Brussels, 24 March 2020

COST 035/20

DECISION

Subject: **Memorandum of Understanding for the implementation of the COST Action "European Network to Advance Best practices & technoLogy on medication adherencE" (ENABLE) CA19132**

The COST Member Countries and/or the COST Cooperating State will find attached the Memorandum of Understanding for the COST Action European Network to Advance Best practices & technoLogy on medication adherencE approved by the Committee of Senior Officials through written procedure on 24 March 2020.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA19132
EUROPEAN NETWORK TO ADVANCE BEST PRACTICES & TECHNOLOGY ON MEDICATION ADHERENCE (ENABLE)

The COST Member Countries and/or the COST Cooperating State, accepting the present Memorandum of Understanding (MoU) wish to undertake joint activities of mutual interest and declare their common intention to participate in the COST Action (the Action), referred to above and described in the Technical Annex of this MoU.

The Action will be carried out in accordance with the set of COST Implementation Rules approved by the Committee of Senior Officials (CSO), or any new document amending or replacing them:

a. "Rules for Participation in and Implementation of COST Activities" (COST 132/14 REV2);
b. "COST Action Proposal Submission, Evaluation, Selection and Approval" (COST 133/14 REV);
c. "COST Action Management, Monitoring and Final Assessment" (COST 134/14 REV2);
d. "COST International Cooperation and Specific Organisations Participation" (COST 135/14 REV).

The main aim and objective of the Action is to create a multidisciplinary network of relevant stakeholders that work collaboratively towards economically viable implementation of medication adherence enhancing technologies across different European healthcare systems. This will be achieved through the specific objectives detailed in the Technical Annex.

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 88 million in 2019.

The MoU will enter into force once at least seven (7) COST Member Countries and/or COST Cooperating State have accepted it, and the corresponding Management Committee Members have been appointed, as described in the CSO Decision COST 134/14 REV2.

The COST Action will start from the date of the first Management Committee meeting and shall be implemented for a period of four (4) years, unless an extension is approved by the CSO following the procedure described in the CSO Decision COST 134/14 REV2.

OVERVIEW

Summary

Due to an ageing society, there is a steady increase in chronic diseases and multi-morbidity in Europe. This rise of chronic diseases and multi-morbidity requires a multidisciplinary response, which often involves lifestyle changes combined with lifetime medication use.

Medication non-adherence affects however up to half of the chronic medication users, poses considerable challenges in managing chronic diseases, and is associated with almost 200,000 deaths and €80-125 billion of potentially preventable direct and indirect costs in Europe. Technological advances (e.g. smart pillboxes, digital inhalers, tracking devices, e-injection pens, e-Health, big data), have significant potential to support healthcare professionals and empower patients in detecting and managing non-adherence.

Awareness of healthcare professionals on the availability and implementation of adherence enhancing technology is limited and there is a lack of collaboration between stakeholders. Successful European-wide implementation of adherence enhancing technology is further hampered by a lack of insight in different European healthcare systems, reimbursement pathways and policy regulations that significantly differ between countries. This affects not only patients and healthcare professionals, but also manufacturers of technology (mostly SMEs) in their innovation capacity and competitiveness.

To address these challenges, the European Network to Advance Best practices & technoLogy on medication adherencE (ENABLE) aims to (1) raise awareness of adherence enhancing technological solutions, (2) foster and extend multidisciplinary knowledge on medication adherence at patient, treatment and system levels, (3) accelerate translation of this knowledge to useful clinical application and (4) work collaboratively towards economically viable implementation of adherence enhancing technology across European healthcare systems.

Areas of Expertise Relevant for the Action	Keywords
● Health Sciences: Health services, health care research ● Clinical medicine: General and internal medicine ● Medical engineering: Medical engineering and technology ● Health Sciences: Nursing ● Basic medicine: Pharmacology, pharmacogenomics, drug discovery and design, drug therapy	● Medication adherence ● eHealth ● Chronic diseases ● Pharmaceutical care ● Digital health

Specific Objectives

To achieve the main objective described in this MoU, the following specific objectives shall be accomplished:

Research Coordination

● Benchmark, assess and raise awareness on current practices on tackling non-adherence in different healthcare settings across Europe. This entails the exchange of best practices, facilitators/barriers, experiences and expertise of different healthcare providers (GPs, specialists, pharmacists, nurses, health psychologists) and patients in dealing with non-adherence issues in daily life and practice.

● Accelerate the availability and implementation of adherence enhancing technologies across Europe. This entails the exchange (e.g. through webplatforms, social media) of multidisciplinary knowledge and creates awareness among healthcare providers on the availability and potential of innovative adherence measurement methods and adherence enhancing technology for clinical practice.

● Gather expert input for future market applications and implementation of cutting-edge adherence enhancing technology. Knowledge exchange on cost-effectiveness, patient access pathways, and reimbursement could help the implementation.

Capacity Building

● Bringing together currently isolated stakeholders and building up a network to achieve breakthroughs in the development of new process to advance the implementation of adherence enhancing technologies. This will be achieved by hosting meetings, workshops and conferences.

● Developing a platform to exchange and foster adherence knowledge, including a repository of best practices and technologies that can enhance medication adherence. Per intervention, an independent assessment of its effectiveness and cost-effectiveness will be provided by a panel of multidisciplinary experts.

● Translate and disseminate knowledge on technologies to specific target groups such as Early Career Investigators (ECIs) and researchers from less research-intensive countries. This will be achieved by hosting meetings and workshops, organizing Training Schools and opportunities for Short-Term Scientific Missions (STSMs).

TECHNICAL ANNEX

1 S&T EXCELLENCE

1.1 SOUNDNESS OF THE CHALLENGE

1.1.1 DESCRIPTION OF THE STATE-OF-THE-ART

In 2003, the influential World Health Organization (WHO) report “Adherence to long-term therapies: evidence for action” was published.[1] This report was based on an exhaustive literature review on adherence definitions, measurements, epidemiology, economics and interventions applied to nine chronic conditions and risk factors. It highlighted the scope of the problem (only 50% of patients adhere to long-term therapy) as well as the significant consequences for health and economics. It stimulated new thinking on policy development and action to improve adherence to long-term therapies.

In the years that followed, a wealth of studies provided new insights into the different reasons for nonadherence. Notably, these can be situated at the patient level (e.g. beliefs, cognition, comorbidities, knowledge), at the treatment level (e.g. side effects, dosing regimen, co-medication) and/or at the system level (access to medication, relationship with healthcare providers, social support).

