



**European Cooperation
in the field of Scientific
and Technical Research
- COST -**

Brussels, 22 November 2013

COST 078/13

MEMORANDUM OF UNDERSTANDING

Subject : Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action TD1305: Improved Protection of Medical Devices Against Infection (iPROMEDAI)

Delegations will find attached the Memorandum of Understanding for COST Action TD1305 as approved by the COST Committee of Senior Officials (CSO) at its 188th meeting on 14 November 2013.

MEMORANDUM OF UNDERSTANDING
For the implementation of a European Concerted Research Action designated as
COST Action TD1305
Improved Protection of Medical Devices Against Infection (iPROMEDAI)

The Parties to this Memorandum of Understanding, declaring their common intention to participate in the concerted Action referred to above and described in the technical Annex to the Memorandum, have reached the following understanding:

1. The Action will be carried out in accordance with the provisions of document COST 4114/13 “COST Action Management” and document COST 4112/13 “Rules for Participation in and Implementation of COST Activities”, or in any new document amending or replacing them, the contents of which the Parties are fully aware of.
2. The main objective of the Action is to reduce the risks of device-associated infections by a comprehensive, highly transdisciplinary approach, addressing clinical needs and combining novel concepts of surface modifications and improved procedures of testing for efficacy *in vitro* and *in vivo*. The resulting materials are comprehensively characterized and tested chemically and biologically also considering industrially relevant perspectives.
3. The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EUR 32 million in 2013 prices.
4. The Memorandum of Understanding will take effect on being accepted by at least five Parties.
5. The Memorandum of Understanding will remain in force for a period of 4 years, calculated from the date of the first meeting of the Management Committee, unless the duration of the Action is modified according to the provisions of section 2. *Changes to a COST Action* in the document COST 4114/13.

GENERAL FEATURES**Initial Idea:**

Device-Associated Infection (DAI) constitutes one of the key reasons for clinical failure, impaired functionality, and reduced lifetime of medical devices, resulting in high distress for the patients and huge socioeconomic costs. The prime objective of this Action is the identification and assessment of recently developed anti-DAI approaches in a comprehensive pan-European effort. Understanding and combating DAI is a device-dependent, highly complex and transdisciplinary challenge requiring collaborations between clinics to define the practical boundary conditions and unmet needs, material and surface engineering to elaborate on enhanced material/drug combination systems, pharmacology and (micro)biology to explore novel antimicrobial active compounds and establish advanced, DAI-relevant test systems *in vitro* as well as in dedicated animal models. The most promising concepts and engineered prototypic devices are finally evaluated in a preclinical setting. Action Members from the medical device industry and insurance business will proactively exchange knowledge on technical, regulatory, risk analysis and economic issues, all of which are of utmost importance for a successful translation of academic innovation to engineered systems that fulfil the overall requirements of the different stakeholders involved. This Action will provide an extensive, interdisciplinary training program including scientific/technical, regulatory, market and social skills contents; this will contribute to strengthen the interactions within the Action consortium and improve the chances of early-career researchers on the job market. Overall, success in this Action will contribute to improved healthy-life expectancy of patients, reduction in health care costs, and increase the competitiveness of the European medical device industry on the world market.

Keywords: Life science, medical device, infection, implant, functional material, smart coating, antimicrobial, antibiotic, nanocontainer, drug release, *S. aureus*, *S. epidermidis*, biosensor, biocompatibility, toxicity, *in vitro* assay, *in vivo* study, regulatory aspect, nanomaterial, bioabsorbable polymer, surface analysis

STRATEGY

Objective 1 (A.2) - Type: Coordination of information seeking, identification, collection and/or data curation

1. Unpublished Aspects of Knowledge Creation, including experimentation and testing, scientific experiment or test.
2. Joint peer-reviewed publication, open access.
3. Action Science and Technology Meeting, Working Group.
4. Internal and External Communication, Virtual Network: any web-based resource needed for work coordination among Action Members.
5. Science and Technology Coordination, Short-Term Scientific Missions (STSM).

Objective 2 (A.5) - Type: Development of knowledge needing international coordination: new or improved theory / model / scenario / projection / simulation / narrative / methodology / technology / technique

1. Science and Technology Event or Meeting, Action Conference.
2. Scientific Publication (including Science and Technology study and excluding handbooks, guidelines and best practices. Excluding Joint Peer-Reviewed Publication), behind pay wall.
3. Science and Technology Coordination, Application for Funding to Intergovernmental Programs or Agencies.
4. Science and Technology Event or Meeting, Training School.
5. Science and Technology Output, New Patent(s) Held by Action Members.

Objective 3 (A.8) - Type: Input for future market applications (including cooperation with private enterprises)

1. Handbook, Guidelines, Best Practices, for S&T purposes.
2. Science and Technology Coordination, Application for Funding to Intergovernmental Programs or Agencies.
3. Science and Technology Output, Prototype, Demo or Tool.
4. Delivery of Written Input to a Stakeholder (excluding business enterprises), to a standards organization.
5. Input to Other Science and Technology Funding Scheme for the Formulation of Calls for Proposals, unwritten - national.

