Brussels, 25 May 2021

COST 062/21

**DECISION**

Subject: Memorandum of Understanding for the implementation of the COST Action "Harmonizing clinical care and research on adrenal tumours in European countries" (HARMONISATION) CA20122

The COST Member Countries will find attached the Memorandum of Understanding for the COST Action Harmonizing clinical care and research on adrenal tumours in European countries approved by the Committee of Senior Officials through written procedure on 25 May 2021.

**MEMORANDUM OF UNDERSTANDING**

For the implementation of a COST Action designated as

**COST Action CA20122**
**HARMONIZING CLINICAL CARE AND RESEARCH ON ADRENAL TUMOURS IN EUROPEAN COUNTRIES (HARMONISATION)**

The COST Members through 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, 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 document amending or replacing them.

The main aim and objective of the Action is to Create a multidisciplinary network to harmonize clinical care and research on adrenal tumours, to encourage interactions between the Action stakeholders, to promote translational research and to facilitate next generation clinical trials assisted by artificial intelligence technology.. This will be achieved through the specific objectives detailed in the Technical Annex.

The present MoU enters into force on the date of the approval of the COST Action by the CSO.

## OVERVIEW

**Summary**

Adrenal tumours affect more than 3% of the population aged > 50 years, and their absolute prevalence is increasing due to population aging. Most of these tumours are benign and hormonally inactive. However, 2-10% of them are at risk of malignancy, and 20-40% present hormone over-secretion, leading to significant morbidity.

Management of adrenal tumours is quite heterogeneous, and this leads to substantial inequality in patient care throughout Europe. In this context, the goal of HARMONISATION is to constitute a multidisciplinary network to harmonize clinical care and research on adrenal tumours throughout Europe. Our focus will be on COST Inclusiveness Target Countries (ITCs). In addition, this collaborative network will establish a modern framework to develop a new generation of real-time and real-life randomized clinical trials, which will be federated and registry-based. For this purpose, HARMONISATION will be organized in five Working Groups: 1. Harmonizing clinical practice for adrenal tumours; 2. Harmonizing adrenal tumour research and -omics practice; 3. Harmonizing Information Technology (IT)/Artificial Intelligence (AI) tools towards a standardized registry; 4. Harmonizing the ethical and legal framework required for federated European trials; and 5. Communication, dissemination, and inclusiveness.

The successful execution of HARMONISATION's goals is guaranteed by the collaboration of clinicians, researchers, and experts from other relevant fields, including artificial intelligence, data science data protection, legal and ethical issues, and patients' representatives.

| **Areas of Expertise Relevant for the Action** | **Keywords** |
|---|---|
| ● Clinical medicine: Endocrinology and metabolism (including diabetes, hormones)<br>● Clinical medicine: Databases, data mining, data curation, computational modelling<br>● Clinical medicine: Ethics of clinical medicine<br>● Health Sciences: Health services, health care research<br>● Computer and Information Sciences: Artificial intelligence, intelligent systems, multi agent systems | ● Adrenal tumours<br>● Adrenal clinical care and research harmonization<br>● Legal and ethical trial framework<br>● Federating information technologies<br>● Patients' reported outcomes |

**Specific Objectives**

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

Research Coordination

● Develop common diagnostic algorithms and treatment guidelines to homogenize clinical practice, targeting the highest standards, and bringing information/technology to all European countries.
● Establish standard operating procedures for the collection of clinical information on sampling, for quality assessment, and for data analysis, from high throughput platforms.
● Coordinate the development of a biobank devoted to adrenal tumours.
● Create an artificial intelligence-based digital framework for semi-automated treatment of medical records. This will establish the bases for a new federated registry, which will serve to implement and run next generation clinical trials
● Prepare nation-specific adaptations of a common European ethical and regulatory framework promoting federal research at the European level.

● Facilitate co-creating input by patient representatives to allow patient-driven priority setting of the research agenda, co-creating input into interventional study designs and the development of patient-reported outcome measures.
● Disseminate knowledge and seed standard operating procedures for translational research, promoting future federated European research.
● Advocate adrenal tumour patients' feelings and opinions towards the medical, research, industrial, and institutional communities.