Within an individual patient, one or more of these reasons could result in three main types of nonadherence (WHO definitions). Two of these are also characterized as unintentional and include erratic non-adherence (i.e. forgetfulness) and unwitting non-adherence (i.e. lack of knowledge). In the case of intentional non-adherence at personal level, a patient deliberately alters or discontinues prescribed therapy due to a conscious decision, such as lack of necessity or fear of side effect or high costs.[1] In addition, many studies have focused on estimating specific rates of adherence across different (chronic) diseases (e.g. asthma, diabetes), medications (e.g. inhaled corticosteroids, metformin), patient populations (e.g. elderly, adolescents) and geographical areas (e.g. urban, areas with high/low socioeconomic status). These studies show profound differences between studied groups (e.g. a higher number of medications per patient was associated with higher non-adherence rates). Over the past decades, the inconsistent use of adherence definitions has hampered fair cross-study comparison however since 2012, consensus has been reached that the adherence process consists of three **distinctive phases** including initiation, implementation and persistence.[2]

To **enhance adherence**, multiple **intervention strategies** have been tested with varying results. Notably, most studies took one-size-fits-all approaches and did not select patients based on the underlying causes of non-adherence. In addition, interventions were usually applied once, thereby neglecting the chronic nature of adherence. Due to better understanding of underlying reasons for nonadherence, it has become increasingly clear that a one-size-fits-all approach is likely to fail. In addition, it is now recognised that there exists an interplay between medication adherence and lifestyle change, in chronic diseases. This may implicate that the two phenomena should be addressed together and interventions may best work when technological and behavioural strategies are combined.

A personalized approach may be the way forward in tackling non-adherence, particularly if solutions are based on the type of non-adherence in question and its underlying causes. For example, patients with erratic non-adherence may benefit from reminders; patients with unintentional non-adherence may need support in habit formation, while patients with intentional non-adherence would benefit from education, motivational interviewing, reimbursement or shared decision making processes.[2]

In current clinical practice, healthcare providers are short of knowledge and insights on how to monitor adherence and apply the appropriate interventions for individual patients. In addition, patients are insufficiently empowered and lack tools to self-monitor, self-manage and optimize their drug use. In particular when embedded in existing behavioural change frameworks and combined with proper communication strategies, new technology may assist both patients and healthcare providers in managing non-adherence on a continuous basis instead of the current one-time interventions.

1.1.2 DESCRIPTION OF THE CHALLENGE (MAIN AIM)

Mainly due to an ageing society, there is a steady increase in chronic diseases and multi-morbidity in Europe. The rise of chronic diseases and multi-morbidity requires a multidisciplinary response, which often involves lifestyle changes and lifetime medication use. Despite the availability of many effective drugs, it has been estimated that **medication non-adherence** is associated with almost **200,000 deaths** and **€80-125 billion** of potentially preventable direct (e.g. hospitalizations, waste of medication) and indirect (e.g. work productivity losses) costs in the European Union (EU) alone.[3] Unfortunately, medication non-adherence affects, depending on definitions used, **up to 20-50%** of patients that use chronic medication.[1] Moreover, in the last decades, there has been little improvement in adherence across the spectrum of multiple chronic diseases. Notably, data show profound variance in adherence within- and between- countries. In line with other factors that may affect adherence, e.g. low socio-economic status[4], this suggests inequitable implementation of adherence enhancing solutions. This is one of the reasons the WHO has qualified medical adherence as a key indicator for quality of care.[5]

Recently developed **technological advances** (e.g. smart pill-boxes/packaging, digital inhalers, audio and vibration-based tracking devices, pill-tracers and e-injection pens, e-Health self-management applications, big data) can greatly support healthcare professionals and empower patients in detecting and managing non-adherence. However, currently the application of these innovative technologies is still mainly **limited to clinical trial settings**, thereby not reaching the healthcare professionals and patients in real-life practice. In addition, awareness of healthcare professionals on the availability and implementation of adherence enhancing technology is limited, the technology is usually not embedded in a broader understanding of the reasons for suboptimal adherence and there is a lack of collaboration between key stakeholders to jointly work towards shared implementation goals.[6] Moreover, the successful European-wide implementation of innovative adherence enhancing technology in daily practice, is further hampered by a **lack of insight** in the different European healthcare systems, reimbursement pathways and policy regulations that significantly differ from country to country.

Most of the recent innovations in adherence enhancing technology derives from the medical device industry, represented by about 25,000 companies of which the vast majority (+/-95%) small and medium-sized enterprises (SMEs). Besides being the main employer of 575,000 people in the EU, these SMEs are responsible for €100 billion of sales.[7] Yet, SMEs in particular face **many challenges** at national, European and international levels which affects their innovation capacity and competitiveness. Notably, only 7% of SMEs in the EU sell cross-borders, a reason for which the EU has promoted the Digital Single Market strategy.[8] Main challenges are related to **bridging the gap** between the technological innovation being developed and validated and their sustainable implementation in daily clinical practice. In particular, for SMEs it is of utmost importance to provide patients and providers with early access to their technology whilst simultaneously ensuring that reimbursement is in place across healthcare systems in Europe and further around the globe.

In summary, there is a rich foundation of knowledge on medication (non) adherence, its societal impact, adherence enhancing interventions, and the potential of technological solutions. Nevertheless, the compilation and translation of this knowledge into practice is lacking. Stakeholders are inadequately informed about non-adherence and the availability of technological solutions, and collaborative efforts to push forward their implementation are scarce.

The overarching objective of the **E**uropean **N**etwork to **A**dvance **B**est practices & techno**L**ogy on medication adheren**E** (**ENABLE)** is to create a network of relevant stakeholders that (1) **raise awareness of adherence enhancing solutions**, (2) foster and extend **multidisciplinary knowledge** on medication adherence at patient, treatment and system levels, (3) **accelerate translation** of this knowledge from producers to useful **clinical application** and (4) work collaboratively towards **economically viable implementation** of adherence enhancing technology across different European healthcare systems.