Objective 4 (B.13) - Type: Bridging separate fields of science/disciplines to achieve breakthroughs that require an interdisciplinary approach

1. Stakeholders Outreach, including Unwritten Inputs and Dissemination, to end users/practitioners.
2. Action Science and Technology Meeting, Working Group.
3. Science and Technology Coordination, Joint Student Supervision (at Master's or Doctoral Level).
4. Science and Technology Coordination, Application for Framework Programme Funding.
5. Science and Technology Event or Meeting, Action Conference.

A. CHALLENGE

Background

The European medical device industry accounts for more than 11'000 companies with combined annual sales of €72 billion, representing 33% of the world market. In Germany alone, more than with 2.5 million medical devices are used per annum. The majority of such devices serve its purpose in restoring/replacing diseased/damaged body function. Millions of patients worldwide benefit from permanent implants comprising various biomaterials such as prosthetic joints, dental implants, stents, vascular grafts, and pacemakers, or from temporary inserted devices such as intravascular and urinary catheters.

However, a non-negligible fraction of **devices fail in practice due to Device-Associated Infections (DAI)**, often with severe consequences for the patient as revision surgeries are required leading to a substantial increase in socioeconomical costs. DAI is always connected with microbial contamination of an implant or device, either inferred during surgery (e.g. through implant-skin contact) or later through activation of interfacial microbials. Subsequently, microorganisms proliferate rapidly as biofilms, in which they are protected against both antibiotics and immune clearance. Bacterial species living in a biofilm have great viability advantages requiring 500–5000 times higher doses of antibiotics to get eradicated compared to planktonic organisms. Antimicrobial strategies supplemental to systemically administered antibiotics therefore often focus on modifying implant or device surfaces. However, the extensive use of antibiotics worldwide during the last decades has led to a threatening situation where a large number of bacteria have developed resistance against conventional antibiotics. This has resulted in a number of infectious diseases, for which limited treatment exists. As a result, development of new effective antimicrobial compounds and

treatment alternatives is an important part of the European action plan against the rising threats from antimicrobial resistance [COM/2011/748].

The medical profession is aware of the importance of peri-operative hygiene to reduce DAI. As a result however, **DAI is increasingly classified as preventable medical errors**, especially when occurring acutely after implantation. Moreover, **insurance companies start to refuse payments** for replacing infected implants and devices. These socio-economic developments are a serious threat for the use of materials in medical practice with a rapidly increasing societal pressure to achieve relevant design improvements because “we all desire a guarantee, that the service or implant will have lasting positive effects without a risk of infection”. There is an urgent challenge for the research community to address DAI-related unmet needs and develop clinically relevant solutions.

To date, many potent **antimicrobial active compounds (AACs)** drugs are available to treat infectious disease systemically, but only a few are suited for use in combination with DAI, and even fewer can be bound onto and incorporated into surfaces while retaining their activity and meeting additional functional specifications, including displaying the desired release rate, spectrum width, avoidance of side-effects and induction of resistance, and capacity to integrate in tissues. Despite substantial, rapidly increasing research efforts on antibacterial strategies, **there is currently no effective clinical solution**. The few AACs containing devices rely on delivery of massive amounts of antibiotics, or on release of silver essentially limited to topical applications. For example, there are first antibiotic-loaded nail systems in Osteosynthesis and first silver-release wound pad applications, but the safety of silver, in particular, is highly disputed when considered for permanent medical implants *in vivo*. **Timed presentation at and local delivery of AACs from device surfaces** is considered key for reducing the incidence of DAI in the future.

Reasons for the so far limited translational success of AAC/material combination approaches and related need for urgent actions of the different stakeholders include:

(a) The complexity of research projects in this field requires a highly interdisciplinary team and expertise across disciplines; only very few comprehensive DAI investigations exist which encompass both materials and surface development and characterization, *in vitro* as well as *in vivo* (animal) testing.

- (b) Successful translation to application strongly depends on the very early involvement of clinical researchers, industry and notifying bodies.
- (c) Each implant type has specific requirements in terms of risks of biofilm flora. There is no “one size fits all” solution.
- (d) Correlations between *in vitro* data, *in vivo* animal results and clinical outcome are largely unknown, and therefore lack of predictive *in vitro* tests are a main hurdle for efficient screening of anti-DAI concepts.
- (e) Lengthy and costly approval process for so-called combination devices (i.e., implants or devices supplemented with secondary on-board drug therapies) is a further reason for the low number of combination devices in the market. However, given the increasing pressure from the various stakeholders involved in DAI, there is an on-going discussion with regulatory bodies on a paradigm change towards acceptance of claims for medical implant and device infection prevention without clinical trials, provided that the primary implant or device function is not adversely affected by adding the antimicrobial functionality. To facilitate translation of such concepts to clinical application, combination devices are now offered unique regulatory review processing.

The Action ***Improved Protection of Medical Devices Against Infection (iPROMEDAI)*** identified device applications in cardiovascular, orthopedics, trauma, urinary incontinence and catheters as critical application areas; they account for half of the medical device market. These sectors are affected in variable degree by DAI and with different consequence: established rates of incidence are 2-5% for orthopaedics, 10% for severe polytrauma, 5.5% for urinary incontinence, or 5-30% for different catheters implants. Not all DAIs exhibit the same consequences; they range from simple replacement of the catheter and antibiotic therapy to the amputation of a limb due to a persistence DAI in a joint, to highly increased long-term mortality associated with infection of cardiovascular devices. Common to all DAI is that they result in high distress for the patients and entail **huge economic and social costs**. Estimates for the cost of caring for patients with central venous catheters-associated blood stream infection alone are up to €1.5 billion/year in the EU. Even more puzzling is that it is well recognized that rates of DAI incidence are increasing, i.e. the rate of cardiovascular implant infection is increasing faster than the rate of implantation.

