*, or other non-fermentative bacteria, and therefore you would be eligible to take part in this study.

4. General information about the project

This project is carried out in accordance with Swiss law. This study also complies with all internationally recognized guidelines. The Cantonal Ethics Committee of Vaud has examined and approved the study.

This study is designed to investigate how accurate Resistell AST (new device) is at determining which bacteria are resistant to antibiotics by analyzing your blood sample. To achieve the goals of this study, three hundred samples will be analyzed collected at CHUV. We estimate that the study will take about 12 months to complete.

5. How the study will unfold

If you agree to take part in this study, we will use your blood sample(s) that has been left over after the routine Antimicrobial Susceptibility Testing (AST) at the microbiology laboratory at CHUV. **Please note that**



only the bacteria extracted from your blood will be used. No other samples (for example, blood cells, genetic material, etc.) will be taken from your blood for this study.

- **The sample(s) will be pseudo-anonymized (identifiable data is replaced) and a unique identification number** will be used to follow the patient and find out which antibiotic treatment they received whilst their time in the hospital.
- The doctor treating you will be asked to fill in a questionnaire before reviewing the results obtained from the Resistell AST device and then consequently asked to fill in a second questionnaire after they have seen the Resistell AST results.
- The questionnaire will allow us to understand whether the results obtained by Resistell AST could influence a doctor's clinical decision making to improve the outcome for the patient.

We may need to withdraw you from the project before the end of the study. This can happen if you are diagnosed as having multiple types of bacteria in their blood. We will inform your attending physician of your participation in this project. If you would rather that your treating physician was not informed about your participation in the study, please discuss this with the investigating physician / project manager.

Other diagnostic tests will also be routinely performed by the hospital and these include:

- The disk diffusion test (Kirby-Bauer test); this test enables doctors to understand which bacteria can be killed with which antibiotics.
- VITEK 2 ® or BD Phoenix ™ systems; these automated systems determine both bacteria-killing antibiotics as well as the lowest concentration of antibiotic needed to prevent bacterial growth.
- Epsilometer test; this test enables doctors to determine the lowest amount of an antibiotic that is needed to stop the bacteria from growing.

In addition, a complete medical history including your past and current medical conditions, age, gender, site of infection if present, race, ethnic origin, height (in cm), body mass index (in kg/m² with one decimal), allergies, and surgical procedure history will be recorded.

6. Benefits for the participants

Participation in this study will not bring you any personal benefit. However, the results of the research could be important for people affected by similar bacterial infections in the future.

7. Rights

Participation in this project is optional. If you do not wish to participate or if you later change your decision regarding the study, you will not have to justify yourself. This will not affect your treatment or medical care. You can ask questions about participation and the project at any time. To this end, please contact the person listed at the end of this fact sheet.

8. Obligations

As a participant in the project, there are no obligations arising from the project except to sign the consent form.

9. Risks

As we intend to use blood that had already been collected from you, you will not be exposed to any additional risks by participating in the study.

10. Results

The physician-investigator/project manager will notify you of any new discoveries that may affect the benefits or safety of the study and, thus, the consent to participate.

11. Confidential processing of data and samples

For this project, we will record your personal and medical data. Only a limited number of people will have access to this data in an uncoded format and this access will exclusively be granted for tasks that are necessary in order to complete the project. **All the information will be coded and, therefore, pseudo-anonymized when the results are reviewed. Encoding (pseudo-anonymizing) means that all patient-identifying data (name, date of birth) is erased. Each patient is assigned a unique code and the key to decode this will remain at the hospital (CHUV). Without this unique code and key, it is not possible to**



link the data to the patient. On occasion, scientific journals require access to individual data (raw data). If this is the case, it will always be coded and therefore does not identify you as a person. Everyone involved in the project is bound by professional secrecy.

Throughout the project, the site may be inspected by the relevant ethics commission or by the institution that commissioned the project. For these inspections, the project manager must grant access to the relevant investigators and allow them to see your personal and medical data.

12. Withdrawal from the project

You can withdraw from the study at any time if you wish to. The data and samples collected up until the your withdrawal will not be used for any further analysis. The samples will be stored in the hospital in accordance with the CHUV hospital specifications.

13. Repairing damage

You will not receive compensation for the participation in this project.

14. Liability

Damage related to the research project is covered by the institution or company that commissioned it and is responsible for its conduct. The conditions and procedures are regulated by law. This is a category A study according to Human Research Ordinance (HRO). The personnel involved in the study are covered under general liability insurance provided by the Sponsor according to Art. 19 of the Swiss Human Research Act (HRA).

15. Funding

This project is funded by Resistell AG and Innosuisse – Swiss Innovation Agency.

16. Contact person

If you have any doubts, concerns or emergencies during or after the project, feel free to contact the team using the information below:

On site study management: Gilbert Greub

Complete address and telephone number contactable on weekdays and email address:

Institute of Microbiology CHUV

Rue du Bugnon 48

CH-1011 Lausanne, Switzerland

Tel: +41 21 314 4056

Email: gilbert.greub@chuv.ch



Statement of consent

Written Declaration of Consent for Participation in a Research Project

Please read this form carefully. Do not hesitate to ask questions if there is anything that you do not understand or would like further clarification on. For patient participation, your written consent is required.