1.2 PROGRESS BEYOND THE STATE-OF-THE-ART

1.2.1 APPROACH TO THE CHALLENGE AND PROGRESS BEYOND THE STATE-OF-THE-ART

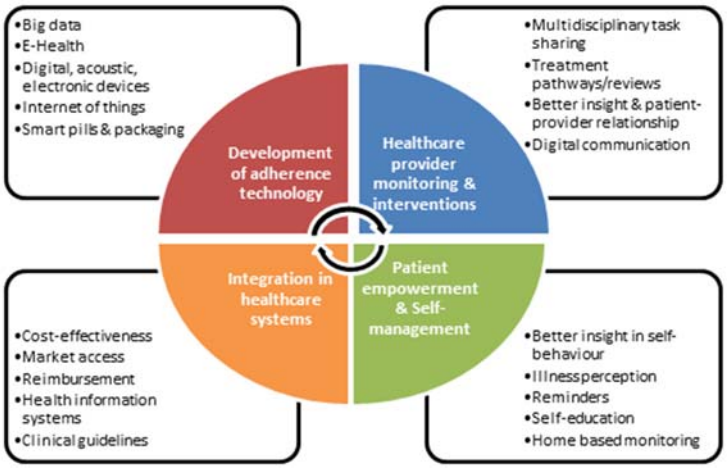
ENABLE will establish a knowledge base beyond the current state of play, and actively engage the private sector to foster innovative technology based solutions to tackle non-adherence.

In order to select the right interventions for the needs of individual patients (i.e. personalized medicine), in-depth insights into longitudinal patterns of drug utilization are required. This could be accomplished by digitally engaging healthcare providers with patients for optimal monitoring and timely interventions in the process of adherence.

It is important to note that the management of adherence is not pushing for more pills taken, but rather to reach an optimal treatment exposure for each patient. This can only be achieved if reliable and detailed adherence data are integrated in the healthcare system. Currently, several companies, mostly SMEs, are in advanced stages of developing innovative adherence enhancing technology such as inhalers based on acoustic sound or vibration-based technology to track frequency and quality of use, electronic pill blisters, linked real-life patient medication records, self-management support apps with wearable reminders, movement based injectables and digital tracers.

Despite the multitude of examples of great technological innovation, true progress can only be made if stakeholders **work together towards sustainable implementation**, which requires the involvement of stakeholders throughout the development process.

A recent example is the co-application at the United States Food and Drug Administration (FDA) of a drug manufacturer and a technology SME with an ingestible sensor embedded in a tablet that can measure adherence and other vital functions which communicates through digital platforms to be used by patients and in healthcare provider-patient interactions.[9] This example is the result of early engagement of all relevant stakeholders, but is still not or very rarely seen in European markets.



In order to successfully implement non-adherence technologies, stakeholders in multiple levels of the healthcare system need to be prepared to accept and employ these solutions. ENABLE will serve as a stepping stone towards the ultimate goal of achieving **full integration** of healthcare provider insights, patient education and empowerment, and digital adherence management technology within a sustainable healthcare system that is ready to receive it, both clinically and economically (Figure 1).

Figure 1: Integration of healthcare provider insights, patient empowerment and technology in a sustainable system

More concretely, ENABLE will promote the establishment of unique local "**medication adherence expertise centers**" where multidisciplinary knowledge is combined on a regional or national level. Notably, these centers will not only serve as a knowledge hubs, but could also provide educational courses and play important roles as implementation platforms for effective interventions.

Approach to the challenge

By connecting cutting-edge adherence enhancing technology engineers with a range of healthcare stakeholders (i.e. providers, patients, as well as payers) the ENABLE network works towards a fully **integrated and individualized adherence strategy**. Given the scope of the problem and because SMEs may aim to work across the borders of a country, ENABLE aims to create a multidisciplinary network of as many European countries as possible. Within each country, representatives of different

key stakeholders will be identified on a continuous basis and added to the previously mentioned local "medication adherence expertise centers". The first Action general meeting will be organized at a central European location in which the main challenges of ENABLE will be outlined and presented to the multidisciplinary audience. The main session will be followed by smaller scale break-out sessions where specific issues will be discussed and presented in the subsequent plenary session. The medication adherence expertise centers will continue their collaboration by sharing their experiences with adherence technology, health care practice and healthcare systems on a **freely-accessible web platform** with country/setting specific information to guide optimal implementation of adherence enhancing technology. Beyond the COST Action and the web-platform, expertise center representatives are also foreseen to keep on meeting at designated annual adherence conferences such as those organized by the European adherence society ESPACOMP. The ultimate goal is not to create new technology (though innovative technologies will be rapidly adopted as they emerge), but to create **a new process** to stimulate **early & easy access of technology** to providers and patients and to make use of the existing technology in the most cost-effective way. In that sense, the true innovation lies in the collaboration of stakeholders who usually do not work together. Through engaging and connecting stakeholders ENABLE will **benchmark** current practice, explore their potential for **scalability** and eventually fuel the **sustainable implementation** of technology across diverse European healthcare systems, to create impact within both health & socio-economic settings.

1.2.2 OBJECTIVES

1.2.2.1 Research Coordination Objectives

In order to tackle the challenges related to implementing solutions to reduce medication non-adherence, three research coordination objectives have been formulated to stimulate private-public networking and cutting-edge collaborative and multidisciplinary research:

1. **Benchmark, assess and raise awareness on current practices** on tackling non-adherence in different healthcare settings across Europe. This entails the exchange of best practices, facilitators/barriers, experiences and expertise of different healthcare providers (GPs, specialists, pharmacists, nurses, health psychologists) and patients in dealing with non-adherence issues in daily life and practice.

2. **Accelerate** the availability and implementation of adherence enhancing technologies across Europe.This entails the exchange (e.g. through webplatforms, vlogs, social media) of multidisciplinary knowledge and creates awareness among healthcare providers on the availability and potential of innovative adherence measurement methods and adherence enhancing technology (electronic monitoring, eHealth apps & tools) for clinical practice.

3. **Gather expert input for future market applications and implementation** of cutting-edge adherence enhancing technology as developed by small and medium size enterprises (SMEs). Many technologies have large potential, but may fail when they are not fit for a healthcare system that is not ready to receive it. In addition, SMEs' innovations may fail if they do not embed their technology in the broader context of behaviour change. Knowledge exchange on cost-effectiveness, patient access pathways, pricing, reimbursement and permanent integration of innovative adherence interventions in different European healthcare systems and clinical guidelines could help to overcome this hurdle and better prepare new technologies for smooth patient access and integration in existing systems.

1.2.2.2 Capacity-building Objectives

1. **Bringing together** currently isolated stakeholders and building up a network to achieve breakthroughs in the development of new process to advance the implementation of adherence enhancing technologies. This will be achieved by hosting meetings, workshops and conferences.

2. Developing a **platform** and trans-national practice & policy community to exchange and foster knowledge. To achieve this, a web platform will be compiled and hosted which will include a repository of best practices and technologies that can enhance medication adherence and examples of successful implementation and patient access pathways. Per intervention, an independent assessment of its effectiveness and cost-effectiveness will be provided by a panel of multidisciplinary experts not having a conflict of interest. Industry (pharmaceutical, IT) may propose an intervention to be included on the platform but cannot provide the aforementioned assessment.