It is the objective of the Action to establish a **network across leading European academic and clinical research groups, and industry** with the aim of providing a scientifically sound, clinically relevant, industrially feasible and timely contribution to these socioeconomic most relevant topics. The issues and problems addressed in the Action are those that are considered to be key for the

overall goal of reducing the number of DAIs in general and specifically in the five device applications identified together with at least five industrial partners who will join the Action once it is accepted.

Based on a matrix of initial performance criteria, novel solutions are discussed and investigated in a comprehensive approach across different Domains. The Action will address specifically the list of reasons for the so far limited translational success as mentioned above (a-e). The candidates with the best property profiles will be pre-selected for subsequent advanced and later application-specific investigations.

Discussion with Action members from industry and insurance companies as well as with Regulatory Bodies will ensure that the **overall technical, societal and economic requirement profiles** for each application are taken into consideration to find an efficient strategy for adapting the developed material platforms to meet the specific requirements. Working towards different lead applications greatly improves the chances for at least partial **success in the translation to clinical evaluation**.

The Action is also a platform for discussing and preparing **European and national funding applications**. The new EU program “Horizon 2020” will offer opportunities to provide input to the formulation of new calls and to submit proposals as a strong European consortium. Furthermore, established collaboration with industry in this Action will foster applications to EUREKA, EUROSTARS or national R&D funding schemes.

The COST Action aims at

- (1) investigating the scientific, engineering and clinical issues that have been identified as the key challenges in addressing the problem of DAI;
- (2) finding dedicated solutions for the unmet needs in the translational process to applications (points (a)-(e) above);
- (3) identifying novel designed biomaterials/surfaces with enhanced antimicrobial device functionality and improved long- term stability;
- (4) documentation of comprehensive sets of standard and novel test methods with appropriate reference materials allowing for comparison of outcomes;
- (5) establishment of structure/property/function relationships and correlations between *in vitro* and *in vivo* data

(6) providing dedicated and integrated training programs across the technical disciplines and socioeconomic aspects of the field.

The expected impacts of the COST Action are:

- (1) improved therapeutic outcomes by reduction of device-associated, early infections and in part delayed infections;
- (2) solutions that improve patient quality of life and reduction of health care costs (estimate >€50mio (long term) for 25% reduction in listed applications) through reduced risk of infection and longer life-expectancy of the devices;
- (3) an increased competitiveness of European medical device industries thanks to better products.

The **five Working Groups** cover the key aspects along the “value chain” from materials to clinical application:

WG1. Antimicrobial Material & Surface Strategy

Background

Drug/medical device combination has received increasing attention from both medical device companies and drug producers and a promising new opportunity for improving implanted prosthetic device performance. Current applications cover mostly cardiovascular (drug-eluting stent) and few orthopaedic (e.g. antibiotic nail) applications. Moreover, they mostly rely on “passive” release of AACs, e.g. purely physical by diffusion or chemical by degradation of a polymer coating containing AAC and often deliver massive amounts of antibiotics, or release of silver which is likely to be limited to topical applications. Few have addressed smart approaches such as responsive polymers with bacterial kill and release function.

Challenges (selected)

The Action Members in WG1 will address these challenges through their expertise in the field and technological achievement in running, non-COST funded projects. For example:

- triggerable linker components (TLC) that release AACs based on the host response to bacterial infection (e.g., via infection-associated MMPs, quorum sensing, bacterial RNA);
- biomaterials with adjustable properties and AAC-loaded nanoconstructs for spatiotemporal AAC release;

- novel anti-adhesive (“non-fouling”) and degradable polymers as an alternative to AAC loaded systems;
- stable dual-functional surface coatings presenting covalently immobilised molecular layers of AACs that are functionally active and prevent adhesion of bacteria and the formation of bacteria biofilms.

Impact (selected)

- bacterial sensors which trigger the release of drugs from a reservoir will be instrumental to better target the bacterial infections themselves and reduce the overall exposure to antimicrobial drugs;
- recently developed responsive nanosystems, which preserve functionality when immobilised / entrapped in active surfaces / coatings will present a new and versatile strategy to fight against device-associated infections;
- anti-adhesive and dual-functional surfaces are promising candidates for selected applications with the advantage of less demanding regulatory requirements.

WG2. Antimicrobial Active Compounds (AACs)

Background

Antimicrobial peptides (AMP, e.g. Synthetic Antimicrobial and Antibiofilm Peptides, SAAP) as well as their combinations with metal ion systems have emerged as a promising alternative for the treatment of various infections exhibiting fast and broad-spectrum action and precluded resistance development. AMPs can display direct antimicrobial effects, immune- modulating and anti-inflammatory properties, as well as prevention and breakdown of biofilms. Despite this, to date no product based on AMPs has reached the market. In addition, nature offers interesting opportunities in AAC design. For example, the pharmacological potential of natural plants has been explored only to a very limited extent, despite long use for traditional use in indigenous medicines.

All these AACs have not yet benefited from their combination with smart/responsive delivery systems.

