



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

---

**Brussels, 15 May 2014**

**COST 022/14**

**MEMORANDUM OF UNDERSTANDING**

---

Subject : Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action BM1401: European Network on Raman-based applications for clinical diagnostics (Raman4clinics)

---

Delegations will find attached the Memorandum of Understanding for COST Action BM1401 as approved by the COST Committee of Senior Officials (CSO) at its 190th meeting on 14 May 2014.

---

**MEMORANDUM OF UNDERSTANDING**  
**For the implementation of a European Concerted Research Action designated as**  
**COST Action BM1401**  
**EUROPEAN NETWORK ON RAMAN-BASED APPLICATIONS FOR CLINICAL**  
**DIAGNOSTICS (Raman4clinics)**

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 develop a collaborative network of top European experts working towards the progress of the emerging field of Raman-based applications for clinical diagnostics aiming to establish a pan-European research program.
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 48 million in 2014 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.

**A. ABSTRACT AND KEYWORDS**

The aim of the Action *Raman4clinics* is to develop a collaborative network of top European experts working towards the progress of the emerging field of Raman-based applications for clinical diagnostics. The Action coordinates research run by diverse yet complementary research groups in Europe on novel, label-free and rapid technologies based on a wide variety of Raman spectroscopies for the clinical diagnostics of body fluids, bacteria, cells and tissues. International interdisciplinary networking opportunities are offered between scientists within biophotonics, chemometricians and physicians/clinicians. Main goal of the network is to give a major impetus in this vibrant field of research by aligning it to clinical requirements and application aspects (the unmet medical need) by means of COST as the best mechanism to progress the state-of-the-art. The Action creates a platform for scientific communication, exchange, collaboration and for new research activities, combining the partners' expertise in technology, component, system and methodology development and medical application. As a result, novel technology portfolios for clinical diagnostics will emerge to the benefit of patients as well as to the economy. The interest of the next generation of promising scientists will be attracted, thereby ensuring that Europe will remain at the frontline of research into clinical diagnostics.

**Keywords:** Molecular microscopy, Raman-based applications for clinical diagnostics, fiber optics, microfluidics and chemometrics, characterization of body fluids, cells and tissues, early cancer diagnostics

**B. BACKGROUND****B.1 General background**

Cells and tissues are characterized by a specific dynamic biochemical composition and molecular structure. In a similar way, each pathology or cellular abnormality is accompanied by biochemical and molecular changes, which may also be dynamic in nature (for example, as a cancer cell progresses to a vascularized system). Optical and spectroscopic techniques that correlate the biochemical composition, molecular structure, and its variations with the diagnosis would provide powerful clinical tools. Raman spectroscopy fulfils these requirements and has several unique advantages: (i) molecular vibrations of all constituents are probed simultaneously without external labels giving a specific fingerprint; (ii) this information can be obtained at various excitation wavelengths and intensities that are non-destructive to living organisms, and can be tuned with

resonance measurements to specific chemical species; (iii) combination with microscopic techniques is capable of mapping molecular species at submicrometer resolution, as well as the ability to collect images as a function of depth as well as space ; (iv) combination with fiber optic probes enables minimal invasive application during endoscopy. The potential of Raman-based techniques in clinical diagnostics has been proven in many reports. *Raman4clinics* will foster the collaboration between established research clusters of scientists within biophotonics and physicians/clinicians. It will advance the conversion of scientific findings into clinically relevant, practicable and economically feasible diagnostic methods and systems, setting up a technology portfolio based on Raman spectroscopy. The main objective of the Action is to create and develop a collaborative network of top European researchers working towards the progress of the emerging field of Raman techniques for the assessment of body fluids, pathogens, cells and tissues and their translation into clinical practice. The development and translation require an active interaction and exchange of knowledge between a wide range of disciplines; laser instrumentation, microscopy, spectroscopy, fiber optics, the life, chemical, biological and physical sciences. While each community has well-established networks, there exists no joint overarching forum to communicate future needs, plant conceptual ideas or present practical solutions toward the implementation of Raman spectroscopy into the clinics beyond the labs. COST as a precursor of advanced multidisciplinary research is the ideal vehicle for establishing such a forum, as its open character matches the need of an expanding research field and favors the formation of a dynamic network on European level, while individual experts from different disciplines easily can join without previous connections.

Why a European Network on Raman applications for clinical diagnostics supported by COST:

-Capacity building: to strengthen European competences in each individual research area as well as successful cooperation, -Accelerating clinical trials for such an innovative methodology. A collaborative network will help the groups to bridge the gap of evaluation between tissue/physical models and clinical testing. -Connecting research infrastructures to all potential users. Expertise in the assessment of Raman devices for commercialization (Technology Readiness Levels), protection of intellectual property, technology licensing, and “spin-off” opportunities will be shared. – Combining nationally funded research programs with a strong demand to join forces, networking and capacity-building activities for exchanging high-quality knowledge, -Generating SOPs (standard operating procedures) from sample collection and analysis to data processing (chemometrics) all aimed towards improved patient outcome along with biological understanding of pathophysiological changes. -Match other initiatives world-wide.