3. **Translate and disseminate knowledge** on technologies to specific target groups such as PhD students, Early Career Investigators (ECIs, defined as PhD + up to 8 years) and researchers from less research-intensive countries. This will be achieved by hosting meetings and workshops, organizing Training Schools and opportunities for Short-Term Scientific Missions (STSMs). Through these STSMs, the specific target groups can learn from experienced investigators and policy makers on the use and regulations of technology in other countries. Alternatively, they can learn directly from engineers at SMEs that are developing these adherence enhancing technologies or from regulatory policy makers that are assessing these technologies. At the same time, the researchers' clinical and academic experience and country-specific knowledge could benefit the SMEs in further optimizing their technologies to make them fit for purpose.

2 NETWORKING EXCELLENCE

2.1 ADDED VALUE OF NETWORKING IN S&T EXCELLENCE

2.1.1 ADDED VALUE IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

Through the ENABLE network, stakeholders are able to collaborate and work towards a mutual objective: sustainable implementation of adherence enhancing solutions in order to improve patient outcomes and decrease total healthcare costs. Close and early collaboration with national action plan leaders (e.g. through focus groups and round-table processes), patient groups as well as decision makers will be sought to optimally **leverage national research investments.**

Networking is not only necessary within countries and between national stakeholders, but especially between countries. Notably, much of the current knowledge is centered in Western European research settings, while the **transfer of this knowledge** (to e.g. Eastern Europe) lags behind, resulting in **unequal access** to promising technology and best practices. Of note, challenges related to nonadherence are very similar between countries and sharing knowledge will enable the early access to best practices and **prevent unnecessary reinventing of the wheel** in each single country. Lastly, most SMEs that develop adherence enhancing technology are usually based in one country, but aim to sell their products in **multiple countries** and therefore require a European wide network for optimal implementation of their technology.

The existing efforts at the European and/or international level are outlined below.

- **ESPACOMP**: formally European, this is the only of its kind in the world scientific society that focuses on research and methods related to medication adherence. The audience is mainly academic and has limited involvement of SMEs and policy makers. The ENABLE Action aims for collaboration with ESPACOMP, which could play a potential role in knowledge dissemination and advocacy of ENABLE's findings.
- **ABC** (FP7 project, ended in 2012): This was the first EU funded effort on standardizing adherence taxonomy and identification of current pitfalls in adherence research. Yet, this project was mostly performed before the adherence technology era. Still, this COST Action could built onto the knowledge that was gained in the ABC project.
- European Innovation Partnership on Active and Healthy Ageing (**EIP-AHA**): This is a very broad initiative aiming at health aging and who recently published the report "Blueprint on digital transformation of health and care for aging society". Specifically the Action Plan A1 (Prescription and adherence action at regional level) and Plan B3 (Integrated Care) are of relevance in relation to this Action.
- **Digital Single Market** (European Commission): This project aims to tear down regulatory walls and moving from 28 national markets to a single one. The ENABLE vision fits perfectly with its focus on European wide implementation of adherence enhancing technology.
- **EARIP & ASTROLAB** (FP7 project, ongoing): both projects focus on asthma treatment issues and have adherence included as part of their objectives. While the focus is on asthma only, data may be of interest for ENABLE.
- International Society For Pharmacoeconomics and Outcomes Research Medication Adherence and Persistence Special Interest Group (**ISPOR MAP**): aims to stimulate research and evaluation on issues related to medication adherence, treatment persistence, and implications for health outcomes. ISPOR - the leading global professional society in pharmacoeconomics

and outcomes research - could assist with the dissemination of ENABLE's findings to a broader audience.

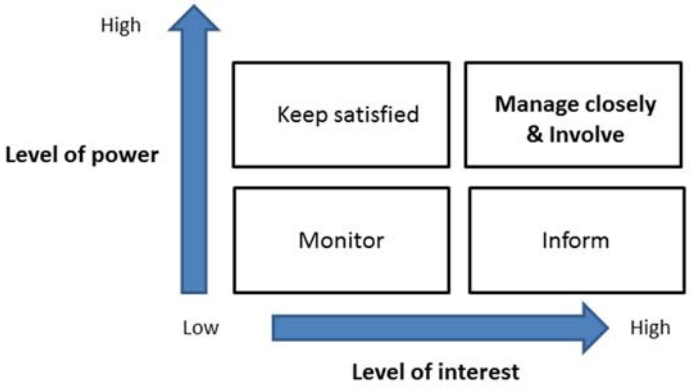
As compared to existing efforts outlined above, the ENABLE COST Action will have a unique and **specific focus** that goes beyond the objectives of the existing efforts. It will be **disease and discipline overarching**, is multidisciplinary (providers, patients, policy makers), incorporates the latest state-of-the-art adherence enhancing **technology** through SME involvement and has a strong focus onsustainable, **cost-effective implementation** across Europe.

2.2 ADDED VALUE OF NETWORKING IN IMPACT

2.2.1 SECURING THE CRITICAL MASS AND EXPERTISE

The ENABLE network has the mutual objective to accelerate the development, availability and sustainable implementation of adherence enhancing technologies in daily clinical practice. The ENABLE network agrees that multidisciplinary, pan-European and private-public networking is the best way to address current challenges. Notably, ENABLE network members will be selected because of their excellent complimentary expertise, reputation as well as relevant network in the field.

The total **pan-European network** of collaborators will include **healthcare professionals**, **researchers**, **policy makers**, **patient organizations** and **SMEs.** The partners from **Eastern and Western European countries** have complimentary expertise on medical and pharmaceutical practice and sciences, nursing, engineering, health psychology, communication, implementation science, health economics and policy. Notably, many future collaborators are working on adherence-related issues on a daily basis, are leaders in their respective sub-fields and are represented in (or are on boards of) (inter)national academic/policy associations, guidelines and related national or international initiatives on adherence. Altogether, ENABLE will benefit from a **multidisciplinary, well-balanced and impactful network** that will maximize the chances that the critical mass and key stakeholders across Europe are reached and involved for successfully addressing the key challenges and objectives related to the global challenge of non-adherence to medication.



The ENABLE Action plans also to involve and expand a critical mass of other essential stakeholders that can impact the implementation of adherence enhancing interventions immediately (e.g. by involving partners with high power and interest) and in the future (e.g. by also involving ECIs). For stakeholder selection and management a **Power/Interest grid** (Figure 2), will be created for each country within ENABLE.