BASEC number of the research project (after submission to the relevant ethics COMMISSION) :	2020-01622
Title (scientific and usual) :	Nanomotion-based Resistell AST to determine the antibiotic susceptibility of Gram-negative bacteria causing bacteraemia and/or sepsis.
Responsible institution (project manager and full address) :	Gilbert Greub Institute of Microbiology CHUV Rue du Bugnon 48 CH-1011 Lausanne, Switzerland
Study location :	CHUV Lausanne
Project manager on site : Name and surname in capital letters :	
Participant : Name and surname in capital letters : Date of birth :	<input type="checkbox"/> female <input type="checkbox"/> male

- I acknowledge receiving written and oral information from the physician-investigator about the objectives, the scope, possible benefits, disadvantages and risks of participating in the above-mentioned study.
- I take part in this study voluntarily and accept the written and oral information. Furthermore, I also acknowledge that I had enough time to make an informed decision.
- I have received the answers to the questions I have asked in relation to participation in this project, I will keep the information sheet and receive a copy of my consent statement.
- I agree that my treating physician should be informed of my participation in the research project.
- I accept that the competent specialists of the management/principal of this project, the competent ethics commission, may consult my uncoded data in order to carry out checks, provided, however, that the confidentiality of this data is strictly assured.
- I know that personal data (including the samples) can only be transmitted in a coded format and for research purposes as part of this project.
- I may, at any time and without having to justify myself, revoke my consent to participate in this study, without adversely affecting my medical treatment/management. Data and samples collected to date will, however, still be analyzed for project purposes.
- The hospital/institutional civil liability covers any damage that may result from the project.
- I am aware that the obligations mentioned in the fact sheet must be met for the duration of the project. The investigating physician may exclude me at any time if this is deemed necessary.



Location, date	Name and surname in capital letters : Signature:
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Certificate from the investigating physician/investigator: I hereby certify that I have explained to the participant the nature, importance and scope of the project.

I declare that I meet all legal obligations related to this project. If I was to become aware, at any time during the project, of elements likely to influence the consent of a participant to take part in the research project, I agree to immediately inform the participant.

Location, date	Name and surname in capital letters of the physician-investigator/investigator providing the information : Signature of the physician-investigator/investigator :
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NANO-RAST : Nanomotion-based Resistell AST to determine the antibiotic susceptibility of Gram-negative bacteria causing bacteremia and/or sepsis.

This research project is organized by Resistell AG, Hofackerstrasse 40B, 4132 Muttenz

Dear Madam, Sir,

The patient has been integrated into a research project in an emergency situation. In all likelihood, the patient will remain permanently incapable of discernment and, therefore, of communicating their wishes. As you represent the patient as one of their relatives, we have prepared this document to inform you about our research project and allow you to confirm the patients presumed wishes. In addition, we ask you to grant us, with retroactive effect, as the patients relative, your consent to allow the patient to participate in this project.

Below, is an introduction to the project. Please do not hesitate to ask further questions if there is anything you do not understand or would like further clarification on.

1. Aim of the study

In this project, we want to investigate how accurate a new device is at predicting whether a particular medicine will work against certain bacterial infections in patients that are currently at the Lausanne University Hospital – Centre Hospitalier Universitaire Vaudois (CHUV) due to these infections. The new device is called Resistell AST.

2. Resistell AST

When bacteria develop the ability to defeat the drugs (antibiotics) designed to eradicate them, this results in the drug becoming ineffective and the bacteria continue to grow — this phenomenon is called antibiotic resistance. Infections caused by such bacteria can be life-threatening and very difficult to treat and may require alternative antibiotic medicines.

In such situations, it is very important to know early during an infection whether a drug will work against a bacterial infection or not. Currently, several tests exist that can assess this. These tests are called antibiotic susceptibility tests (ASTs). However, the time to result can range from 8 to 48 hours, depending on the test.

Resistell AST is a rapid test that could significantly reduce the time needed to obtain a result by a minimum of 6 hours to a maximum of 46 hours, giving an approximate time to result of about 2 hours. This time is crucial in life threatening situations and starting patients on the right treatment is important to improve survival.

3. Who can participate?

Participation is open to all people who are admitted at CHUV due to certain bacterial infections that can be detected in the blood of the patient. This condition is called bacteremia. However, due to logistical restraints we can only enroll patients whose blood tests positive for the bacteria before 12:00 (noon) on weekdays.

If the patient (your relative) has more than one kind of bacteria in their blood, they cannot take part in this study.

Your relative is eligible to take part in this study because their blood showed the presence of the following bacteria that we are interested in: *Escherichia coli*, *Klebsiella* spp., other Enterobacteriaceae, *Pseudomonas aeruginosa*, or other non-fermentative bacteria.

4. General information about the project

This project is carried out in accordance with Swiss law. This study also complies with all internationally recognized guidelines. The Cantonal Ethics Committee of Vaud has examined and approved the study.