## **B.2 Current state of knowledge**

In the past decade, Raman spectroscopy has evolved as a versatile bioanalytical tool enabling label-free, and chemically and spatially resolved assessment of cells and tissues at molecular level. Biomolecules such as proteins, lipids, nucleic acids and carbohydrates are probed within complex matrices without preparation, even under in vivo condition. The physical mechanism behind Raman spectroscopy is inelastic light scattering of monochromatic laser radiation. As the red shifted portion of the Raman spectrum can overlap with fluorescence emission and Raman signals are relatively weak, intense excitation lasers and sensitive detection schemes are used. Near infrared excitation (as does excitation in the deep UV) minimizes unwanted contribution from fluorescence. Improved diagnostic methods are needed in various clinical fields. Numerous European research groups have reported proof of concept studies demonstrating the potential of Raman spectroscopy in microbial pathogen detection, analysis of body fluids, cancer diagnostics, cytopathology and histopathology. The development of Raman spectroscopies as clinical tools in Europe has been supported within initiatives like the Network of Excellence of Biophotonics Photonics4Life (2008-2012) or the EU project BINASP (the project was devoted to the development of nanotechnologies and new diagnostic tools for applications in the biomedical field). National projects in Germany and The Netherlands developed Raman systems for detection and identification of microbial pathogens. These dedicated systems are highly automated. They consist of a microscope with a video system for optical inspection and defining particles of interest. Subsequently, Raman spectra are collected from single bacteria that are identified at a strain and species level using properly trained classification models. Because identification can be achieved on a single cell level, cultivation time is short or can even be omitted. Endoscopy has been combined with fiber optic Raman probes to perform optical biopsies. The requirements for such probes are compact size and flexibility to be compatible with the working channel of commercial endoscopes. The main technical challenge of all prototypes is to integrate and miniaturize optical fibers on the tips of excitation and collection fibers. Proof of concepts studies have been reported in hollow organs such as the oral cavity, larynx, esophagus, gastrointestinal tract and arteries. High probe costs and probe-to-probe variations are the main obstacles for a wider translation of fiber-optic Raman approaches into the clinic. Among the main competitors of European researchers are the company EMvision (USA) and groups at MIT (USA) and Singapore, so there is no doubt that the present Action is very timely.

## **B.3 Reasons for the Action**

The translation of Raman-based diagnostic methods from the laboratory into the hospital requires a close cooperation between technology and method developers with clinical and biomedical end-users. Although local clusters of research groups and clinical partners have been established for years, cooperation between these clusters is still too sporadic within the European research landscape. Only a concerted Action by offering networking opportunities for the local research clusters can accelerate progress in the field and align it closely to the end-users' and patients' needs. The translation of novel Raman spectroscopic techniques to clinics as well as to the market will be fostered – so *Raman4clinics* necessarily addresses the entire value chain - ensuring that Europe remains at the frontline of Raman spectroscopy research in the increasing competition from Asia and America.

Europe sits on powerful resources in the research field of Raman spectroscopy for clinical applications. This can take us to the frontline if we only had instruments to coordinate the efforts. Currently, the network consists of 20 groups with experience in Raman spectroscopy. There are more yet unrelated groups with extended experience in diagnostic topics of Raman spectroscopy as taken from recent scientific literature. To that a large number of isolated clinical and industrial groups can be added developing compact, high output, stabilized and narrow bandwidth laser sources, fast and sensitive detectors, dedicated microscopes and fiber optic probes, instrument control software and classification routines for various applications within life sciences and clinical diagnosis. This COST Action takes full advantage of these presently widely distributed and isolating resources and to make the most out of the unique collective knowhow and experience to foster clinical Raman spectroscopy. This is necessary to be able to (i) take up the challenge with the leading groups outside Europe, (ii) to drive the development of the underlying technology by close interaction with industrial partners and (iii) to transfer Raman spectroscopy to the clinical environment for routine use. The immediate and future benefits for the establishment of the network are:

- Openness: Raman spectroscopy as a biophotonic tool is a dynamic research field where new approaches, technology and application will emerge during the coming four years. Experts can join at any stage, forming a network adaptable to the technological progress within biophotonics.
- The sum is greater than the parts: a broad network has better chances of creating awareness for and promoting research in- and outside Europe.

- Focus: instruments such as workshops and Working Group activities unify groups in different disciplines with a single goal, Raman spectroscopy for clinical applications, enabling efficient exchange of knowhow and technology.
- Dissemination: efficient instruments are offered to reach unrelated groups with complementary expertise to support the transfer of Raman spectroscopy to clinics.
- Overbridging: connections to European developing countries with complementary knowhow can be established, otherwise difficult due to limited national financial means.
- Preparing the future - next generation leaders: young scientists can form an international network and get international scientific training already at an early stage of their career.
- EC research proposals: research is increasingly funded through EC agencies rather than national and involves multiple partners from different disciplines and European countries. The COST Action provides an ideal platform for initiating and coordinating EC research proposals with the potential to attract substantial financial means for future scientific work.
- Other COST Actions: the annual COST meetings open up for efficient and beneficial interactions with other COST Actions on complementary topics.

Immediate and future benefits of this Action are of both scientific/technological and economic/societal character, as outlined in section C4.