Challenges (selected)

- overcoming stability of peptides and other labile AACs, both in formulations and after administration, by novel formulation strategies and advanced delivery technologies;
- designing nanostructured materials in a size range that enables transport across physiological barriers, ease of engineering and functionalization, combined with approaches to control the release (WG1);
- combination surfaces releasing antimicrobial metal ion compounds and antibiotics or AMPs to exploit (synergistic) application;
- combination of therapy and diagnostics with addressable nanoparticle-based antimicrobial systems for drug release at the site of action and in a dose-on-demand set-up, and potentially also theragnostic monitoring of treatment outcome.

The Action Members in WG2 will combine the passive and triggerable delivery systems (WG1) with active components from WG2 including (i) AMPs such as SAAPs, (ii) inorganic nanoparticles (INPs) and tailored metal ion coordination compounds, (iii) natural AACs from indigenous plants, and (iv) combinations with conventional antibiotics for optimal performance on biofilm-based infections in particular.

Impact (selected)

- improved biological acceptance of medical devices through efficient antimicrobial action and anti-inflammatory effects for improved wound healing;
- improved efficacy on multiresistant pathogens through combination effects of AMPs or metal ion coordination compounds and antibiotics;
- reduced use of antibiotics and other AACs through localized delivery translating into lower contribution to resistance development.

WG3. Mechanistic Studies, *in vitro* Testing, Sensing and Modelling

Background

There is an unmet need for efficient and microbiological test protocols of engineered antimicrobial surfaces with predictiveness for the *in vivo* case. Advanced (multi phenotype, 3D) *in vitro* tests may be able to complement the *in vivo* approaches. These systems can reveal the detailed responses of

relevant cell types (in combinations) to biomaterials, and are pivotal for initial testing of antimicrobial actives.

To study the initial immune responses to biomaterials in a whole animal with high throughput capacity, zebrafish embryos (*in vitro*) models are an attractive new platform, particularly since immunity genes and regulatory pathways of the zebrafish show good resemblance to those of humans. Use of the zebrafish embryo model for biomaterial-associated infection and immune responses has recently been demonstrated.

Challenges (selected)

- *in vitro* (multicell type 3D) models to assess biomaterials-cell interactions and efficacy of antimicrobial actives and systems;
- *in vitro* microbiological test conditions that better reflect bacterial contamination of implants with typically only a few bacteria transferred from the patients skin to the implant during surgery;
- *in vivo* real time sensing of foreign body reaction and biomaterial-associated infection in mouse models;
- use of the zebrafish model for efficacy testing of antimicrobial systems for biomaterials, with possibility of high throughput testing/screening.

Impact (selected)

- online *in vitro* and *in vivo* monitoring bacterial-surface interactions provides a dedicated method to follow the time evolution of adherent and non-adherent bacteria in interaction with antimicrobial surfaces;
- *in silico* predictive modelling may offer a fast method to assess risks of the material characteristics in combination with the *in vivo* application;
- the zebrafish model will provide detailed understanding at the molecular level of biomaterial-associated immune responses, high throughput selection of materials, assessment of activity of antimicrobials without or with antimicrobial release system, in a novel whole animal model system.

WG 4. Advanced *in vivo* Testing and Preclinical Studies

Background

The testing of anti-infective implants adds a significantly more challenging task for preclinical *in vivo* models compared to standard implant studies. In addition, the ideal *in vivo* testing model for an anti-infective device must also consider the local antibiotic pharmacokinetics in the tissues surrounding the implant, the relevance of the total amount of antimicrobial versus the volume of distribution within the host animal and how this compares with what is achievable in a human situation. Overall, to aid the development of novel anti-infective solutions, the candidate technologies must be tested in standardized animal models, and the successful and most potent candidates must be tested in subsequent models that represent the clinical situation as closely as possible.

Challenges (selected)

- use of a standardized murine subcutaneous biomaterial associated infection model to serve as a standard model for testing across all delivery platforms;
- development of a sheep model to study the biology of two-stage hardware exchange due to implant related osteomyelitis;
- use of a rabbit model suitable for testing the prevention and treatment of infection of an intramedullary nail;
- use of a mouse model suitable for testing the prevention and treatment of infection of an internal fracture fixation device;
- murine model of infection of intramedullary nail.

Impact (selected)

- the use of a standardized murine DAI model will serve as a reference point for testing novel technologies. This will enable unbiased comparison of various anti-infective technologies in one defined model;
- the availability of a two stage implant exchange model will allow for a robust testing of any novel anti-infective solution, mimicking a crucial clinical scenario particularly at risk of infection i.e. reinfection after failed septic revision.

WG5. Clinical Background and Needs

Background

The management of implanted medical devices infections is turning more and more to an international challenge, in the communities as well as hospitals. Microorganisms involved in these infections are usually not only virulent, but also multi-resistant. Furthermore, the isolation of metabolic variants known as small colony variants (SCVs) have been frequently associated with persistent and relapsing infections, such as Osteomyelitis (OM) or prosthetic joint infections (PJI), the clinical causes of these recurrent infections are diagnostic and therapeutic failures. At least three aspects characterize the microbiology of these infections: (i) the isolation of a wide range of pathogens; (ii) production of biofilm, and (iii) low predictivity by traditional microbiological diagnostics.

The risk of DAI is continuously increasing due to an increasing number of implanted medical devices. Each class of device requires a separate therapy scheme and the management of infections relies on a basic understanding of the pathogenesis and the microbial population.