This study is designed to investigate how accurate Resistell AST (new device) is at determining which bacteria are resistant to antibiotics from a blood sample. To achieve the goals of this study, three hundred patients will be recruited at CHUV. We estimate that the study will take about 12 months to complete.

As this study is being carried out at the CHUV hospital, including the intensive care unit (ICU), emergency room, and other departments, it is likely that we would have to include patients in this study under emergency situations. Meaning, that we may not have time for the patient's medical condition to improve and to obtain their consent to participate in the study. Hence, we ask the patients relatives for their consent whenever possible.



5. How the study will unfold

If you agree for the patient (your relative) to take part of this study, we will use the blood sample(s) that was left over after the routine Antimicrobial Susceptibility Testing (AST) at the microbiology laboratory at CHUV.

Please note that only the bacteria extracted from the patient's (your relative's) blood will be used. No other samples (for example, blood cells, genetic material, etc.) will be taken from the patient's (your relative's) blood for this study.

- **The sample(s) will be pseudo-anonymized (identifiable data is replaced) and a unique identification number will be used** to follow the patient and find out which antibiotic treatment they received whilst in the intensive care unit or emergency room.
- The doctor treating the patient or your relative in the intensive care unit or the emergency room will be asked to fill in a questionnaire before reviewing the results obtained from the Resistell AST device and then consequently asked to fill in a second questionnaire after they have seen the Resistell AST results.
- The questionnaire will allow us to understand whether the results obtained by Resistell AST could influence a doctor's clinical decision making to improve the outcome for the patient.

We may need to withdraw the patient from the project before the end of the study if they are diagnosed as having multiple types of bacteria in their blood. We will inform the attending physician of the participation of the patient in this project. If you would rather that the treating physician was not informed about the patient's participation in the study, please discuss this with the investigating physician / project manager.

Other diagnostic tests will also be routinely performed by the hospital and these include:

- The disk diffusion test (Kirby-Bauer test) ; this test enables doctors to understand which bacteria can be killed with which antibiotics.
- VITEK 2 ® or BD Phoenix ™ systems; these automated systems determine both bacteria-killing antibiotics as well as the lowest concentration of antibiotic needed to prevent bacterial growth.
- Epsilometer test ; this test enables doctors to determine the lowest amount of an antibiotic that is needed to stop the bacteria from growing.

In addition, a complete medical history including past and current medical conditions, age, gender, site of infection if present, race, ethnic origin, height (in cm), body mass index (in kg/m² with one decimal), allergies, and surgical procedure history will be recorded.

6. Benefits for the participants

Participation in this study will not bring any personal benefit to the patient (your relative). However, the results of the research could be important for people affected by similar bacterial infections in the future.

7. Rights

Participation in this project is optional. If the patient does not wish to participate or if you as a relative later change your decision regarding the study, you will not have to justify yourself. This will not affect the treatment or the medical care of the patient (your relative). You can ask questions about participation and the project at any time. To this end, please contact the person listed at the end of this fact sheet.

8. Obligations

For the study participant, there are no obligations arising from the project except to sign the consent form.

9. Risks

As we intend to use blood that has already been collected from the patient (your relative), they will not be exposed to any additional risks by participating in the study.

10. Results

The physician-investigator/project manager will notify you, as a relative, of any new discoveries that may affect the benefits or safety of the study and, thus, the consent to participate.

11. Confidential processing of data and samples

For this project, we will record the patient's personal and medical data. Only a limited number of people will have access to this data in an uncoded format and this access will exclusively be granted for tasks that are



necessary in order to complete the project. **All the information will be coded and therefore pseudo-anonymized when the results are reviewed. Encoding (pseudo-anonymizing) means that all patient-identifying data (name, date of birth) is erased. Each patient is assigned a unique code and the key to decode this will remain at the hospital (CHUV). Without this unique code and key, it is not possible to link the data to the patient.** On occasion, scientific journals require access to individual data (raw data). If this is the case, it will always be coded and therefore does not identify the patient as a person. Everyone involved in the project is bound by professional secrecy.

Throughout the project, the site may be inspected by the relevant ethics commission or by the institution that commissioned the project. For these inspections, the project manager must grant access to the relevant investigators and allow them to see patient's personal and medical data.

12. Withdrawal from the project

The patient can withdraw from the study at any time if they wish to or if you, as a relative decide to do so. The data and samples collected up until patient withdrawal will not be used for any further analysis. The samples will be stored in the hospital in accordance with the CHUV hospital specifications.

13. Repairing damage

The patient does not receive compensation for their participation in this project.

14. Liability

Damage related to the research project is covered by the institution or company that commissioned it and is responsible for its conduct. The conditions and procedures are regulated by law. This is a category A study according to Human Research Ordinance (HRO). The personnel involved in the study are covered under general liability insurance provided by the Sponsor according to Art. 19 of the Swiss Human Research Act (HRA).

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This project will be funded by Resistell AG and Innosuisse – Swiss Innovation Agency.