#### **B.4 Complementarity with other research programmes**

Most participants in this Action have ongoing research projects which are financially supported from national resources (with limited means for international networking) including: Germany: RamanCTC: Identification and characterisation of circulating tumor cells in blood by using Raman-spectroscopy, micro-fluidics and micro-arrays. (2.9 m. €) 2013-2016 / UK: Raman needle probe for lymphoma diagnostics. (£689K) 2013-2016 / Ireland: Identification of clinically important, high risk oral lesions using Raman spectroscopy, (149 K€) 2012-2016 / The Netherlands: RASKIN - Development of a Raman spectroscopic device for objective assessment of pigmented skin lesions. Innovative research Program – Photonic Devices – Ministry of Economic Affairs / UK: Multi-purpose instrument for advanced Raman spectroscopy techniques. (£409K) 2014 / Poland: Molecular Sciences for Medicine: Searching of markers for the development of oxidative stress in tissues using vibrational spectroscopy (1.5 m. €) 2011-2015/ UK: National Network “Clinical

applications of Infrared and Raman Spectroscopy CLIRSPEC” (£188K) 2014-2016/ Denmark: a current project on fast live cell Raman imaging in cell incubator environments. 2013-2015.

Via some members, complementary and valuable links exist to the international Biophotonics4Life Worldwide Consortium (BP4L) which connects nodes of biophotonics researchers, educators, organizations, companies, and other enthusiasts to better harness global talent and resources and focuses them on the most important end-user needs. The ICT-FP7 projects FAMOS (addressing functional anatomical molecular optical screening) and MINERVA (Mid- to NEaR infrared spectroscopy for improved medical diagnostics) might deliver complementary expertise in their lifetime to the Action. However, no research program exists that supports networking within the emerging field of clinical Raman spectroscopy on a European level.

## **C. OBJECTIVES AND BENEFITS**

### **C.1 Aim**

The main objective of the Action is to develop a collaborative network of top European experts working towards the progress of the emerging field of Raman-based applications for clinical diagnostics. Specific aims of the Action include (i) to offer networking opportunities for the scientific and technical communities of instrumentation, spectroscopy, microscopy, fiber optics probes and chemometrics for efficient development of the emerging category of clinical Raman spectroscopy; (ii) to reach out to potential users within the medical and life sciences to push Raman spectroscopy beyond proof of principle measurements; (iii) setting up the framework for preclinical trials for such an innovative methodology and (iv) to attract the interest of the next generation of promising scientists and thereby ensuring that Europe remains at the frontline of biophotonic research in the increasing competition from Asia and America. Of major importance is that the leading experts in biomolecular diagnostics based on Raman spectroscopy all over Europe support this COST Action aiming to establish a pan-European research program. Consequently, Raman4clinics will develop research proposals to be submitted for future calls.

### **C.2 Objectives**

Scientific objectives of the Action: - I. To further develop Raman technology for clinical applications (improve laser sources for Raman excitation, develop dedicated microscopy techniques, enable automated imaging with high molecular specificity for cells and tissues, push the sensitivity down to sub-seconds per spectrum with microscopes and fiber optic probes, achieve



image acquisition times of few minutes, develop objective automatic classification routines (algorithms) for diagnosis of cells and tissues based on Raman data) - II. To identify clinical applications and transfer Raman technology into the clinical environment (monitor disease state and prognosis, visualize the margin of pathologies) Deliverables: (i) data bases of Raman spectra of cells and tissues; (ii) new and improved approaches for user-friendly Raman spectroscopy techniques with increased sensitivity, specificity, resolution and speed; (iii) new laser sources and detectors. Networking objectives of the Action: - I. Establish interdisciplinary links between presently unrelated biophotonics groups in academia and industry. - II. Reach out to potential users within bio- and life sciences. - III. Facilitate transfer of knowledge, technology, analytical tools, chemometric tools, samples and data. Promote open dissemination and discussions of scientific results.- IV. Support the career development of early stage researchers (ESRs). - V. Support female networking. - VI. Identify appropriate funding schemes for collaborative research projects in the field. - VII. Spread knowledge and excellence towards developing European countries. - VIII. Welcome the interaction with leading groups outside Europe to promote and consolidate the role of Europe in the field of clinical Raman spectroscopy. Deliverables: (i) international workshops and conferences on clinical Raman spectroscopy techniques; (ii) training and summer schools for ESR; (iii) an increasing number of members / participating groups; (iv) an early stage scientist forum; (v) a mentorship group for female scientists; (vi) joint EC research proposals; (vii) workshop participants from groups outside Europe; (viii) short term scientific missions (STSMs). Results will be disseminated via publications in high-impact journals, conference contributions, and an Action webpage clearly acknowledging the support from COST. Two special issues in relevant scientific journals, e.g. Journal of Biophotonics, will be organized. General awareness of the Action's accomplishments is enhanced by contributions in media and press releases.

### **C.3 How networking within the Action will yield the objectives?**

The scientific objectives will be achieved by optimal coordination of the research into Working Groups and by active exchange of competences through STSMs and collaborations with clinical partners. Close communication with the biophotonics industry involving conceptual tests will enable the instrumental development required. Access to libraries of Raman reference spectra / images of cells and tissues, data analysis tools and experimental protocols will be offered via Raman4clinics web site to form a platform of common fundamental knowledge. Special workshop sessions will be devoted to clinical applications of Raman spectroscopy to encourage the participation of scientists within the bio- and life sciences. The networking objectives will be

achieved by the arrangement of a yearly workshop with invited contributions from experts in and outside Europe. Through advertising by flyers, e-mail, newsletter and web site, and special invitations, stakeholders with the natural and life sciences and associated industries will be reached in order to encourage their participation. An extended training school for ESRs will be arranged where students will be supported by traveling grants. A large part of the budget will be devoted to STSMs, primarily intended for the career development of ESRs and collaborations with scientists from the clinical sciences. Since female scientists tend to have difficulties in getting actively involved in male-dominated networks, a mentorship group composed of female senior scientists will also be formed also to promote female networking.