Challenges (selected)

- early identification of DAI with improved diagnostics tools;
- investigation of possible genetic predispositions for increased risk of DAI;
- development of standard guides for treating DAI in various classes of devices and patient co-morbidities/predispositions;
- diagnosis of DAI by sonication and Real Time-PCR;
- Antimicrobial Susceptibility Testing (AST) of biofilm producing organisms;
- management and treatment for PJIs by “Microbiological Case Report Form” (CRF).

Impact (selected)

- reduced risk of antibiotic resistance through a better understanding of DAI;
- improved outcome of DAI therapies for patient and socioeconomic benefit;
- improved diagnostic methods to detect and identify involved microorganisms by: study of antibiotic-resistance traits; molecular characterization; assessment of biofilm production; detection of small-colony variants; study of chronic infections;
- correlation of microbiologic characteristics with clinical characteristics and outcome.

B. ADDED VALUE OF NETWORKING

How the research requires the reciprocal interaction between these Domains

Past history has shown that the development of medical devices exhibiting antimicrobial activity has produced *relatively few commercially available solutions*, despite much focus and investment in R&D. This may in part be attributed to a lack of interaction between sectors (academia, industry of various types, and the clinics). Academic institutions have repeatedly developed sophisticated and elegant solutions that are rarely developed all the way to clinical application, e.g. in the form of available prototypes. This may be due to a lack of awareness (on the part of academics) of the requirements for preclinical testing, IP protection, market requirements, or the actual clinical needs, and therefore, these ideas often peter out at some point in the development process. Similarly, industry may not independently develop the best possible material solutions without access to the state-of-the-art, and world leading opinions available in academia.

Close partnerships between academic, clinical and industrial partners is required so that the vision for developing antimicrobial active medical devices can be set from the first stage with input from all sectors giving the best possible chance of a successful clinical application. Such *networks and mobility of ideas, resources, and people between industrial and academic environments* are particularly important in the era of open innovation, where an ever increasing part of industrial R&D, notably in an earlier development stage, is performed through academic groups and research-intensive CROs. In addition, involvement of clinicians and microbiologists is required in both academic and industrial research to facilitate focus on real and not on fictive issues. This information is decisive for selection of AACs which are tested for efficacy and toxicity. From the *biological work*, important input parameters for material, coating, and drug delivery system design is obtained, e.g., regarding which release profiles are needed (from pharmacokinetic input), which actives should preferably be loaded into or tethered onto these materials (chemical structure/function relationship), and which other material properties are needed (non-fouling, biodegradability, from toxicity profiles).

Reciprocally, *materials scientist* can adjust their engineered biomaterials (actives, loading level, etc.) based on biological data on efficacy and toxicity. In both directions, establishment of new

platform technologies for material design and evaluation are key for maximizing this reciprocal benefit. The whole development is an iterative process requiring intense collaboration and discussion across the disciplines. Of course, the participating groups are involved in such cross-disciplinary collaborations already, as this is a prerequisite for successful research in the area.

Through this COST Action, however, a broader set of integrated and coordinated collaborations can be obtained, expected to substantially help developments in fundamental science, technology design, and dissemination.

Why within the scientific approach, the reference to common theoretical concepts and methods as well as to their common evolution is needed for all involved Science Fields

Furthermore, standardization and use of reference materials/compounds is of utmost importance for advancement of the field since cross-comparison of results generated in different research laboratories is only feasible if in addition to the research-specific samples and characterization methods a common reference material and standard test method is used as control. This has to be applied within the same technologies, but also between the same approach and different biological contexts. This will facilitate not only rational material development, but also provide guidance in terms of “lower hanging fruits”, for which the present approaches are most likely to yield beneficial translation into the clinic and assessment of the outcome by industry.

Finally, all ***translational efforts have to be coupled to health economic considerations*** in order to secure that the optimal combinations of medical need and technological opportunity are identified. From a scientific perspective, and in order to reach maximum impact of the research, methodological development work, detailed experimental studies on physical as well as biological aspects, and theoretical modelling of selected aspects (e.g., release rates, pharmacokinetics, etc.) need to be combined.

Why the Action iPROMEDAI leverages non-COST funded human and physical resources

The Action Members will cover dedicated expertise in materials and surface science, engineered molecular systems for highly controlled presentation/release of drugs and AACs, tools to investigate microbiological and biofilm-related mechanisms both *in vitro* and *in vivo*, advanced *in vitro* cell- and microbiological assays, infection-specific *in vivo* (animal models) and clinical

infectiology research and practice. Action Members will establish contacts to medical device industries, and other business members (e.g. health insurances), and to Governmental Bodies and Standard Organisations; inviting them to join the Action once it has started.

This COST Action therefore provides to the scientific community a ***unique chance for an integrated approach*** covering all aspects of the “value chain” from materials to device demonstration tools at the pre-clinical level, with the following key aspects:

The ***Action Members in clinics will define the specific needs and requirements*** that are key for a potential success in the translation to (pre)clinical exploitation, separate for the five model application areas identified in this Action. New technologies and systems in the hands of academic partners (already available or to be developed in running parallel research projects) can therefore be checked against clinical need and specific requirements (which differ greatly for a non-permanent device such as a catheter and a permanent device such as an orthopedic implant). This is for most academic partners a unique opportunity to judge their achievements in terms of chances for translational success and to consider already at an early stage application-relevant criteria in running R&D projects.