16. Contact person

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On site study management: Gilbert Greub

Complete address and telephone number contactable on weekdays and email address:

Institute of Microbiology CHUV

Rue du Bugnon 48

CH-1011 Lausanne, Switzerland

Tel: +41 21 314 4056

Email: gilbert.greub@chuv.ch



Statement of consent

Written Declaration of Consent for Participation in a Research Project

Please read this form carefully. Do not hesitate to ask questions if there is anything that you do not understand or would like further clarification on. For patient participation, your written consent as a relative is required.

BASEC number of the research project (after submission to the relevant ethics COMMISSION) :	2020-01622
Title (scientific and usual) :	Nanomotion-based Resistell AST to determine the antibiotic susceptibility of Gram-negative bacteria causing bacteraemia and/or sepsis.
Responsible institution (project manager and full address) :	Gilbert Greub Institute of Microbiology CHUV Rue du Bugnon 48 CH-1011 Lausanne, Switzerland
Study location :	Intensive Care Unit (ICU) or Emergency Room, CHUV Lausanne
Project manager on site : Name and surname in capital letters :	
Participant : Name and surname in capital letters : Date of birth :	<input type="checkbox"/> female <input type="checkbox"/> male

- As a relative of the aforementioned patient, I acknowledge receiving written and oral information from the physician-investigator about the objectives, the scope, possible benefits, disadvantages and risks of participating in the above-mentioned study.
- I confirm that I am making the decision on behalf of the patient as a relative and consent that the patient can participate in this clinical study. On the patient's behalf, I accept the written and oral information. Furthermore, I also acknowledge that I had enough time to make an informed decision.
- I have received the answers to the questions I have asked in relation to participation in this project, I will keep the information sheet and receive a copy of my consent statement.
- I agree that the patient's treating physician should be informed of his or her participation in the research project.
- I accept that the competent specialists of the management/principal of this project, the competent ethics commission, may consult the patient's uncoded data in order to carry out checks, provided, however, that the confidentiality of this data is strictly assured.
- I know that personal data (including the samples) can only be transmitted in a coded format and for research purposes as part of this project.
- On behalf of the patient, I may, at any time and without having to justify myself, revoke my consent of the patient to participate in this study, without adversely affecting the patients' medical treatment/management. Data and samples collected to date will, however, still be analyzed for project purposes.



- The hospital/institutional civil liability covers any damage that may result from the project.
- I am aware that the obligations mentioned in the fact sheet must be met for the duration of the project. The investigating physician may exclude the patient at any time if this is deemed necessary.

Location, date	Name and surname in capital letters : Relationship with the patient (spouse/son or daughter etc.) : Signature of the relative :
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Certificate from the investigating physician/investigator: I hereby certify that I have explained to the relative of the participant the nature, importance and scope of the project.

I declare that I meet all legal obligations related to this project. If I was to become aware, at any time during the project, of elements likely to influence the consent of a participant to take part in the research project, I agree to immediately inform the patient's relative.

Location, date	Name and surname in capital letters of the physician-investigator/investigator providing the information : Signature of the physician-investigator/investigator :
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NANO-RAST : Nanomotion-based Resistell AST to determine the antibiotic susceptibility of Gram-negative bacteria causing bacteremia and/or sepsis.

Form

This research project is organized by Resistell AG, Hofackerstrasse 40B, 4132 Muttenz

Dear Madam, Sir,

We would like to inform you about our research project and we would like to obtain your retrospective consent to enroll the patient in this study. However, at this point the patient is unable to communicate their wishes, and therefore unable to consent. Therefore, we provide you with this fact sheet, which will allow you to verify whether you agree to involve the person you represent. You can give your consent as a legal representative.

Below, is an introduction to the project. Please do not hesitate to ask further questions if there is anything you do not understand or would like further clarification on.

1. Aim of the study

In this project, we want to investigate how accurate a new device is at predicting whether a particular medicine will work against certain bacterial infections in patients that are currently at the Lausanne University Hospital – Centre Hospitalier Universitaire Vaudois (CHUV) due to these infections. The new device is called Resistell AST.

2. Resistell AST

When bacteria develop the ability to defeat the drugs (antibiotics) designed to eradicate them, this results in the drug becoming ineffective and the bacteria continue to grow — this phenomenon is called antibiotic resistance. Infections caused by such bacteria can be life-threatening and very difficult to treat and may require alternative antibiotic medicines.

In such situations, it is very important to know early during an infection whether a drug will work against a bacterial infection or not. Currently, several tests exist that can assess this. These tests are called antibiotic susceptibility tests (ASTs). However, the time to result can range from 8 to 48 hours, depending on the test.

Resistell AST is a rapid test that could significantly reduce the time needed to obtain a result by a minimum of 6 hours to a maximum of 46 hours, giving an approximate time to result of about 2 hours. This time is crucial in life threatening situations and starting patients on the right treatment is important to improve survival rates.

3. Who can participate?

Participation is open to all people who are admitted at CHUV due to certain bacterial infections that can be detected in the blood of the patient. This condition is called bacteremia. However, due to logistical restraints we can only enroll patients whose blood tests positive for the bacteria before 12:00 (noon) on weekdays.

If the patient had more than one kind of bacteria in their blood, they cannot take part in this study.