Figure 2: Stakeholder power/interest grid

2.2.2 INVOLVEMENT OF STAKEHOLDERS

Per country, around five representatives from clinical practice will be involved, such as **healthcare professionals** involved in enhancing adherence (physicians, pharmacists, psychologists & nurses), especially those involved in clinical guideline development or with a key position in national or European clinical societies. In addition, **patient associations, informal care associations** and **regulators** (registration authorities, payers and health insurance policy makers) from each country will be targeted through the existing networks of ENABLE Action participants but also by actively reaching out. Naturally, other main participants are the **engineers** that develop these technologies, mostly working in SMEs. Lastly, experts with specific expertise in e.g. communication and dissemination on a European level, such as participants involved in patient advocacy, will be asked to join the ENABLE Action. Stakeholder involvement will mainly be carried out through the **networks** of the Management Committee members in the ENABLE Action, centrally coordinated by the responsible Working Group (WG 1, see Figure 3). To maximize exposure, materials will become available in local languages and will take into account the level of information is also accessible for people with low literacy.

In addition, engagement with stakeholders will be created through **(1)** an overarching ENABLE **website** with aims, collaborators and news/blogs/vlogs, recent findings where also links to the local "medication adherence expertise centers" will be provided; **(2) local adherence awareness events** (preferably with media attention) surrounding the launch of the local expertise centers in each country; **(3)** establishment of national "**Adherence Awareness Days**"; **(4)** the **first conference**: to identify and actively invite key stakeholders and to create a roadmap with unmet research and policy needs; **(5) stakeholder meetings linked to existing clinical/scientific conferences** (e.g. ESPACOMP, EuroDURG, disease focused conferences): to network and disseminate knowledge to non-specialist audiences; **(6) Short-Term Scientific Missions** aiming to increase knowledge, awareness and visibility; **(7) editorials/call-for-actions** in scientific, clinical and policy oriented conferences and journals, as well as on online network platforms such as LinkedIn, Twitter and ResearchGate.

2.2.3 MUTUAL BENEFITS OF THE INVOLVEMENT OF SECONDARY PROPOSERS FROM NEAR NEIGHBOUR OR INTERNATIONAL PARTNER COUNTRIES OR INTERNATIONAL ORGANISATIONS

Given the initial focus on implementation of adherence enhancing technologies and strategies in the European healthcare systems, currently no Near Neighbour Countries are involved in the ENABLE Action. Yet, the Action will be open for their participation and, moreover, from the beginning they will be able to indirectly benefit from the deliverables of this Action, such as the freely accessible webplatform with demonstrations of innovation in digital technologies that can enhance medication adherence. International organisations are also not yet directly involved in this stage, but many future participants of this Action are actively involved in relevant international clinical, patient and policy organizations that could become collaborators for the Action. In particular, it is anticipated that these organisations could play a complimentary role in promotion, member expansion, knowledge dissemination and scale up of adherence interventions both inside and outside Europe.

3 IMPACT

3.1 IMPACT TO SCIENCE, SOCIETY AND COMPETITIVENESS, AND POTENTIAL FOR INNOVATION/BREAK-THROUGHS

3.1.1 SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS (INCLUDING POTENTIAL INNOVATIONS AND/OR BREAKTHROUGHS)

ENABLE will tackle a highly relevant issue with substantial cross-sectorial impact. Systematic reviews indicate a wide-ranging negative impact of non-adherence, and reveal consistent associations of nonadherence to worse clinical (i.e. 200,000 deaths) as well as economic outcomes (i.e. €80-125 billion) across the full spectrum of chronic diseases. In current practice, suboptimal response to an initial drug is usually followed by the addition of a 2nd or 3rd drug without checking and optimizing adherence to the initial drug, leading to unnecessary side-effects and medication costs. For example in asthma, when patients are non-adherent to their regular inhaler (e.g. budesonide/formoterol, costing +/-€500 annually) and this is not checked and optimized, physicians may assume the drug is not working sufficiently and may subsequently prescribe a more invasive and expensive biological drug (e.g. mepolizumab, costing €15,000 annually). In 2005, a systematic review on adherence enhancing interventions already indicated that "improving adherence seems to be fairly low on the policy agenda, but better use of existing drugs is likely to be more cost-effective than many new drugs".[10] Despite efforts to address the issue, a large study published in 2015 across Europe that compared ten national - adherence policies concluded that implementation of medication adherence policy solutions had failed.[6] Furthermore, the most recent epidemiological studies on medication adherence continue to indicate consistently low adherence rates, highlighting the potential impact of innovative implementation strategies focusing on proper medication use. Given the above, it is anticipated that ENABLE could have scientific, technological and/or socioeconomic impacts and has potential for innovation as further detailed below.

Short term impact

In the short-term, several important scientific and technological impacts are anticipated due to increased multidisciplinary and private-public collaboration on medication adherence. These include:

(1) The establishment of an interdisciplinary pan-European **network** of stakeholders that develops, assesses and works with adherence enhancing technology and exchanges this knowledge within and beyond the network itself

(2) Increased **awareness** about non-adherence among the network's internal and external stakeholders

(3) Increased **visibility and benchmarking** of novel adherence enhancing solutions, to identify the most promising ones, worth scaling up

(4) Engagement and **training of PhD students and ECIs** in a highly multidisciplinary environment (e.g. by offering STSMs at SMEs, regulators or labs of experienced investigators in other countries), preparing them to become the next generation of highly creative and skilled researchers

(5) Dissemination of implementation strategies for healthcare professionals, patients, decision makers and SMEs across Europe and the world, by means of development of an interactive and **freely accessible web platform**, and

(6) Advocating for **broad implementation** and reimbursement of cutting-edge technologies of adherence management to the benefit of all stakeholders.

Long term impact

In the long-term, ENABLE envisages significant clinical, economic and technological impact which will foster healthy ageing and contribute to sustainable and equitable healthcare systems. Three forms of impact have been identified.

(1) **Technological impact**: once clinical and behavioural context, pathways to patient access and reimbursement are clear, more SMEs will invest in tailored medical devices thereby accelerating innovation

(2) **Clinical impact**: patients and providers will have better awareness and earlier and easier access to new technology. Uptake of adherence enhancing technology in clinical guidelines could further stimulate its use, implementation and beneficial effects. Ultimately, this could lead to fewer medical complications, hospitalizations, a more efficient use of medication, lower mortality rates and better quality of life

(3) **Economic impact**: fewer complications and more efficient use of medication will lead to lower healthcare costs and more work productivity. In addition, due to positive stimulation of European SMEs, more jobs will be generated

Innovation potential

Engineers are brilliant at designing technology, but in the case of medical technology they will also have to take into account medical professionals' and patients' knowledge, preferences and habits as ell as the challenging differential healthcare markets and systems across Europe. The ENABLE Action will allow innovative medical technology, aimed at enhancing medication adherence, to be **readily applicable** in real-world clinical practice and will find their way to patients and providers more efficiently. Through the shared development of **new processes**, patients and providers are allowed **earlier access** to innovative medical technology and practical guidance on adherence management.