Technology-push efforts can therefore be matched in our Action by ***application-oriented pull aspects*** with the great chance of identifying among the diverse scientific technologies those that appear best suited for translation. This is a great asset that would certainly not be possible to this extent without a pan-European Action, given that for basically all Action Members it would be difficult or impossible to receive national funding at a level sufficient for such a broad interdisciplinary programme.

An important bottleneck in this particular field is that the majority of ***DAI concepts and developments get lost in translation***. A key reason is the high costs for the regulatory procedures and associated clinical investigations that medical device companies have to submit. However, the regulatory costs depend strongly on both the type of applications and the material/drug system. An important objective for the Action is an active participation of business/industrial members. The industrial Action members will also provide ***specific contacts to the European Medicines Agencies (EMA) and other Regulatory Bodies for a continued interaction along the Action duration***. More than five medical device companies have expressed explicit interest to participate in the Action it has been started. This presents a highly valuable opportunity for periodic discussion and early

feedback from both industrial and clinical members as well as EMA on regulatory aspects related to particular technologies and concepts developed by Action members. At the same time, the Action will allow for a *win-win situation* with the industrial Action Members getting access to latest developments and their technological performance. Without such a transdisciplinary and transnational collaborative effort between academic, S&T, clinical, business and governmental organisation partners in a COST framework allowing for extensive interactions, this would be highly unlikely to take place.

The COST Action will provide excellent opportunities to form active consortia among Action Members for *future applications to national, transnational and European funding schemes* such as Horizon 2020, EUREKA, etc., but also with industry, or other funding sources (e.g. the Wellcome Trust). We expect this to happen in relation to both basic science topics with new ideas that will emerge in the Action as well as application-near, industry-oriented topics for which sufficient feasibility results have been gathered in the Action. This will substantially widen further the scope and leverage chances for successful translation to products and therefore contributions to improving patients' quality of life.

Access of Action Members to infrastructure of partners: The scientific topics covered by the Action require access to specialized materials and surface characterization techniques.. Action Members will therefore greatly profit from either services provided by other Action Members or by inviting researchers from other members to perform analyses and characterisations themselves. Similarly, members will provide access and support in micro- and cell-biological investigations and assays. Such collaborative effort would not be impossible without a pan-European consortium, but it is greatly facilitated by the COST framework.

This pan-European network will furthermore ***impact transdisciplinary education***. In the context of the two Training schools I and II, Action Members will provide teaching material such as slide collections and information on key book and publications in the field compiled specifically to the needs of the consortium members, in particular Ph.D. students and early career researchers. These training schools will provide teaching, discussion and student activities across S&T topics, clinical needs and practice as well as translational aspects (with contributions by business stakeholders) including regulatory issues, industrial practice and business case studies. There will be important benefits of the Training Schools across the network for both the collaborative technical Action activities (thanks to improved knowledge base, establishing a student network and communication

forum) as well as for the longer-term career of the students and early-career researchers. Through COST, a powerful tool is provided to facilitate training undergraduate curriculum activities as well as industrial contract training programs to provide students with the latest development in this broad area, and do build up a network of contacts of fellow students and teachers from a broad range of disciplines.

C. MILESTONES AND DELIVERABLES: CONTENTS AND TIME FRAMES

The following types of activities are part of the COST Action:

Kick-off meeting

A kick-off meeting of all COST Action members is. One of the tasks aside the formal organization will be to identify possible fields of research related to the Action challenges which are underrepresented in the COST Action at the present time point and to name additional Action Members (e.g., Academic: computation/modelling task; Business: insurance company) to be invited to join the Action. It is also used to nominate Action Members for a first STSM to organize the Action S&T Meeting of year 1.

Action S&T Meeting

A total of four Action S&T Meetings will be organized. These meeting will be held in conjunction with either Action workshops or conferences. Aside the usual WG Meetings, and coordination of research activities, the Action S&T Meetings will cover lateral topics, i.e. topics that include aspects across different domains. For example an Action S&T Meeting could be dedicated to a specific application, e.g. a catheter, and topics discussed during the meeting will include clinical problems, needs for technological solutions, *in vitro* and *in vivo* tests and industrial input. The specific topics will be identified during the early phase of the Action. Only the first Action S&T Meeting in Year 1 and the last in Year 4 will be of general nature and dedicated to the research of all Action Members.

The aims of Year 1 Action S&T Meeting will include

- generation of a common S&T knowledge base as regards the current state-of-the-art in

addressing biomaterial- associated infection (cross-domains) and unmet needs;

- presentation by Action Members of their expertise, available database and specific technologies at hand relevant to the Action as well as their current and future activities and goals in the field;
- industrial perspectives on translational aspects and regulatory issues.

Deliverables:

- all Action S&T Meetings output is summarized and put on the Actions Website;
- summaries of the topics will be published as joint review/current opinion type of papers;
- harmonized methods will be converted to SOP and reference materials will be defined;
- unpublished aspects of knowledge creation, including experimentation and testing; first compilation of realistic application areas (medical device types, clinical indication, etc.).