The patient was eligible to take part of this study because their blood showed the presence of the following bacteria that we are interested in: *Escherichia coli*, *Klebsiella* spp., other Enterobacteriaceae, *Pseudomonas aeruginosa*, or other non-fermentative bacteria.

4. General information about the project

This project is carried out in accordance with Swiss law. This study also complies with all internationally recognized guidelines. The Cantonal Ethics Committee of Vaud has examined and approved the study.

This study is designed to investigate how accurate Resistell AST (new device) is at determining which bacteria are resistant to antibiotics by analyzing the patients' blood sample. To achieve the goals of this study, three hundred patients will be recruited at CHUV. We estimate that the study will take about 12 months to complete.

As this study is being carried out at the CHUV hospital, including the ICU (intensive care unit), emergency room, and other departments, it is likely that we would have to include patients in this study under emergency situations. Meaning, that we may not have time for the patient's medical condition to improve and to obtain their consent to participate in the study. In this case, the patient has a lasting lack of judgment and therefore we ask you, as the patients legal representative to consent retrospectively on their behalf.



5. How the study will unfold

If you agree for the patient to take part in this study, we will continue to use the blood sample(s) that has been left over after the routine Antimicrobial Susceptibility Testing (AST) at the microbiology laboratory at CHUV. **Please note that only the bacteria extracted from the patient's blood will be used. No other samples (for example, blood cells, genetic material, etc.) will be taken from the patient's blood for this study.**

- **The sample(s) were pseudo-anonymized (identifiable data was replaced) and a unique identification number** was used to follow the patient and find out which antibiotic treatment they received whilst their time in the hospital.
- The doctor treating the patient was asked to fill in a questionnaire before reviewing the results obtained from the Resistell AST device and then consequently asked to fill in a second questionnaire after they have seen the Resistell AST results.
- The questionnaire will allow us to understand whether the results obtained by Resistell AST could influence a doctor's clinical decision making to improve the outcome for the patient.

We may need to withdraw the patient from the project before the end of the study if they are diagnosed as having multiple types of bacteria in their blood. We informed the attending physician of the participation of the patient in this project. If you would rather that the treating physician was not informed about the patient's participation in the study, please discuss this with the investigating physician / project manager.

Other diagnostic tests have also been routinely performed by the hospital and these include:

- The disk diffusion test (Kirby-Bauer test); this test enables doctors to understand which bacteria can be killed with which antibiotics.
- VITEK 2 ® or BD Phoenix ™ systems; these automated systems determine both bacteria-killing antibiotics as well as the lowest concentration of antibiotic needed to prevent bacterial growth.
- Epsilometer test; this test enables doctors to determine the lowest amount of an antibiotic that is needed to stop the bacteria from growing.

In addition, a complete medical history including past and current medical conditions, age, gender, site of infection if present, race, ethnic origin, height (in cm), body mass index (in kg/m² with one decimal), allergies, and surgical procedure history has been recorded.

6. Benefits for the participants

Participation in this study will not bring any personal benefit to the patient. However, the results of the research could be important for people affected by similar bacterial infections in the future.

7. Rights

Participation in this project is optional. If the patient does not wish to participate or if you as a legal representative later change your decision regarding the study, you will not have to justify yourself. This will not affect the treatment or the medical care of the patient. You can ask questions about participation and the project at any time. To this end, please contact the person listed at the end of this fact sheet.

8. Obligations

As a participant in the project, there are no obligations arising from the project except to sign the consent form.

9. Risks

As we used blood that had already been collected from the patient, they were not exposed to any additional risks by participating in the study.

10. Results

The physician-investigator/project manager will notify you, as the patient's legal representative, of any new discoveries that may affect the benefits or safety of the study and, thus, the consent to participate.

11. Confidential processing of data and samples

For this project, we will record the patient's personal and medical data. Only a limited number of people will have access to this data in an uncoded format and this access will exclusively be granted for tasks that are



necessary in order to complete the project. **All of the information will be coded and therefore pseudo-anonymized when the results are reviewed. Encoding (pseudo-anonymizing) means that all patient-identifying data (name, date of birth) is erased. Each patient is assigned a unique code and the key to decode this will remain at the hospital (CHUV). Without this unique code and key, it is not possible to link the data to the patient.** On occasion, scientific journals require access to individual data (raw data). If this is the case, it will always be coded and therefore does not identify the patient as a person. Everyone involved in the project is bound by professional secrecy.

Throughout the project, the site may be inspected by the relevant ethics commission or by the institution that commissioned the project. For these inspections, the project manager must grant access to the relevant investigators and allow them to see patient's personal and medical data.

12. Withdrawal from the project

The patient can withdraw from the study at any time if they wish to or if you, as a legal representative decide to do so. The data and samples collected up until the patient's withdrawal will not be used for any further analysis. The samples will be stored in the hospital in accordance with the CHUV hospital specifications.

13. Repairing damage

The patient does not receive compensation for their participation in this project.

14. Liability

Damage related to the research project is covered by the institution or company that commissioned it and is responsible for its conduct. The conditions and procedures are regulated by law. This is a category A study according to Human Research Ordinance (HRO). The personnel involved in the study are covered under general liability insurance provided by the Sponsor according to Art. 19 of the Swiss Human Research Act (HRA).