Capacity Building
● Promote the highest standards of clinical practice for adrenal tumour management, by acting as a stakeholder platform and a trans-national practice community.
● Foster knowledge exchange and develop a joint research agenda on adrenal tumours at the European level.
● Bridge the fields of medical research, information technology, and ethics/regulations, creating a multidisciplinary task force. This will lead to a new generation of clinical trials featuring AI for real-life, real-time, and federal implementation.
● Involve and train early-career clinicians and researchers, especially from ITCs, and make them into the next generation of adrenal experts.
● Train researchers in using new technologies in molecular biology, such as genomic tools, to find and interpret molecular biomarkers.
● Actively promote the inclusion of new researchers and other reference networks.

# 1. S&T EXCELLENCE

The overarching aim of HARMONISATION is to constitute a multidisciplinary European network addressing adrenal tumour practices through a combination of different fields: clinic, research, ethics/law, data science, and artificial intelligence. The Action will focus on COST Inclusiveness Target Countries (ITCs). Beyond improving practices towards high standards, the Action will create a modern framework to develop a new generation of real-time and real-life federated clinical trials.

## 1.1 Soundness of the Challenge

### 1.1.1. DESCRIPTION OF THE STATE-OF-THE-ART

**Medical background of Adrenal Tumours:** adrenal tumours are frequent, with a prevalence of more than 3% in individuals aged > 50 years. Moreover, their absolute prevalence is increasing due to population aging. The four most relevant tumour entities of the adrenal glands are: (i) adrenocortical carcinoma (**ACC**, rare [see Table1], highly malignant, and sometimes with steroid hormone excess); (ii) pheochromocytoma and paraganglioma (**PPGL,** rare [see Table 1], leading to potentially life-threatening catecholamine excess); (iii) aldosterone-producing adenomas (**APA**, the most common cause of surgically curable secondary hypertension related to excess aldosterone); and (iv) non-aldosterone-producing cortical adrenal adenomas (**NAPACA**, the largest group, including a subgroup with autonomous cortisol secretion).

**Basic research:** high throughput molecular studies have profoundly changed our understanding of adrenal tumours, identifying distinct biological subtypes for every tumour type, each related to specific molecular alterations. New genomic markers have emerged that have potential for personalized clinical management, including markers of prognosis and treatment response.

**Diagnosis and prognosis:** most adrenal tumours are detected incidentally, and diagnosed during imaging for other purposes. They are usually benign and hormonally inactive, not requiring intervention. However, 2-10% become malignant, and 20-40% present hormone over-secretion leading to significant morbidity. There are published recommendations for assessing incidentally discovered adrenal tumours, malignant adrenal tumours, and hypersecreting tumours. However, these recommendations are only partially applied, especially in centres with less experience. Another important difference between centres is the detection of molecular markers for decision making. These tools have recently emerged as important markers of prognosis and treatment choice. However, despite their convincing clinical benefits, their use as prognostic and therapeutic factors is currently limited by the unavailability of specific techniques for their detection in most centres.

**Clinical research and trials:** to date, randomized controlled trials (RCTs) are the Gold Standard experimental framework for evaluating the effectiveness and safety of therapeutic interventions. By randomly assigning patients to experimental and control arms, randomized controlled trials ensure the greatest reliability and validity of the results by reducing the impact of known and unknown biases. However, RCTs are expensive and not always suitable or feasible for rare diseases.

**Intervention and treatment:** there have been few randomized trials for adrenal tumours. The FIRMACT study successfully compared etoposide, doxorubicin, and cisplatin plus mitotane regimen with the second regimen employing streptozotocin plus mitotane in advanced ACC. More recently, ADIUVO studied the benefit of adjuvant therapy after complete surgery in patients at low risk of tumour recurrence, but was unable to recruit a sufficient number of patients. Finally, two on-going trials are testing treatments in advanced adrenal cancers, with limited recruitment so far, and are at risk of not reaching the expected numbers. **All other clinical practices** for these tumours have **not yet been validated** by RCT.