Action Workshop

At least two Action Workshops will provide (a) a detailed working plan and choice of materials, test methods and common reference materials and methods for collaborative R&D actions within and across the five different Working Groups (WP) and with Action business members. The basis will be information exchanged at the kick-off meeting and outcome of continued interactions between the WP Leaders and Teams; (b) identification by Action business and clinical members of the most realistic scenarios for translation of the technology to be developed considering technological, regulatory and cost issues.

Deliverables:

- unpublished Aspects of Knowledge Creation, including Experimentation and Testing;
- first compilation of realistic application areas (medical device types, clinical indication, etc.);
- joint publications in forms of reviews/current opinion type of publications or guest-edited special issues of a high- impact journal.

The focus of the second workshop is on compilation of established methods and considerations/approaches to DAI and preparation of drafts and work items to be discussed with Standard Organizations. Contact with Standard Organizations is established prior to the workshop and member of these organizations will be attending the workshop and will give introduction to the different formats of standards and help to draft on standard guidelines, standard practice and standard test methods for selected applications. Some COST Action members are active in standard

organizations. Same holds for at least one Insurance Company to join the Action with the task of providing views on the future handling of hospital-infection-related cases (e.g., reliability issues), providing statistical data on clinical outcomes in the field, and results of the evaluation of the benefit for solutions to the problem in the different fields of the Action as well as other application fields.

Deliverables:

- well-defined standard protocols for the Action Members;
- at least five standards test methods and one standard guide drafted for discussion with the Standard Organizations.

Action Conference

Two international/European high-level conferences will be organized to expose the Action Members to a wider community in the field. These conferences will be organized in collaboration with European societies and organization, e.g. in collaboration with European Study Group for Implant Associated Infection or European Cells and Materials Conference. The conferences will be equally attractive to participants from academia, clinics, business/industry and governmental organisations, and is open for non-Action Members. Each conference will address specific topics to be defined at the appropriate time point.

Deliverable:

- proceedings of COST Action Conference published in international scientific journals;
- public media statements, broadcasts or interviews disseminated in the Action Countries.

Training School I and II

Two Training Schools (3-4 days each) will be organized with the aim of providing interdisciplinary education to the students of the Action Members and occasional partners. The Training Schools address the fundamental aspects of the Action in a tutorial style, and few, selected cutting edge scientific and clinical research topics. This will efficiently contribute to education of young and early-career scientists in particular. Academic, clinical and business members of the Action will actively participate as teachers; additional invited keynotes by non-Action Members. The training schools will also provide different schemes for the active participation of trainees.

Deliverables:

- documentation of training course (presentation slides, selected publications);
- intense scientific exchange between Action members.

Other Activities

Apart from organization of the different Action Activities, described above, another important activity will be the creation of “Action Codes”, i.e. documentations and internal guidelines on regulation of confidentiality aspects and general intellectual property guides to be used as a basis in all collaboration efforts. Other activities will be on setting up internal/external websites, the communication policies and guides for webinars and virtual meetings (Webex type).

Deliverables:

- various, strongly STSM dependent.

Short Term Scientific Missions

The Mobility program in form of STSM is for members of the Action research groups, in particular (but not exclusively) for PhD students and early career scientist. It is the aim to encourage and enable internships lasting typically 1-6 month. Key element of this Action are: (a) exchange of students between labs of complementary expertise in the same field (e.g. in materials and surface science, characterization and *in vitro* testing, etc.), and (b) between labs of different fields (e.g. mobility between materials science, microbiological test labs, clinical research, and potentially with industrial Action Members).

Deliverables:

- >30 months researcher exchange between partners;
- reports on exchange;
- intense scientific exchange between Action members.

Virtual Working Group Meetings

Virtual meetings within the five WGs will be held periodically, at least every six month for WG and project-based exchange of information every three month to ensure optimum planning, coordination, and critical evaluation of achieved progress. The WP-Leaders, Action Chair/Vice-Chair, DM and STSM Managers (forming the **Steering Committee**) will interact at least twice a

year to coordinate planning, activities and follow-up actions.

Deliverables:

- minutes;
- unpublished aspects of knowledge creation.

Timetable of foreseen Activities

Event /Quarter	Year 1				Year 2				Year 3				Year 4			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Kick-off meeting	■															
Action S&T Meetings		■				■						■				■
Action Workshops		■										■				■
Action Conferences						■						■				
Training Schools					■						■					
Virtual WG meetings	■		■		■		■		■		■		■		■	
Mobility of Action			■	■	■	■	■	■	■	■	■	■	■	■	■	■

Other Milestones

(in addition to the activity milestones)

Time Measure/Deliverables

Q4 >10 Industrial Action Members

It is the aim of having at **least 10 industrial Action Members covering the five foci of application.**

Q6 1 report

An **internal intermediate report** will summarize the combined Action knowledge gathered during the first 18 months of the Action. This will serve the business members of the Action to formulate specific plans for future activities regarding translation and exploitation towards medical devices with reduced infection risks.

Q7 > 3 submitted

Individual or collaborative project funding applications (>3) by Action Members submitted to national or transnational (e.g. EUREKA/EUROSTAR) funding agencies. This will also be an (additional) opportunity for Joint Student Supervision (at Master's or Doctoral Level).

Q8 > 2 prototypes

Prototypes of at least two model devices equipped with novel functional coatings/properties, developed in the Action and ready to be tested across domains in a comprehensive approach including *in vivo* (animal) studies.