15. Funding

This project is funded by Resistell AG and Innosuisse – Swiss Innovation Agency.

16. Contact person

If you have any doubts, concerns or emergencies during or after the project, feel free to contact the team using the information below:

On site study management: Gilbert Greub

Complete address and telephone number contactable on weekdays and email address:

Institute of Microbiology CHUV

Rue du Bugnon 48

CH-1011 Lausanne, Switzerland

Tel: +41 21 314 4056

Email: gilbert.greub@chuv.ch



Statement of consent

Written Declaration of Consent for Participation in a Research Project

Please read this form carefully. Do not hesitate to ask questions if there is anything that you do not understand or would like further clarification on. For patient participation, your written consent is required.

BASEC number of the research project (after submission to the relevant ethics COMMISSION) :	2020-01622
Title (scientific and usual) :	Nanomotion-based Resistell AST to determine the antibiotic susceptibility of Gram-negative bacteria causing bacteraemia and/or sepsis.
Responsible institution (project manager and full address) :	Gilbert Greub Institute of Microbiology CHUV Rue du Bugnon 48 CH-1011 Lausanne, Switzerland
Study location :	CHUV Lausanne
Project manager on site : Name and surname in capital letters :	
Participant : Name and surname in capital letters : Date of birth :	<input type="checkbox"/> female <input type="checkbox"/> male

- As a legal representative of the aforementioned patient, I acknowledge receiving written and oral information from the physician-investigator about the objectives, the scope, possible benefits, disadvantages and risks of participating in the above-mentioned study.
- I confirm that I am making the decision on behalf of the patient as a legal representative and consent that the patient can participate in this clinical study. On the patient's behalf, I accept the written and oral information. Furthermore, I also acknowledge that I had enough time to make an informed decision.
- I have received the answers to the questions I have asked in relation to participation in this project, I will keep the information sheet and receive a copy of my consent statement.
- I agree that the patient's treating physician should be informed of his or her participation in the research project.
- I accept that the competent specialists of the management/principal of this project, the competent ethics commission, may consult the patient's uncoded data in order to carry out checks, provided, however, that the confidentiality of this data is strictly assured.
- I know that personal data (including the samples) can only be transmitted in a coded format and for research purposes as part of this project.
- On behalf of the patient, I may, at any time and without having to justify myself, revoke my consent of the patient to participate in this study, without adversely affecting the patient's medical treatment/management. Data and samples collected to date will, however, still be analyzed for project purposes.
- The hospital/institutional civil liability covers any damage that may result from the project.



- I am aware that the obligations mentioned in the fact sheet must be met for the duration of the project. The investigating physician may exclude the patient at any time if this is deemed necessary.

Location, date	Name and surname in capital letters : Signature of the legal representative :
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Certificate from the investigating physician/investigator: I hereby certify that I have explained to the legal representative of the participant the nature, importance and scope of the project.

I declare that I meet all legal obligations related to this project. If I was to become aware, at any time during the project, of elements likely to influence the consent of a participant to take part in the research project, I agree to immediately inform the patient's legal representative.

Location, date	Name and surname in capital letters of the physician-investigator/investigator providing the information : Signature of the physician-investigator/investigator :
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Written confirmation from a doctor that has no association with the research project

Written confirmation for a doctor not associated with the research project, who is not involved in the research project mentioned below and who defends the interests of the person taking part in the study (HRA art 30).

Information on the research project

Title of the research project : Nanomotion-based Resistell AST to determine the antibiotic susceptibility of Gram-negative bacteria causing bacteraemia and/or sepsis.	
Research project number : 2020-01622	
Place where the research project is taking place : Institute of Microbiology CHUV Rue du Bugnon 48 CH-1011 Lausanne, Switzerland	
Surname and first name of the principle physician investigator : Greub Gilbert	
Surname and first name of the participant :	
Date of birth (optional) :	Gender (optional) :

I have received and have read the summary of the clinical trial protocol mentioned above.

I certify that the interests of the participant are respected and that their medical follow-up is guaranteed.

Place, date	Surname, first name and telephone number of the doctor not associated with the research project (in capital letters) :	Signature of the doctor not associated with the research project :
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I hereby certify that I have explained the nature, importance and scope of the project to the doctor not associated with the research project. If I was to become aware, at any time during the project, of elements likely to influence the consent of a participant to take part in the research project, I agree to immediately inform them of this.

Place, date	Surname, first name and telephone number of the principle investigator (in capital letters) :	Signature of the principle investigator :
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NANO-RAST : Nanomotion-based Resistell AST to determine the antibiotic susceptibility of Gram-negative bacteria causing bacteremia and/or sepsis.

This research project is organized by Resistell AG, Hofackerstrasse 40B, 4132 Muttenz

Dear Madam, Sir,

We would like to inform you about our research project. An independent doctor consented for us to be able to use some of your blood that was collected whilst you were at the Centre Hospitalier Universitaire Vaudois (CHUV). When you were enrolled on the study, you were unable to consent however, an independent doctor consented on your behalf to ensure that your wishes and rights were always upheld. Therefore, we now provide you with this fact sheet, which will allow you to verify whether you agree retrospectively for your data to be used in this study. An independent doctor read through the study protocol, which allowed them to ensure that your rights and wishes were always upheld whilst participating in this study. You can now give your consent retrospectively as the patient.