## 1.1.2. DESCRIPTION OF THE CHALLENGE (MAIN AIM)

Below, we report the challenges for HARMONISATION's networking activities.

**Heterogeneous clinical practice in Europe, especially in centres from ITCs:** European guidelines have been implemented for some (e.g. ACC, PPGL, and incidentally detected tumours), but not all adrenal tumours. These interdisciplinary recommendations aimed to establish a consensuated state-of-the-art diagnostic work-up and therapeutic standards to be followed to provide best care for all patients. Unfortunately, these recommendations are not widely applied in Europe, such that patients' care is heterogeneous and often insufficient throughout Europe. Thus, the lack of consensus on best practices for diagnosis and therapeutics further increases inequity in patient care in Europe. A prototypical example of heterogeneous practice is the use of molecular markers derived from 'omics' studies. **Studying the molecular markers of patients from ITCs is a current challenge** because of the experimental costs, and the need for well-trained molecular experts.

**Cohorts of rare adrenal diseases:** ACC and PPGL are examples of rare adrenal diseases, with annual incidence of 1 and 5 per million, respectively (Table 1). Of note, patients from most ITCs are currently not included in trials, partly due to the heterogeneous clinical practice mentioned above. Beyond the need for homogeneous clinical practice throughout Europe, the insufficient recruitment of patients in clinical trials raises **ethical and regulatory issues** specific to each country.

| | **Population** | **Annual incidence** | |
|---|---|---|---|
| | | **ACC** | **PPGL** |
| **Inclusiveness Target Countries (ITC) (n=22)** | 145.2 million | 145 | 726 |
| **Other COST member countries (n=16)** | 413.3 million | 413 | 2066 |

*Table 1: Population and annual incidence of two rare diseases - adrenocortical carcinoma (ACC) and pheochromocytoma/paraganglioma (PPGL) - in European countries stratified in Non-Target and Inclusiveness Target Countries.*

**The need for a new clinical research paradigm, especially for rare diseases**: **most studies on adrenal tumours are non-randomized trials**. This is because of the limited number of patients (especially for rare adrenal tumours), and because of the cost and the complexity of randomized trials. Indeed, for most diseases that are not targeted by big pharmaceutical companies, for their limited appeal and numbers, clinical trials - if any - are run by academic institutions with limited resources. This leads to small sample sizes and methodological constraints. With regard to the results obtained, unlike controlled randomized trials, trials lacking a control arm and those using historical controls have repeatedly been shown to exaggerate the results on treatments' efficacy. Similarly, early clinical trials on small or diverse patient samples are less reliable and prone to finding higher response rates than those in subsequent randomized studies. Therefore, the management of adrenal tumours and the potential hormone excess associated with them remain mainly empirical, with limited validation of current approaches to diagnosis, therapeutics, and follow-up.

**Heterogeneous collection of clinical data:** There are numerous challenges in addressing this problem. Clinical data collection must be performed both reliably and timely, but registries are still being manually curated, requiring extensive and expensive manpower/time to collect the data. This also causes negative effects on data quality. Another challenge is the need for approval by regulatory and ethics committees in each country. Indeed, not all countries are up to date on the implications of relatively new technologies such as **Artificial Intelligence (AI).** Another obstacle is the sheer complexity of managing and coordinating data throughout Europe. Finally, a highly multidisciplinary task force is needed, including all expertise and stakeholders required to share information, data, techniques, tools, perspectives, and theories from all angles.

**Positioning European adrenal tumours expertise in a fast-changing World:** There is an unacceptably high inequality in patient care for adrenal tumours throughout Europe. Therefore, an urgent and unmet need is to **improve clinical practice to its higher standards**. Although experts in the field from different European countries have federated into a few clinical and research networks,

there has been only limited progress in establishing best practices. This is especially true in ITCs, where various processes are still in their infancy: multi-centre clinical trials, sharing of biomaterial, and clinical data collection in registries. Moreover, there are few and inconsistent clinical cohorts and trials. By creating the largest ever European network for adrenal tumours, we will generate and share clinical guidelines for patient management, while mutually benefitting from a significantly increased cohort size.