#### **C.4 Potential impact of the Action**

For patients: They will benefit from improved management of diseases by rapid, more accurate and less invasive treatment options. Using the Raman signal to obtain improved diagnosis facilitating better targeting of lesions, application of earlier less invasive endoscopic therapies, reduce patients pain & biopsy related risks and costs. For the society and healthcare system: They will benefit from reduced treatment costs and shorter hospital stays of patients. For the European scientific community: The Action assures that European countries remain on the very frontline of clinical Raman spectroscopy despite the increasing competition from the USA and Asia by the establishment of expertise knowledge and innovative concepts and technology. For the Action members: dead ends and new openings can easily be communicated between groups so that the collective time spent on experiments leading nowhere will be minimized. Resources such as analytical tools, experimental protocols and algorithms for data analysis can be shared. Collaborations can readily be identified and joint proposals for EU research funds can more easily be organized. For ESRs: adequate training in clinical applications of Raman spectroscopy, support with career development, access to an international network, of experienced senior scientists as well as more informal contacts with other early stage scientists, opportunity of international research expertise through STSMs. For female scientists: access to a female network and mentorship from female senior scientists in a male dominated community. For developing countries: the development of compact low cost clinical and/or portable Raman systems will make it possible also for groups from less favored and new member states to set up Raman spectroscopy in clinics and actively contribute to the research field. For industrial stakeholders: technology development opens commercialization opportunities. More Raman systems will be available for further applications after the coming four year period. For the European photonics market: Clinical Raman research

motivates companies and scientists to develop dedicated light sources, intelligent detection instrumentation, automated microscopes, sensitive fiber optic probes which are of more general interest and use (water control, food control, process control etc.). This will create opportunities for the formation of new innovative companies and to strengthen the European photonics market. Point-of-care test systems for medicine and the life sciences are an important, strategic growth market, which is estimated to amount to several billions of Euros for the benefit of the economy.

### **C.5 Target groups/end users**

Academic groups within the field of Raman spectroscopy and their clinical partners: 20 groups from 12 countries have already been involved in the proposal. Early stage researchers: The Action will efficiently support the international training of young European scientists with a future career within a broad range of disciplines. Clinicians, doctors, and physicians who have been actively involved in the preparation of the Action have a great interest in translating research into clinical practice and will exploit the benefits for public health. Patients will benefit from improved management of diseases by rapid, more accurate and less invasive treatment options. Industrial stakeholders: The photonics technology specialized in Raman spectroscopy is characterized by a few larger companies accompanied by multiple innovative and university related smaller companies. Most of the participants collaborate with local companies ensuring efficient knowledge transfer. Scientists within life sciences and industry: All partners of the Action have ongoing collaborations with clinical partners spreading the awareness of the unique capabilities of Raman technologies beyond the photonics laboratories. The tentative Action Chair represents and promotes Raman4clinics in Photonics21, the European Technology Platform for photonics, with the mission to form public use of these technologies through core sites with open access for European scientists to advanced Raman-based infrastructure.

## **D. SCIENTIFIC PROGRAMME**

### **D.1 Scientific focus**

*Raman4clinics* presents a concerted Action towards advancing cutting-edge technology for the efficient, fast on-site diagnosis of body fluids, infectious pathogens, cells and tissues.

Raman4clinics is innovative in offering a unique interdisciplinary approach at the interface between Raman spectroscopy and the clinical diagnostics of body fluids, bacteria and cells. The complementary nature of each partner will cross-fertilize new ideas that are necessary to take

Raman-based applications to the clinics. This includes also emerging areas such as deep tissue penetration Raman spectroscopy or surface enhanced spatially offset Raman scattering (SESORS). The Action shall deliver innovative scientific concepts for the diagnosis of infections, monitor the onset and treatment of cancer, resection of targeted biopsies, delineation of tumor margins and characterization of atherosclerotic plaques. Depending on the individual analytical challenge, diagnostic methods must fulfill one or several of the following requirements:

- Deliver fast, accurate, and reproducible results
- Work in a repetitive mode to allow the monitoring of a health state, a contamination, etc.
- Work on-site/ at the point of care, easy and reliable operation even by non-specialized personnel
- Deliver quantitative results that are validated by established tools (“gold standards”).
- Deliver further relevant parameters that complement established tools.