Below, is an introduction to the project. Please do not hesitate to ask further questions if there is anything you do not understand or would like further clarification on. If you wish to withdraw from the project, please note that all your data and samples will be destroyed and not used for any further analysis.

1. Aim of the study

In this project, we want to investigate how accurate a new device is at predicting whether a particular medicine will work against certain bacterial infections in patients that are currently at the CHUV hospital due to these infections. The new device is called Resistell AST.

2. Resistell AST

When bacteria develop the ability to defeat the drugs (antibiotics) designed to eradicate them, this results in the drug becoming ineffective and the bacteria continue to grow — this phenomenon is called antibiotic resistance. Infections caused by such bacteria can be life-threatening and very difficult to treat and may require alternative antibiotic medicines.

In such situations, it is very important to know early during an infection whether a drug would work against a bacterial infection or not. Currently several tests exist that can assess this. These tests are called antibiotic susceptibility tests (ASTs). However, the time required to obtain a result can range from 8 to 48 hours, depending on the test.

Resistell AST is a rapid test that could significantly reduce the time needed to obtain a result by a minimum of 6 hours to a maximum of 46 hours, giving an approximate time to result of about 2 hours. This time is crucial in life threatening situations and starting patients on the right treatment is important to improve survival rates.

3. Who can participate?

Participation is open to all people who are admitted to the CHUV hospital due to certain bacterial infections that can be detected in the blood. This condition is called bacteremia. However, due to logistical restraints we can only enroll patients whose blood tests positive for the bacteria before 12:00 (noon) on weekdays.

If you were found to have more than one kind of bacteria in your blood, you would not have been able to take part in this study.

When you were in the CHUV hospital, you were eligible to take part in this study because your blood showed the presence of the following bacteria that we are interested in: *Escherichia coli*, *Klebsiella* spp., other Enterobacteriaceae, *Pseudomonas aeruginosa*, or other non-fermentative bacteria.

4. General information about the project

This project is carried out in accordance with Swiss law. This study also complies with all internationally recognized guidelines. The Cantonal Ethics Committee of Vaud has examined and approved the study.

This study is designed to investigate how accurate Resistell AST (new device) is at determining which bacteria are resistant to antibiotics by analyzing your blood sample. To achieve the goals of this study, three hundred patients will be recruited at CHUV. We estimate that the study will take about 12 months to complete.



As this study is being carried out at the CHUV hospital, including the ICU (intensive care unit), emergency room, and other departments, it is likely that we would have to include patients in this study under emergency situations. Meaning, that we may not have time for the patient's medical condition to improve and to obtain their consent to participate in the study. Hence, in your case, we initially asked an independent doctor to read through the study protocol and ensure that your rights and wishes were always upheld. We now ask you to give your own consent to participate in this study retrospectively.

5. How the study will unfold

If you agree retrospectively to take part in this study, we will continue to use the blood sample(s) that was left over after the routine Antimicrobial Susceptibility Testing (AST) at the microbiology laboratory at CHUV.

Please note that only the bacteria extracted from your blood will be used. No other samples (for example, blood cells, genetic material, etc.) will be taken from your blood for this study.

- **Your sample(s) were pseudo-anonymized (identifiable data was replaced) and a unique identification number** was used to follow you throughout your time in the hospital (CHUV) and find out which antibiotic treatment you received.
- The doctor that treated you at CHUV was asked to fill in a questionnaire before reviewing the results obtained from the Resistell AST device and then consequently asked to fill in a second questionnaire after they have seen the Resistell AST results.
- The questionnaire will allow us to understand whether the results obtained by Resistell AST could influence a doctor's clinical decision making to improve the outcome for the patient.

We may need to withdraw you (the patient) from the project before the end of the study if you are diagnosed as having multiple types of bacteria in your blood. We informed the attending physician of your participation in this project. If you would rather that the treating physician was not informed about your participation in the study, please discuss this with the investigating physician / project manager.

Other diagnostic tests have also been routinely performed by the hospital and these include:

- The disk diffusion test (Kirby-Bauer test) ; this test enables doctors to understand which bacteria can be killed with which antibiotics.
- VITEK 2 ® or BD Phoenix ™ systems; these automated systems determine both bacteria-killing antibiotics as well as the lowest concentration of antibiotic needed to prevent bacterial growth.
- Epsilometer test; this test enables doctors to determine the lowest amount of an antibiotic that is needed to stop the bacteria in your body from growing.

In addition, a complete medical history including past and current medical conditions, age, gender, site of infection if present, race, ethnic origin, height (in cm), body mass index (in kg/m² with one decimal), allergies, and surgical procedure history has been recorded.

6. Benefits for the participants

Participation in this study will not bring any personal benefit to you (the patient). However, the results of the research could be important for people affected by similar bacterial infections in the future.