Q10 > 1 contribution in at least 4 Action Countries each

Outreach and media coverage including videos or other multimedia content realized in > 4 Action countries for either end users (clinicians) or the public on specific projects or the general Action topic.

Q15 > 5 reviews/ >8 original publications

A collection of at least **five reviews** presenting the main critical aspects of the fields covered by the Action, to be published in a high impact review journal plus **eight original joint publications** by at least two Action Members will be published during the remaining Action duration

Q15 > 2 submitted

Two proposals by a consortium of at least five Action Members of at least five Action countries, using knowledge created within the COST Action will be submitted to EU Framework program Horizon 2020

Q16 > 8 industrial events

During the course of the COST Action **at least 8 industrial events** in the form of national industry workshops, technological aperitifs, evening talks or similar formats will be organized by the Action Members to foster the contacts between academia/clinics and relevant industries.

Dissemination

Dissemination of the results and know-how generated in the COST Action has high priority in this Action. As listed above, various activities are organized during the duration of the COST Action and results will be disseminated in different formats and through various channels during the whole

duration of the COST Action:

- scientific results are published jointly in peer-reviewed journal, edited books, or proceedings;
- standard methods, standard procedures, and standard guides are submitted to leading international organization;
- close collaboration and interaction are installed with divers national and international societies that address DAI issues;
- the general public awareness on the topic of DAI and on this COST Action is fostered via contributions to international magazines, newspapers, and national radio/TV broadcasts;
- policy makers, notified bodies, and funding agencies are approached by direct personal contacts of Action Members or through the general outreach activities as listed above;
- awareness by business stakeholders is established during conferences and workshops, and by inviting representatives of industry to specific events at the national and international level;
- awareness of the medical community on novel developments.

D. ACTION STRUCTURE AND PARTICIPATION – WORKING GROUPS, MANAGEMENT, INTERNAL PROCEDURES

The Action will be overseen and steered by the **Management Committee (MC)**, created according to the COST framework rules.

The MC will oversee and coordinate the scientific, financial and outreach activities and the integration of industry related Action plans. It will decide on overall strategic planning of the Action, nomination of STSM coordinators and working group members, dissemination policy, conceptual frame of Action Conferences, Workshops, Training Schools, and support with any intellectual property issues that may come up. Particular attention will be given by the MC on gender issues and support and education of early-stage researchers, both technical and soft skills, e.g. in terms of assignment of appropriate tasks and responsibilities to foster their management skills, and training across disciplines.

MC will meet twice a year with intermediate web-based/phone conferences.

The **MC in collaboration with the SC** will be responsible to closely monitor achievement of the organizational and scientific milestones and provide support as elucidated in section C:

- Website set-up
- Training Schools
- Coordination Between Working Groups
- Action S&T Meetings, Workshops and Conferences
- Mobility of Action Members
- Intermediate and Final Action Reporting
- Production of Dissemination Material and Media Coverage
- Submission of transnational/European proposals
- Publication submission involving two or more Action Members.

The **Steering Committee (SC)** will be set up encompassing the MC Chair, MC Vice-Chair, the five WG Leaders, the STSM managers and the DM. The SC will coordinate specific research group activities, particularly collaborative efforts between the WGs. The SC will prepare the agendas of events; in particular workshops, training schools, conferences, STSMs, organize the reporting, and provide general support to the MC. The SC will meet twice a year with additional web-based interfacing.

A **Dissemination Manager (DM)** will be nominated by the MC to initiate and coordinate activities such as website set-up, including intranet options for information on activities, resources and protocols available to all Action Members. The DM will further identify opportunities for publications in journals and radio/TV as well as to contribute to conferences outside the Action, thus fostering actions to increase the visibility of the Action.

Short-Term Scientific Mission (STSM) Coordinators will be nominated by the MC to plan and carry out specific tasks, in particular (a) the organization of two Training Schools, (b) exchange stays of researchers between different Action Members, (c) funding applications to transnational/European funding agencies, and (c) preparation of written input to standard organizations (as detailed in Section C). STSM coordinators will be preferentially selected among early-career researchers (backed up by a senior Action member) to provide opportunity for training management and communication skills.

At the 1st MC meeting will start the Action. This meeting will provide the final management structure with assignments of functions to individual members, and the first work plans, publication

of the Action and call for additional members to join the above specified WGs.

Working Groups (WGs): The COST Action has five WGs (contents detailed in Section A) covering:

WG1: Antimicrobial Material & Surface Strategy

WG2: Antimicrobial Active Compounds

WG3: Mechanistic Studies, in vitro Testing, Sensing and Modeling

WG4: Advanced in vivo Testing and Preclinical Studies

WG5: Clinical Background and Needs

The five **WG Leaders** foster optimum flow of information among its WG members and with the leaders of the other WGs, coordinate specific actions within their WGs, and prepare all necessary documentations for the MC and SC meetings. The WG Leaders meet twice a year to guarantee active collaboration and cross-fertilisation among the scientific and technological disciplines covered by the Action. The WG Leaders will also support the DM in terms of identifying opportunities for dissemination of Action achievements of the WGs to the scientific community and public in order to increase visibility of the Action and media coverage.

When feasible, necessary physical meetings of members will be combined with other events such as conferences, training courses to optimize travel budget, providing more resources for Training School and STSM, key aspects for successful transdisciplinary actions and education schemes.