The ultimate scientific goal of the clinical Raman spectroscopy community is to coordinate our collective knowhow and instrumentation in order to develop tools for label-free, non-destructive and rapid assessment of bodyfluids, cells and tissues by probing the natural vibrational properties of molecules. Through the development of user-friendly technology and collaborative clinical studies, its use will spread within life sciences. The works will be separated into seven research tasks:

- Detection of anti-tumoral drugs and antibiotics in body fluids (blood/plasma/serum) – Therapeutic drug monitoring at the bedside of patients will contribute to make effective therapy with fewer side effects.
- Acute, life-threatening human infections – The prevalent death causes in non-cardiologic intensive care units are pathogen-induced sepsis and its most extreme form, septic shock. A faster and more detailed diagnosis can help save lives in the future.
- Tumor cells circulating in the blood and urine of cancer patients – The number of these cells is an important prognostic and diagnostic factor to monitor the onset of a cancerous disease and its treatment by e.g. chemotherapy.
- Resection of targeted biopsies – Today, biopsies are often resected randomly to detect e.g. malignant lesions in Barrett’s esophagus. Targeted biopsies improve the accuracy of histopathology and reduce the patient’s pain, and biopsy related risks and costs.
- Delineation of tumor margins – In particular, during resection of brain tumors it is of utmost importance to maximize tumor removal and preserve normal brain tissue. Clinical studies reported that the degree of tumor removal correlates with the recurrence free survival time.
- Intravascular characterization of atherosclerotic plaques – state of the art intravascular tools are based on ultrasound or optical coherence tomography that provide only limited molecular information on type and stability of plaques.

-Histopathology of tissue sections – label free Raman-based methods can complement standard tools to determine tumor type and grade on a molecular level, multiplexed spectral biochemical information.

These tasks and the efficient transfer of knowledge between the different tasks will be coordinated within Working Groups. Groups are typically involved in several of these tasks assuring that the results from fundamental studies and the needs observed in interdisciplinary clinical studies immediately are taken into account in the technology development and in return that new instrumentation and measurement concepts for improved sensitivity, specificity, speed and resolution immediately come to use. The collective access to equipment, hosted by the involved groups is impressive and includes dedicated in-house built and commercial Raman systems from virtually all instrument manufacturers. Each group has established a unique composition of equipment, together allowing for a broad range of clinical Raman spectroscopy concepts within the community: Raman imaging with high and low lateral resolution, fiber-optic Raman spectroscopy, Raman spectroscopy at different excitation wavelength, modulated and shifted excitation Raman spectroscopy. The Action will allow us to compare the qualities of all techniques and thereby identify the most optimal approaches which could guide upgrades of existing instrumentation as diagnostic tools and thereby the use of national funds in a wise way, as well as for the basis for a dissemination of Raman spectroscopy into clinical environment. Moreover, most groups have access to advanced sample preparation labs required for clinical studies such as cell culturing and bioanalytical facilities which enable more advanced collaborative studies.

## **D.2 Scientific work plan methods and means**

The Action will create a European platform for communication and stimulate knowledge exchange between technology/method developers and biomedical end-users. The members will define a work plan as a result of their assessment of important fields of application and promising technological approaches and use it as a road map for the Action. To increase sensitivity, specificity and throughput of Raman spectroscopy for clinical applications, signal amplification techniques will be investigated, including resonance Raman scattering, surface enhanced Raman scattering, tip enhanced Raman scattering or coherent anti-Stokes Raman scattering. Furthermore, methods will be miniaturized and automated. This requires the integration of novel optical components (e.g. laser sources, detectors, diffractive and refractive optics). Enhanced diagnosis will also be achieved by multimodal approaches i.e. combining Raman spectroscopy with other modalities such as OCT or fluorescence. Chemometric algorithms and large numbers of independent specimens – which can

only be achieved on a joint European level – are required to train and validate (both statistically and biologically) robust classification models. In order to meet user requirements, particular attention will be paid to deliver standardized methods including an appropriate quality management. The complete sample handling and processing routine must be managed within the system to ensure maximum ease of use and will be coordinated within nationally-funded research activities. Six Interconnected Working Groups (WG) will carry out the scientific work program:

**WG 1 “Therapeutic monitoring of anti-tumoral drugs and antibiotics in body fluids”:** It is well accepted in the modern treatment of cancer with targeted drugs, monitoring becomes key. This has to do with resistance to treatment that occurs after an average of approximately 3 to 6 months. Until now this can be done in two ways: (1) imaging with MRI or PET scan (that turns to be quite inaccurate and shows alteration in a late stage) and (2) frequently taking biopsies also during treatment (that is stressful for the patient and not without risks). However, an alternative might be monitoring of body fluids, in the context of this action using Raman spectroscopy. Body fluids such as urine are readily available. Other body fluids such as blood are routinely collected in a low invasive way. Raman-based technologies require only small sample volumes and minimal sample preparation. Raman spectra can be collected from liquids in microcuvettes or after injection in microfluidic chips. Aims are to monitor the drug concentration and the health state of the patient. Therapeutic drug monitoring at the bedside of patients will contribute to make effective therapy with fewer side effects.

**WG 2 “Diagnosis of infectious diseases by detection of microbial pathogens”:** The prevalent death causes in non-cardiologic intensive care units are pathogen-induced sepsis and its most extreme form, septic shock. Raman microscopy may bypass time-consuming cultivation procedure before standard microbial testing and identify microbial pathogens on a single cell level in less than three hours. Prerequisites are spectral data bases that include the most frequent pathogens, defined sampling protocols and data collection routines. A faster and more detailed diagnosis can help save lives in the future because an early and targeted disease management improves the prognosis of the patients. Automated Raman microscopic systems need to be developed for this clinical application that follows a similar strategy than the recently introduced Bioparticle Explorer for clean room contaminations.