A new generation of large randomized trials should be based on high-quality data from real life, and should federate numerous centres at a reasonable cost.

Some digitalized improvement of randomized clinical trials has been achieved by using **registries** that can include many centres in a real-life setting. Experience from cardiovascular research demonstrated that registry-based clinical studies can be performed with a cost saving of more than 90% compared to conventional trials.

In parallel, AI is now providing a set of next generation tools, opening the way to registry-based trials. Indeed, AI technology is mature enough to automatically and reliably extract relevant pieces of information from unstructured medical records. This information is required to feed a structured registry of tumours, and it can be obtained instantly from a set of selected patients in any clinical centre. Thus, we can continuously extract simple essential information on tumour features, patient management, and outcomes, providing a real-time and real-life registry.

Finally, clinical practice needs to be homogeneous, and we need very well organized networks and registries; therefore, HARMONISATION is necessary to create federated, registry-based real-time and real-life randomised trials.

## 1.2 Progress beyond the state-of-the-art

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

The originality of HARMONISATION is that it gathers participants from different geographical sub-groups, with a focus on ITCs. Another innovation is that it involves experts in artificial intelligence, databases, data protection, and legal and ethical issues, in addition to researchers and clinicians. We expect that this multidisciplinary and geographically widespread network will generate strong synergisms.

HARMONISATION will advance the current state of the art of patient care and research in the field of adrenal tumours in the following ways.

**Promoting excellence for clinical practice and research on adrenal tumours:** to significantly progress adrenal cancer research, it is necessary to improve the recruitment of patients into clinical research. Long-lasting and practise-changing research requires dedicated scientists, clinicians, and experts from different fields. HARMONISATION will promote excellence by gathering these experts through dedicated networking activities throughout Europe, especially in ITCs. The Action will analyse the issues that these countries face in order to identify common aspects and define methodological strategies for clinical research/trials. The Action will harmonise protocols using either existing guidelines, or creating new ones, and by sharing these best practices among the countries. This will stimulate research and clinical practice, while reducing inequalities between the participants.

**Improving adrenal research by standardizing patient clinical data collection and biomaterial collection, and by analysing -omics data:** patient registries are an important research tool for rare diseases. Modern translational medicine requires connecting clinical data with the results obtained in the related biomaterial repositories/registry. Although there are several European registries on various adrenal diseases, a single unified registry and repository are necessary, and this requires a new network throughout Europe. This network must include and interconnect all clinical and research centres focused on adrenal tumours, ranging from the top experts to the less established ones. HARMONISATION will focus on centres in ITCs, as these have not been significantly involved in most clinical research networks so far. More concretely, HARMONISATION will establish **Standard Operating Procedures** (SOPs) for

clinical data, biomaterial, and genomics analyses in agreement with all partners. These analyses will be feasible in all centres and compatible with best practices. Through this network, some centres will analyse bioinformatic challenges and techniques, while others will complement missing skills and/or technologies in a given place, through masterclasses and short educational exchange programs.

**Implementing future next generation randomized trials using modern technologies:** the HARMONISATION network will serve as a basis to implement a new generation of clinical trials, where specific SOPs will serve to feed a common registry. AI technology tools will be investigated by a main AI expert team that will be specialized in automated extraction of routine medical information from databases. The aim is to automate and reliably collect essential information on tumour features, and patient management and outcomes. This could continuously provide real-time and real-life data to a federal registry. The AI team will work together with local information technology experts to ensure a smooth national implementation, and to allow for adaptation into each language by Natural Language Processing. Considering the FAIR principles (findability, accessibility, interoperability, and reusability), we will create a strategy to coordinate with other research networks, based on shared metadata, common data models, compliance with international standards, and shared algorithms.