Currently, many innovators and investors in medical technology are held back by the opaque healthcare systems across Europe, which hampers realistic sales projections and further technological advances. Notably, the healthcare market is not a traditional seller-buyer market in the sense that the client is not always choosing the technology (the healthcare provider does) and is also not always paying it (in full) (health insurance does, partly). In particular, many of the current adherence enhancing technologies show potential in small-scale research settings and labs, but unfortunately never make it to the patient and market because of a lack of clinical relevance or lack of large-scale investments. The network created through ENABLE will require an **initial effort** from the ENABLE collaborators to bring together and activate the right stakeholders that are able to initiate a new technology implementation process. Challenges are envisaged in the process of convincing national policy makers and urging them to shift their focus from national to a pan-European view. Though there is a risk that policy makers do not want to broaden their views beyond national policy, it is anticipated

that the activities of ENABLE will create new incentives by leading to **scientific breakthroughs** by bringing innovating engineers, healthcare professionals and policy makers together resulting in crossfertilization and the generation of new scientific concepts and processes consisting of state-of-the-art technology that is ready for wide use in current European medical and pharmaceutical practice. Concretely, this would lead to:

(1) patient and provider tailored adherence enhancing technology and
(2) country-tailored implementation and reimbursement strategies for the adherence enhancing technologies.

Information generated and disseminated through the ENABLE Action will stimulate SMEs and investors even more to develop medical technology (**technological impact**), being guided by easily accessible local medication adherence expertise centers and a pan-European web platform that help them to reach their end-users and give them a better and more transparent idea of their potential European market share. As a result of more practical guidance on adherence strategies, patients' adherence will improve resulting in avoidance of unnecessary add-on medication and related side– effects and thus generates **socioeconomic impact**.

3.2 MEASURES TO MAXIMISE IMPACT

3.2.1 KNOWLEDGE CREATION, TRANSFER OF KNOWLEDGE AND CAREER DEVELOPMENT

Knowledge creation

By bringing together innovating engineers, healthcare professionals and policy makers new scientific concepts and processes regarding medication adherence technologies will be created. The open and multidisciplinary environment of ENABLE support cross fertilization and out-of-the-box ideas. At the same time, major challenges regarding implementation of medical adherence enhancing technology will be jointly tackled. This could result in technology that is provider and patient friendly and ready for wide use in current European medical and pharmaceutical practice. As such, this is expected to lead to better knowledge on **(1)** patient and provider tailored adherence enhancing technology and **(2)** country-tailored implementation and reimbursement strategies and early access pathways for adherence enhancing technologies.

Transfer of knowledge

Dissemination targets specific to the domain (professional publications, conferences for health profesionnals) and social media for patients will be identified in advance. Part of the knowledge transfer will be through existing clinical and patient associations, but also a list with abstract submission dates for key pre-identified conferences will be created, and in addition social and mass media (e.g. Twitter, LinkedIn) will be used. To reach the widest audience possible the aim is to publish the ENABLE Action's findings exclusively in open access journals, thereby allowing access to knowledge without payment required. More detailed dissemination plans are outlined in section 3.2.2.

When successfully established, the knowledge on optimal implementation of adherence technologies created through the ENABLE Action network may also serve as a **blueprint for other medical technologies**, such as diagnostic devices, pharmacogenetics or point-of-care tests seeking access to European healthcare markets.

Career development

In WG2 (see also section 4.1.1), special emphasis is placed on the **development of the careers of ECIs**. Whenever possible the Management Committee will consider for leadership positions ECIs who will have a unique opportunity to develop their scientific skills as well as management and networking skills that will be to be invaluable for their future careers. Through the STSMs, ECIs can learn from senior investigators and policy makers on the use and regulations of technology in other countries. Alternatively, they can learn directly from engineers at SMEs that are developing these adherence enhancing technologies or from regulatory policy makers that are assessing these technologies. At the same time, the young investigators' academic and/or clinical experience and country specific knowledge could benefit the SMEs in further optimizing their technologies to make them fit for purpose.

Beyond organizing and attending scientific missions, ECIs will be asked to contribute to the Action by providing content for the COST Action ENABLE platform. Technology oriented STSMs will take place between SMEs, investigators and end-user associations to learn about the practicalities and potential of new adherence enhancing technologies in clinical practice.

3.2.2 PLAN FOR DISSEMINATION AND/OR EXPLOITATION AND DIALOGUE WITH THE GENERAL PUBLIC OR POLICY

ENABLE will have a dedicated Working Group (WG) for dissemination and exploitation of the results (see section 4.1.1) to the scientific community, the professional and policy community as well as the general public. The WG will create a stakeholder platform and a detailed 4-year dissemination and communication plan based on the following strategies;

(1) Stakeholder engagement: relevant stakeholders from the ENABLE countries (healthcare providers, patient associations, policy makers, SMEs) will be involved from an early stage onwards. They are essential in outlining the specific needs and contextual factors. To facilitate networking, the first conference will be organized in the first semester of year 2, followed by at least four smaller-scale face-to-face meetings spread along the Action duration (at least one per year) supplemented by monthly web-meetings.

(2) Professional societies and existing networks: the ENABLE Action network members are represented on many professional organizations on adherence, (primary) care and policy such as ESPACOMP, ISPE, EuroDURG, ISPOR, IPCRG, WONCA, and regulatory bodies. These organizations will serve as hubs for knowledge dissemination, raising awareness and ensuring knowledge is communicated and translated into clinical practice and reflected in policy.

(3) Gold standard open access: to reach the widest audience possible the aim is to publish the ENABLE Action's findings exclusively in open access journals, thereby allowing access to knowledge without payment required.

(4) Searchable knowledge base: The ultimate goal here is the creation of an interactive European web platform that provides a state-of-the-art overview of available technology and specific guidance on implementing adherence enhancing solutions across European healthcare systems. The web platform is envisaged to be a large networking platform on adherence technology, freely accessible for healthcare providers, patients, policy makers and companies.

(5) Engaging with the general public: Dissemination targets specific to the domain of the general public will be identified in advance. Part of the communication will be through traditional media channels and popular magazines, but in addition social and mass media (e.g. Twitter, LinkedIn) will be used. The Action aims for at least half-yearly updates.