**WG 3 “Cytopathology of single cells for cancer cell monitoring”:** For detection and identification of cancer cells circulating in blood and urine of cancer patients, microscopic and lab-

on-a-chip platforms coupled to Raman systems with different excitation wavelengths will be used. The number of circulating tumor cells is an important prognostic and diagnostic factor to monitor the onset of a cancerous disease and its treatment by e.g. chemotherapy. The CellSearch system (Veridex) is a FDA (U.S. Food and Drug Administration) approved method that uses ferrofluids loaded with an EpCAM antibody to capture CTCs that are subsequently visualized by staining with a cocktail of antibodies against cytoplasmic epithelial cytokeratins. However, a gold standard for benchmarking various technologies concerning their absolute accuracy, sensitivity and specificity in detecting CTCs does not yet exist. The Veridex system, for example, suffers from relatively low sensitivity scoring only a fraction of patients with metastatic cancer positive for CTCs, with a median yield of approximately one CTC per milliliter and typically low purity. Raman spectroscopy has been shown to identify cancer cells in a label-free fashion. The challenge is to increase the throughput to probe millions of cells within clinical accepted times (less than an hour). Solutions include to combine optical methodologies for presorting of cells and parallel detection approaches.

**WG 4 “Histopathology of cells and tissue sections and biopsies from cancerous and non-cancerous pathologies“:** Label free Raman images contain the morphological information on the cellular level such as cell density, size of cell nuclei and the biochemical information such as a composition and structure of biomolecules. This constitutes a phenotypic approach that has shown to provide sensitive fingerprints of cell biology. Raman imaging can complement standard histopathologic tools to determine tumor type and grade on a molecular level. Furthermore, using archived patient materials with well documented outcome, the Raman spectra offer the possibility to correlate the data with the prognosis.

**WG 5 “Fiber optic endoscopy for in vivo assessment of cancer and atherosclerosis“:** Today, biopsies are often resected randomly to detect e.g. malignant lesions in Barrett’s esophagus. Targeted biopsies improve the accuracy of histopathology and reduce the patient’s pain, and biopsy related risks and costs. During resection of brain tumors it is of utmost importance to maximize tumor removal and preserve normal brain tissue. Clinical studies reported that the degree of tumor removal correlates with the recurrence free survival time. State of the art intravascular tools are based on ultrasound or optical coherence tomography that provide only limited molecular information on type and stability of plaques. For the assessment of tissues during the resection of biopsies or tumors and intravascular monitoring, fiber optic probes are coupled to Raman systems with efficient suppression of background signals. Ambient light in the operating theater and autofluorescence belong to the most severe background signals. An innovative and efficient way of

suppression is modulated or wavelength shifted excitation of Raman spectra. This requires dedicated lasers and data analysis procedures. Furthermore, Raman probes need to be developed for each application upon careful consideration of the clinical requirements (sterilization, reproducibility, robustness, flexibility, size...).

**WG 6“Outreach to public and industry”:** Many proof of concept studies demonstrated the success and prospects of Raman spectroscopy for clinical applications. Beside methodological challenges, deficits exist in the awareness of the public and industry. Therefore, the outreach to public and industry is within the focus of the Action. This will be achieved by press releases, close collaboration with end-users, contacts to stakeholders, specific workshops with the medical community and/or end-users to exchange best practice and connect closer to the Biomedical users in general, mass media and social media i.e. Facebook, Twitter.

## **E. ORGANISATION**

### **E.1 Coordination and organisation**

*Raman4clinics* is managed by realizing the common methods and means of different WGs as described in section D.2 and by achieving the milestones as described below. The organization of this Action will follow the "Rules for Participation in and Implementation of COST Activities" (doc. COST 4112/13) with some specific variations and will work in good agreement with the COST Science Officer and the Domain Committee. The Management Committee (MC) will be convened by representatives of signatory countries. The MC will elect an Action Chair and a Vice Chair by majority vote. The Action is divided into six WGs. Working Group Leaders and deputies are appointed being responsible for achieving goals and milestones of each WG and reporting their achievements to the MC. Short Term Scientific Missions (STSMs) are regarded as the principal means to carry out collaborative research, and thus will be coordinated by a dedicated STSM Manager. Dissemination of results (cp. part H) is a crucial success factor for the Action and will be coordinated by a Dissemination Manager. A Gender Coordinator will direct and coordinate all gender activities (cp. E.4). The MC appoints a Core Group consisting of the Chair and Vice Chair, WG Leaders, the Grant Holder, the STSM Manager, and the Dissemination Manager. The Core Group will verify and approve all operational and day to day decisions and will help the Chair in smooth running of the action. They will be in contact and liaised from time to time by e-mail or teleconferencing. A high-profile Medical Advisory Board will be established comprising respected clinical members from the Action participants, playing a key role for the Action, to be regularly



consulted to ensure optimum future developments and ongoing support.