7. Rights

Participation in this project is optional. If you (the patient) do not wish to participate or later change your decision regarding the study, you will not have to justify yourself. This will not affect the treatment or the medical care you receive. You can ask questions about participation and the project at any time. To this end, please contact the person listed at the end of this fact sheet.

8. Obligations

As a participant in the project, there are no obligations arising from the project except to sign the consent form.

9. Risks

As we used blood that had already been collected from you whilst you were the CHUV hospital, you were not exposed to any additional risks by participating in the study.



10. Results

The physician-investigator/project manager will notify you, as the patient, of any new discoveries that may affect the benefits or safety of the study and, thus, your consent to participate.

11. Confidential processing of data and samples

For this project, we have recorded your personal and medical data. Only a limited number of people will have access to this data in an uncoded format and this access will exclusively be granted for tasks that are necessary in order to complete the project. **All the information will be coded and therefore pseudo-anonymized when the results are reviewed. Encoding (pseudo-anonymizing) means that all patient-identifying data (name, date of birth) is erased. Each patient is assigned a unique code and the key to decode this will remain at the hospital (CHUV). Without this unique code and key, it is not possible to link the data to you (the patient).** On occasion, scientific journals require access to individual data (raw data). If this is the case, it will always be coded and therefore does not identify you (the patient) as a person. Everyone involved in the project is bound by professional secrecy.

Throughout the project, the site may be inspected by the relevant ethics commission or by the institution that commissioned the project. For these inspections, the project manager must grant access to the relevant investigators and allow them to see patient's personal and medical data.

12. Withdrawal from the project

You can withdraw from the study at any time if you wish or decide to do so. The data and samples collected up until your withdrawal will not be used for any further analysis. The samples will be stored in the hospital in accordance with the CHUV hospital specifications.

13. Repairing damage

You (the patient) do not receive compensation for your participation in this project.

14. Liability

Damage related to the research project is covered by the institution or company that commissioned it and is responsible for its conduct. The conditions and procedures are regulated by law. This is a category A study according to Human Research Ordinance (HRO). The personnel involved in the study are covered under general liability insurance provided by the Sponsor according to Art. 19 of the Swiss Human Research Act (HRA).

15. Funding

This project is funded by Resistell AG and Innosuisse – Swiss Innovation Agency.

16. Contact person

If you have any doubts, concerns or emergencies during or after the project, feel free to contact the team using the information below:

On site study management: Gilbert Greub

Complete address and telephone number contactable on weekdays and email address:

Institute of Microbiology CHUV

Rue du Bugnon 48

CH-1011 Lausanne, Switzerland

Tel: +41 21 314 4056

Email: gilbert.greub@chuv.ch



Statement of consent

Written Declaration of Consent for Participation 'a posteriori' in a Research Project

Please read this form carefully. Do not hesitate to ask questions if there is anything that you do not understand or would like further clarification on. For your participation in this study, your written consent is required.

BASEC number of the research project (after submission to the relevant ethics COMMISSION) :	2020-01622
Title (scientific and usual) :	Nanomotion-based Resistell AST to determine the antibiotic susceptibility of Gram-negative bacteria causing bacteraemia and/or sepsis.
Responsible institution (project manager and full address) :	Gilbert Greub Institute of Microbiology CHUV Rue du Bugnon 48 CH-1011 Lausanne, Switzerland
Study location :	CHUV Lausanne
Project manager on site : Name and surname in capital letters :	
Participant : Name and surname in capital letters : Date of birth :	<input type="checkbox"/> female <input type="checkbox"/> male

- I acknowledge receiving written and oral information from the physician-investigator about the objectives, the scope, possible benefits, disadvantages and risks of participating in the above mentioned study.
- I confirm that whilst an independent doctor previously reviewed the study protocol and ensured that my rights and wishes were upheld, I now accept the written and oral information I have been given. Furthermore, I also acknowledge that I had enough time to make an informed decision.
- I have received the answers to the questions I have asked in relation to participation in this project, I will keep the information sheet and receive a copy of my consent statement.
- I agree that my treating physician should be informed of my participation in the research project.
- I accept that the competent specialists of the management/principal of this project, the competent ethics commission, may consult my uncoded data in order to carry out checks, provided, however, that the confidentiality of this data is strictly assured.
- I know that personal data (including the samples) can only be transmitted in a coded format and for research purposes as part of this project.
- I may, at any time and without having to justify myself, revoke my consent to participate in this study, without adversely affecting my medical treatment/management. Data and samples collected to date will, however, still be analyzed for project purposes.
- The hospital/institutional civil liability covers any damage that may result from the project.
- I am aware that the obligations mentioned in the fact sheet must be met for the duration of the project. The investigating physician may exclude me, the patient at any time if this is deemed necessary.



Location, date	Name and surname in capital letters : Signature of the patient :
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Certificate from the investigating physician/investigator: I hereby certify that I have explained to the participant the nature, importance and scope of the project.

I declare that I meet all legal obligations related to this project. If I was to become aware, at any time during the project, of elements likely to influence the consent of a participant to take part in the research project, I agree to immediately inform them.

Location, date	Name and surname in capital letters of the physician-investigator/investigator providing the information : Signature of the physician-investigator/investigator :
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