(6) Easily accessible local expertise centers: MC members will stimulate the set up of local/national Medication Adherence Expertise Centers where materials and trainings on effective application of adherence technologies and interventions in local language (also interpretable for people with low literacy) are available.

4 IMPLEMENTATION

4.1 COHERENCE AND EFFECTIVENESS OF THE WORK PLAN

4.1.1 DESCRIPTION OF WORKING GROUPS, TASKS AND ACTIVITIES

ENABLE has produced a detailed work plan describing all the Working Groups' (WGs), tasks, activities, timeframes and deliverables in order to assure coherent and effective work of the entire network, and timely achievement of its objectives. In order to fulfil the objectives, the ENABLE Action includes four inter-related Working Groups (WGs) as depicted in Figure 3 and further described below. Each WG will have a WG Leader. The overall Action will be overseen by a Management Committee (MC), that will be support the WGs and guide the overall process to keep the Action on track. The Action MC will consist of up to two representatives for each COST Full or Cooperating Member.

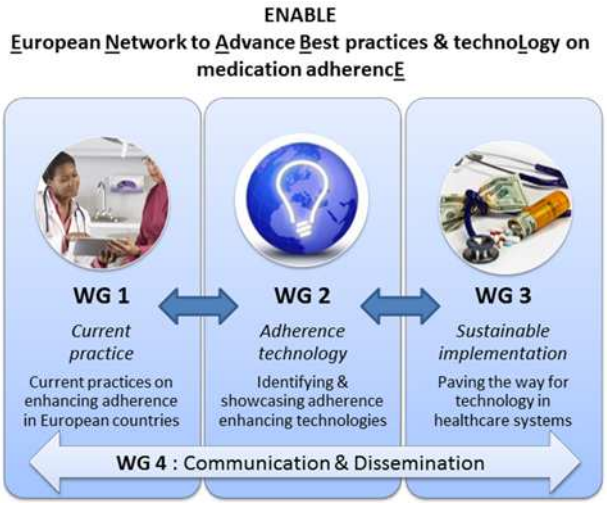


Figure 3: Inter-relationships between Working Groups

The Leaders of the four WGs will have a good gender balance (50/50) and each WG will consist of a mix of representatives from different scientific, age-group and European geographical areas, to allow a multidisciplinary and pan-European approach. At least two of the four Leaders of the WGs (50%) will be members from COST Inclusiveness Target Countries.

WG 1: Current practices and unmet needs

WG1 focusses on the identification of means through which non-adherence is dealt with by healthcare professionals working across all levels of the health care system in Europe (primary care, specialist care, pediatrics, pharmacy care, and nursing). In addition, best practices and successful adherence mamagement strategies in settings within and outside European systems will be identified. The ultimate goal for the WG is to ascertain unmet needs to improve medication adherence in European settings, in order to establish a call-for action.

The COST networking tool used in this WG will be a stakeholder conference, with interactive break-out sessions in groups of max. 10 persons to stimulate participation and interactions. The conference will be attended by relevant stakeholders, with support from WG4. In order to collect necessary information on current practices and unmet needs, a survey will be disseminated to be completed by attendees prior to the conference and a report including (personal and health system) barriers and faciltators for medication adherence in each country will be drafted (D1.1). The final output of this Working Group will be a call-for-action (D1.2). The report and call for action will be published on the COST Action ENABLE platform.

WG 1: Current practices and unmet needs		
Networking Tools	Deliverables	Related deliverables
Conference Round table	D1.1 Report of survey results D1.2 Call for action	D3.2

WG 2: Adherence enhancing technologies

The aim of WG2 is to publicly showcase an extensive range of adherence enhancing technology which is available in Europe (D2.1). This will be achieved through the facilitation of networking activities between SMEs and stakeholders in the healthcare setting, and through the organization of Short-Term Scientific Missions (STSMs) between researchers, SMEs, policy makers and end-user associations.

Technology oriented STSMs will take place between SMEs, (early stage) investigators and end-user associations to learn about the practicalities and potential of new adherence enhancing technologies in clinical practice. In WG2, emphasis is placed on the **development of ECIs**. Beyond organizing and attending STSMs, ECIs will be stimulated to contribute to the Action by providing content for the ENABLE platform. This will include a digital report/database with an overview of exisiting adherence enhancing technologies (D2.1). STSM participants will add a report with user and expert experiences to the technologies they have encountered (D2.2), in formats which can be uploaded on the COST Action ENABLE platform. The content could be supplemented by a blog and/or vlog to communicate and

disseminate their experiences and insights brought about by the STSMs. In order to ensure a wealth of information on adherence enhancing technologies on the ENABLE platform, members of the Action will attend relevant dissemination meetings and ask SMEs to provide additional information to upload on the platform, and organize a final “digital networking market” throughout the Action’s final conference, which will allow SMEs to showcase their products.

WG 2: Adherence enhancing technologies		
Networking Tools	Deliverables	Related deliverables
STSMs Dissemination meetings Conference	D2.1 Online report/database with key adherence enhancing technologies D2.2 Report with user and expert experience	D4.1

WG 3: Sustainable implementation of adherence enhancing technologies

The task of WG3 is to pave the way for adherence enhancing technology to be implemented in European health care settings. This will involve the sharing, collection and dissemination of information on European healthcare systems (e.g. division of clinical tasks and responsibilities between primary care and secondary care as well as access to care) (D3.1), contact information of key stakeholder associations (D3.2) and reimbursement pathways/HTA guidelines (D3.3) for new adherence enhancing technologies. Existing databases with relevant information, e.g. The Health Systems and Policy Monitor, and information on health system barriers and facilitators (D1.1) collected in WG1 will be consulted to avoid a duplication of efforts. Collected information will be publicly disseminated by means of the ENABLE platform.

In addition to the collection and dissemination of information, policy oriented STSMs will be organized to facilitate an exchange of knowledge between healthcare policy makers and providers of technologies. STSMs in WG3 will focus particularly on the regulatory aspects involved in the implementation and use of adherence enhancing technologies in countries throughout Europe.

Information on national policies and guidelines affecting the implementation of adherence enhancing technologies, will be collected through reports about STSMs in different member states, WG meetings during which guest speakers will be invited to speak about the aforementioned issues, and through using existing information/data which will be uploaded to the ENABLE platform by WG4.