Milestones/major achievements of the Action include: 1) An Action specific website will be designed and set up. This website will then be regularly updated, emphasizing the main events and outcomes related to the Action and its activities, both serving the needs of the participants and with the specific aim of ensuring the dissemination or exploitation of the results of the Action. 2) Kick-off meeting; nomination of Management Committee, WG Leaders, Core Group, work plan and task distribution. The Action will work towards organizing a kick-off meeting and special symposium in association with International Conferences . 3) WG annual meetings (annual conferences); where an evaluation of the activities carried out by participating members and the discussion and presentation of state-of-the-art reviews and knowledge transfer plans will take place. Not only scientific results will be presented. Instead the different disciplines and Working Groups will present unmet needs to direct research and development towards these needs. On the other hand techniques and methods will be introduced to generate ideas how these needs can be met. 4-5) two Cross-disciplinary Training Schools to direct ESRs towards interdisciplinarity and bridge the gaps between the disciplines. 6-7) two Specific Workshops dedicated to the current and future clinical local cluster partners and technology end-users connected to the MC meetings, arranged to, where appropriate, set up the framework for preclinical trials and/or the commercial evaluation of the technology. 8) Final conference; where a comprehensive state-of-the-art and dissemination of the results of the Action will be made. 9) Publications; publications in high-impact journals, conference contributions, and an Action webpage will signal major Action achievements. Two special issues in relevant scientific journals, e.g. Journal of Biophotonics, will be organized. General awareness of the Action's accomplishments is enhanced by contributions in media and press releases. 10) To shape the future of the Action, a H2020 proposal will be created to establish a Marie-Curie-Network based on Raman4Clinics (year 3 or 4 of the Action).

## **E.2 Working Groups**

The scientific work program will be carried out by six interconnected Working Groups (see section D.2). WG1 “Therapeutic monitoring of anti-tumoral drugs and antibiotics in body fluids”, WG2 “Diagnosis of infectious diseases by detection of microbial pathogens”, WG3 “Cytopathology of single cells for cancer cell monitoring”, WG4 “Histopathology of cells and tissue sections and biopsies from cancerous and non-cancerous pathologies“, WG5 “Fiber optic endoscopy for in vivo assessment of cancer and atherosclerosis” and WG6 “Outreach to public and industry”. Each WG will have 1-2 leaders who will be responsible for monitoring the progress and the completion of

milestones. Face to face meetings will be held every 6 months.

### **E.3 Liaison and interaction with other research programmes**

The Action will actively seek for exchange and cross-fertilization with complementary research programs. The Action will benefit from parallel engagement of its members in neighboring networks and initiatives (as listed in B.4). Selected opportunities will be seized for joint activities with these. Events might be co-located, and renowned experts from neighboring initiatives might be invited to Raman4Clinics events as speakers or participants. On the other hand, young and experienced researchers will offer to give presentations at meetings of these networks. Integration of local networks: Congresses and workshops are scheduled to move location, giving participants the chance to meet local networks and cooperation partners of their host. Industrial members of neighboring initiatives might be approached to promote valorization of suitable methods, e.g. in Horizon 2020 and national programs (e.g. German Biophotonics Research Program). Collaborations are established with other complementary COST Actions (e.g. TD1305 "Improved Protection of Medical Devices Against Infection", MP1102 "Chemical imaging by Coherent Raman microscopy – microCoR") in theme specific, interdisciplinary COST conferences and joint workshops. Experts participating in these Actions will be invited to MC and/or WG meetings for exchange of information in both directions. Web-based exchange with other consortia might also become an important tool and proceed e.g. through the Action's website.

### **E.4 Gender balance and involvement of early-stage researchers**

This COST Action will respect an appropriate gender balance in all its activities and the Management Committee will place this as a standard item on all its MC agendas. A mentorship group composed of female senior scientists is formed also promoting female networking. The Gender Coordinator ensures that all gender issues related to the Action are taken seriously into account and dedicated actions to resolve these issues will be performed. A Gender Action Plan (GAP) will be continuously updated. The GAP concludes to plan meetings outside major school holidays, variations across participant countries permitting; to advertise local childcare options as a standard part of the conference organisation; to collect requests from participants on whether childcare is needed. The GAP consults genderSTE – a COST Targeted Network on Gender, Science, Technology and Environment aiming at achieving integration of gender dimensions in science, technology and environment, and promoting structural changes in scientific and

technological institutions. The Action will also be committed to considerably involve early stage researchers (ESRs). This item will be placed as a standard item on all MC agendas. The involvement of ESRs will be promoted in STSMs, active participation in state-of-the-art reviews, cross-linking Training Schools, creating a ESR's network within the Action as a "think tank" to strengthen links with each other and with experienced scientists, via selected COST conference grants, the nomination of ESRs as national Action delegates whenever feasible.

## F. TIMETABLE

<b>Year 1</b>	
M1-2	First MC meeting
M3	Website Publication
M3-4	Scientific Kick-Off Meeting, held together with the second MC meeting Special symposium in association with XXIV. ICORS – International Conference on Raman Spectroscopy in Jena, Germany: Action Meeting including all WGs that will serve as a kick-off meeting of the Action
M3-4	Collaborative research starts in all WGs (following the first MC meeting)
M3-12	First round of STSMs
<b>Year 2</b>	
M1-12	Collaborative research in all WGs, establishing inter-WG cooperation
M3-5	3 <sup>rd</sup> MC meeting joint with a Training School and a Specific Workshop dedicated to technology end-users
M1-12	STSMs
M8-11	Annual Action scientific conference (includes all WG)
<b>Year 3</b>	
M1-12	Collaborative research in all WGs
M3-5	4 <sup>th</sup> MC meeting held together with the second Training School and a Specific Workshop dedicated to technology end-users
M1-12	STSMs
M10-12	Annual Action scientific conference (includes all WGs) associated with the 5 <sup>th</sup> MC meeting, preparation of Action final conference and for evaluation
<b>Year 4</b>	

M1-12	Collaborative research in all WGs
M1-12	STSMs
M8-12	Annual Action scientific conference (includes all WG) which will be held jointly together with related overseas programs and European national centers.
less than 6 months after Action closing	Final Conference of the Action and MC meeting to finalize report

## G. ECONOMIC DIMENSION

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: BE, DE, DK, ES, FR, IE, IT, NL, PL, RO, TR, UK. On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 48 Million € for the total duration of the Action. This estimate is valid under the assumption that all the countries mentioned above but no other countries will participate in the Action. Any departure from this will change the total cost accordingly.