**Multidisciplinary networking for success:** HARMONISATION will engage a new generation of high standard clinical and translational research by cross-communicating information, data, techniques, tools, and perspectives among experts from different backgrounds. With this COST Action, we will build a new multidisciplinary network promoting clinical practice and research on adrenal tumours. This network will include:

- **Clinicians** from specialist European clinical centres, including internationally renowned experts and less experienced clinicians. This clinical network will be the cornerstone for improving clinical practice. We propose to put specific focus on Early Career Investigators (ECIs) with dedicated teaching programs.
- **Scientists** specialized in adrenal tumour research, including senior and junior researchers (PhD students, ECIs and post-docs). They will attend short stay exchange programs and courses.
- **Data scientists** and system information experts. They will establish the SOPs required to properly exchange clinical data.
- **Lawyers and ethics experts.** They will tackle ethical and regulatory issues, adapting a common doctrine to the specificities of each country.
- **Pharmaceutical industries.** They will facilitate the translation of the results into clinical practice.
- **Representatives of patient organisations.** They will help to define the goals of the future registry and registry-based trials. They will help the researchers better understand the needs of patients, contributing to co-creation of interventional study designs and, importantly, the development of patient-reported outcome measures (PROM).

## 1.2.2 OBJECTIVES

### 1.2.2.1 Research Coordination Objectives

HARMONISATION aims to build upon the participating groups' current research activities and funding, leveraging them to promote national and transnational initiatives. The Action defines the following Research Coordination Objectives for each working group:

- Develop common diagnostic algorithms and treatment guidelines to **homogenise clinical practice**, targeting the highest standards, and bringing information/technology to all European countries (WG1).
- Establish **SOPs** to collect clinical information on sampling, quality assessment, and data analysis, from high throughput platforms (WG2).
- Coordinate the **development of a biobank** devoted to adrenal tumours (WG2).

- Create an **AI-based digital framework** for semi-automated treatment of medical records. This will establish the bases for a new federated registry, which will serve to implement and run next generation clinical trials (WG3).
- Prepare nation-specific adaptations of a **common European ethical and regulatory framework** promoting federal research at the European level (WG4).
- **Facilitate co-creating input by patient representatives** to allow patient-driven priority setting of the research agenda, co-creating input into interventional study designs and the development of patient-reported outcome measures (WG5).
- **Disseminate knowledge and seed standard operating procedures** for translational research, promoting future federated European research (WG5).

#### 1.2.2.2 Capacity-building Objectives

HARMONISATION will connect a comprehensive collection of experts and other stakeholders throughout Europe and beyond in an open and focused community platform. The capacity building objectives are:

- Promote the highest standards of clinical practice for adrenal tumour management, by acting as a **stakeholder platform** and a trans-national practice community (WG1-5).
- **Foster knowledge exchange** and develop a joint research agenda on adrenal tumours at the European level (WG1, WG2, WG5).
- Bridge the fields of medical research, information technology, and ethics/regulations, creating a **multidisciplinary task force.** This will lead to a new generation of clinical trials featuring AI for real-life, real-time, and federal implementation (WG1-4).
- **Involve and train early-career clinicians and researchers**, especially from ITCs, and make them into the next generation of adrenal experts (WG1, WG2).
- **Advocate adrenal tumour patients'** feelings and opinions towards the medical, research, industrial, and institutional communities (WG5).
- **Train researchers in using new technologies** in molecular biology, such as genomic tools, to find and interpret molecular biomarkers (WG2).
- **Actively promote the inclusion of new researchers** and other reference networks (WG5).

# 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

The HARMONISATION network is necessary to initiate federated registry-based real-time and real-life randomised trials. Indeed, current networks have their strengths but fall short of the goals addressed by the current proposal, for example:

- National adrenal networks include COMETE in France, GANIMED in Germany, and NISGAT in Italy. Although focused on adrenal cancer research, they are intrinsically limited by their national perspective, precluding any large-scale recruitment at the European level.
- The European Network for the Study of Adrenal Tumours is an active network that focuses on research and clinical recommendations. Data have been collected from several thousands of patients in a single registry. However, this registry is retrospectively implemented by manual data entry, creating a time

lag that detrimentally affects reliability and usability of data for clinical trials. In addition, contributors mainly come from Western Europe, and ITCs are marginally implicated.