WG 3: Sustainable implementation of adherence enhancing technologies		
Networking Tools	Deliverables	Related deliverables
WG meetings (incl. guest speakers) STSMs	D3.1 Overview European healthcare systems (report) D3.2 Overview of organizations of key stakeholders (report) D3.3 Overview of reimbursement pathways for new adherence enhancing technologies (report)	D1.1, D4.1

WG 4: Communication and Dissemination

The goal of WG4 is to disseminate and exploit the knowledge collected throughout activities in WG1, WG2, and WG3, and to ensure the active representation of all relevant stakeholders throughout the Action. The WG will do so through the development and maintenance of the COST ENABLE webplatform (D4.1) through which information will be publicly disseminated. Alongside this, WG4 will develop and carry out a communication plan (D4.2) with innovative tools to reach critical mass (incl. SMEs, professionals, policy makers, patients and the public). In line with this, WG4 also plays a key role in the mobilization of stakeholders to participate and contribute to the Action and the knowledge base. Lastly, WG4 will ensure that all findings of the Action are published in open access scientific and policy oriented journals.

WG 4: Communication and Dissemination		
Networking Tools	Deliverables	Related deliverables
WG meetings	D4.1 Development of Action website (COST Action ENABLE Platform) D4.2 Communication plan	D1.2, D2.1, D2.2, D3.1, D3.2, D3.3

4.1.2 DESCRIPTION OF DELIVERABLES AND TIMEFRAME

The deliverables related to the WGs are presented in the tables in section 4.1.1 and the anticipated timeframe is presented in the GANTT diagram in section 4.1.4. The total timeframe is 4 years. The organisation of ENABLE will conform to the "Rules and Procedures for implementing COST Actions".

4.1.3 RISK ANALYSIS AND CONTINGENCY PLANS

Risk of insufficient quality: ENABLE delivers poor quality findings. ENABLE will have a strict quality management system to ensure that all findings and deliverables are of the highest quality. The quality management system consists of reviews by at least two MC members of the Action (internal quality control), and external experts as reviewers of public meetings and journals as part of the dissemination process (external quality control). If any ENABLE deliverable fails to meet the highest possible quality standard it will be returned to the responsible party for revision. Importantly, the participants will not operate alone. If a product is sent back for revision, the reviewers and external experts will provide detailed comments and discuss the quality problems with the authors in order to improve the product.

Risk of delays: ENABLE deliverables cannot be submitted in time. ENABLE will aim to use a set of management software (e.g. SharePoint or Teamwork) to help minimize the risk of delays. At the first indication of a delay, the MC will discuss and develop a risk mitigation strategy. Key mitigation approaches will include: devoting extra resources to the task; running sequential tasks in parallel to avoid delays, and developing plans for reducing time needed to complete follow-on tasks. In some cases these strategies will involve revising ENABLE's internal schedule, but should not affect the overall delivery schedule. Finally, it should be noted that the Action's transparent and comprehensive communications process will help to identify and address any possible delays expeditiously.

Risk of cost overruns: ENABLE costs will be beyond the awarded budget. In the case of cost overruns, the Action will not ask for additional funding although it may ask for permission to adjust some aspects of the ENABLE activities (e.g. invitation of fewer particiapants to attend workshops and dissemination events). Unforeseen risks may require that participants will contribute additional in-kind resources (e.g. staff time) to ensure successful completion of the ENABLE's objectives, i.e. the network will complete the outlined scope within the budget.

Personnel leaving risk: Key personnel become unavailable to complete ENABLE. In the instance that one or more key personnel will leave ENABLE before the end of the Action, members will try to find a suitable replacement (or equivalent expertise) and seek approval for the replacement from the Action MC. A key strength of ENABLE, however, is that each of the particiapnts is expected to have several staff members who could successfully complete the organisations' allocated responsibilities, meaning staff changes should result in minimal loss of knowledge, or have minimal impact on ENABLE overall.

Risk of breach by a party of its obligations or responsibilities: The amount or quality of work provided by a participant does not comply with expectations or obligations. The relevant participant will be informed by the MC about the problem and its impact on the overall ENABLE Action and their need for performance improvements. If the participant fails to respond positively, appropriate measures will be taken by the MC.

Risk of collecting insufficient basic data: to minimise the risk of capturing insufficient data to enable the development of consensus recommendations, the network will be strategically built to ensure a wide range of particiapant from Eastern and Western European countries. Moreover, each collaborating particiapant also has a wider network of relevant stakeholders and contacts that can be called upon, should there be need.

Risk of insufficient extent of dissemination: ENABLE information does not reach the intended target audience. First, ENABLE will utilize a wide variety of communication channels including the internet,

technical publications, public events, conferences, newspaper articles and videos. ENABLE participants will have extensive experience in the dissemination of technical research results and in communication of complex research ideas to colleagues, external parities and the general public. Thus, the use of a wide range of media channels and expert collaborators in the dissemination of ENABLE will ensure the results reach the largest possible target audience.

4.1.4 GANTT DIAGRAM

The Gantt diagram can be found in Table 1.

Table 1: Gantt diagram of the ENABLE COST Action

WP	Tool (T) / Deliverable (D) / milestone (M)		Y1-S1	Y1-S2	Y2-S1	Y2-S2	Y3-S1	Y3-S2	Y4-S1	Y4-S2
N/A	**T1: First MC meeting**									
N/A	**T2: Second MC meeting with First Conference (open event)**									
N/A	**T3: Third MC meeting**									
N/A	**T4: Fourth MC meeting and Final Conference (open event)**									
1		D1.1 Survey results (report)		D1.1						
1		D1.2 Call for action				D1.2				
1	*M1. Call for action signed and submitted*					M1				
2	**T5: Short-Term Scientific Missions (Technology oriented)**									
2	**T6: Digital Networking Market (Conference)**									
2		D2.1 Descriptions of key adherence enhancing technologies			D2.1.1		D2.1.2		D2.1.3	D2.1.4
2		D2.2 Report with review of adherence enhancing technology			D2.2.1		D2.2.2		D2.2.3	D2.2.4
2	*M2. Call for STSMs (technology oriented) posted*			M2	M2		M2		M2	
2	**T7: Attending Dissemination meetings**									
3	**T8: WG Meetings**									
3	**T9: Short-Term Scientific Missions (Policy oriented)**									
3		D3.1 Overview European healthcare systems (report)					D3.1			
3		D3.2 Overview of organizations of key stakeholders (report)					D3.2			
3		D3.3 Overview of reimbursement pathways for new adherence enhancing technologies (report)					D3.3			
3	*M3. Call for STSMs (policy oriented) posted*			M3	M3		M3		M3	
4	**T10: WG Meeting**									
4		D4.1 Development of Action website		D4.1						
4		D4.2 Communication plan		D4.2						
4	*M4. Launch of COST Action ENABLE platform*			M4						

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