## H. DISSEMINATION PLAN

### H.1 Who?

Target group 1: The European and worldwide scientific community, especially (a) research groups developing novel technologies with high potential for clinical diagnostics. This group will especially be offered information on scientific concepts, advancements and results of the Action.

Target group 2: Graduate and post-graduate students at universities and postdoctoral researchers who are of special importance for the long-term development in the field and thus considered as specific target group. They will especially be informed about training and education opportunities, and on general perspectives/attractiveness of the field of research.

Target group 3: Research and development departments of European-based companies committed towards a future commercialization of Raman4Clinics' results. This group will be approached with information on scientific results and their market relevance.

Target group 4: Clinicians, doctors, physicians, and patients. By translating research into clinical practice and promoting the technologies, public health will get benefits. The patients will benefit from improved management of diseases by rapid, more accurate and less invasive treatment options. Using the Raman signal to obtain improved diagnosis based on biochemical information of

early pre-cancerous changes facilitating better targeting of lesions, application of earlier less invasive endoscopic therapies, reduce patients pain & biopsy related risks and costs. *Raman4Clinics* involves clinical partners at all levels.

Target group 5: Decision makers in the European Union and the national states, as well as the interested public in the European Union and other COST countries. *Raman4Clinics* will approach these groups with suitable information to raise their interest in the Action's innovative solutions and the underlying vision of a more equitable, more efficient and more effective health care in Europe.

## **H.2 What?**

The Action will actively disseminate results, concepts and long-term strategies along with the outcome of training schools, annual joint meetings of all WGs and promotion of Early Stage and female researchers, who will be actively involved in the Action. Collaborative projects between partners will be supported. The dissemination will target the four groups outlined in part H.1 to meet the Actions objectives (see parts C1 and C.2) and in working towards harvesting the benefits outlined in part C.4. Efficient dissemination with minimal bureaucratic effort will be achieved by the following means:

1) Creation of a ready-to-use corporate layout, including both the Action's logo (to be created) and the COST logo. 2) Each Action participant will be committed to publish scientific results in high-impact international scientific journals, including acknowledgement of the COST Action. 3) Acknowledgement of the COST Action through all partners in their relevant scientific publications and on their institutes' websites. Wherever applicable, the partners will provide further information on the Action's focus and goals. 4) Creation and maintenance of the Action's web page. The website will provide target-group specific information that is organized in a user-friendly structure, including an area of public concern/for press representatives, an expert area open for public access and possibly an expert area requiring member login. Information will include a) the Action's objective, scientific and structural aims, b) partners, c) scientific program, d) a searchable description of the scientific projects pursued within the Action, e) a database of the scientific publications of the Action, f) a selection of topics of high public interest, covering urgent fields of need for the Action's work, as well as selected results and partners, g) news, press releases and figures/photographs for public use and, h) an up-to-date schedule for the Action's events, STSMs, and events related to the field. As items for internal use, the website provides a web-based mailing list and discussion forum. 5) Creation and maintenance of Action-specific mailing lists for mailings on events and news (in either HTML E-mail or newsletter format). Examples of use include: a)

distribution of press releases to selected media contacts, b) distribution of education and training opportunities to the press offices of European research institutions, c) distribution of a newsletter (HTML or pdf format) to subscribers, c) invitation of interested experts from science and industry to meetings and conferences, 6) publication of press releases to promote information on central scientific results, Action meetings, conferences and Training Schools 7) establishment and maintenance of media contacts, preparation of selected “stories” and key information to raise interest, preparation of suitable background information. Hospitals are actively engaged with clinical workshops showcasing cutting edge clinical and research developments to the general public.

### **H.3 How?**

The Dissemination Manager will coordinate all related measures and guide the participating institutions in this issue. At the start of the Action, he will set up a concise dissemination plan and provide the partners with a short guideline to dissemination, along with required materials (e.g. logos). The Dissemination Manager will report to the Management Committee on a regular schedule, also proposing adjustments to the dissemination plan. The Dissemination Manager will closely interact with the department of public relations of the Action Chair, which will coordinate all issues of public relations (cp. H.2, 1 and 4-7). This group holds considerable experience in handling the public relations of several R&D networks, including the FP7-Network of Excellence “Photonics4Life”, the German Research Campus “InfectoGnostics” and the German Biophotonics Research Program. The office will recommend a suitable set of Actions and their timeline to the dissemination manager. This setup seems most promising, as successful public relations do not only depend on attractive topics and news from within the network (e.g. research projects, Training Schools, conferences), but also requires experience in setting topics and seizing external opportunities.