- The European Registry on Cushing Syndrome is an active research network that focuses on research on endocrine tumours that are responsible for this disease. Since the syndrome is characterized by excess cortisol, researchers involved in this network investigate adrenal tumours secreting cortisol, but not those secreting aldosterone or catecholamines. In addition, most of the patients in this network have pituitary tumours, which are the most common cause of endogenous cortisol excess, and not adrenal tumours. This network also runs a large registry, but with the same limitations as the European Network for the Study of Adrenal Tumours.
- The European Society of Endocrine Surgeons is a highly specialized network that includes endocrine surgeons who coordinate recommendations and research on endocrine surgery, including adrenal surgery. However, their interest is limited to surgical procedures, and thus does not cover medical management nor biological research.
- The European Society of Endocrinology is a network of endocrinologists from all over Europe. This large organization studies endocrine diseases far beyond the adrenal tumours, and it has a strong networking ethic. However, it mainly aims to continuously educate, organize recommendations, and lead advocacy actions, acting more as a European professional society, rather than a research network.
- There are two European Reference Networks for rare diseases that involve adrenal tumours, and were established by the European Union in 2017: the European Reference Network for Rare Adult Cancers, and the European Reference Network for Rare Endocrine Diseases. Both focus on the management of rare diseases (including adrenal tumours) from a public health and healthcare system point of view. These networks do not aim to design innovative trials. In addition, some diseases related to adrenal tumours, such as primary aldosteronism or adrenal adenomas with autonomous cortisol excess, are not listed as rare diseases; therefore, they are out of the scope of these networks.

HARMONISATION will actively interact with all of these networks to integrate the expertise of the different disciplines gathered within them and beyond. The Action will invite all members of the networks to participate in this COST Action and nominate a specific liaison officer to maintain regular exchange with them and the other stakeholders (WG5).

## 2.2. ADDED VALUE OF NETWORKING IN IMPACT

### 2.2.1. SECURING THE CRITICAL MASS AND EXPERTISE

HARMONISATION has assembled the largest consortium to date on adrenal tumours, securing both the critical mass and the expertise needed to successfully implement all of the project's objectives. The Action includes 19 COST countries at its onset, of which 10 (52.6%) are ITCs (Bulgaria, Croatia, Hungary, Lithuania, Montenegro, Poland, Portugal, Serbia, Slovenia, and Turkey) and 9 (47.4%) are other COST countries (France, Germany, Greece, Italy, Netherlands, Spain, Sweden, Switzerland and United Kingdom).

The expertise of the partners covers all Working Group activities. The network includes: (i) health care professionals; (ii) researchers in epidemiology, genetics, genomics, immuno-oncology, metabolomics, and proteomics; (iii) methodologists; and (iv) experts in genomic tools (WG1&2). The Action has also recruited two research groups with extensive expertise in information technology (IT), and in ethical and legal clearance issues. The first group is specialized in medical computing and AI, with strong expertise in medical data storage, sharing, and reuse at the international level (WG3). The second group is specialized in AI, and legal and ethical matters in health. It was the main contributor to major laws recently voted in one European country. Together with the General Data Protection Regulation (GDPR) framework, these laws simultaneously promote the need for innovation and individual protection, and define the responsibilities of all stakeholders (WG4). These two high-level groups will seed their respective expertise in the HARMONISATION partner countries via their contacts with local experts.

Networking will be the key for deploying these unprecedented challenges. Finally, researchers and communication professionals will carry out the dissemination activities (WG5).

A large multicentre network is essential for this Action. Indeed, no individual centre or country has access to enough patients with rare adrenal tumours and research infrastructures to perform adequate clinical and translational research. Leading experts at the national and international level will disseminate best practices and knowledge through measures like master classes and training schools. ECIs account for 29% of the experts in the network, and we will make a special effort to encourage them to participate in the Action's activities. The Action will also actively monitor gender balance, and boost participation from ITCs by positioning ITCs representatives at the lead of this project, and of two working groups.

HARMONISATION keeps an "open door" policy and will integrate newcomers involved and/or interested in adrenal tumours, including experts and early career professionals from other networks (WG5). In a broader way, the network aims to include hundreds of health care professionals, researchers with expertise in adrenal tumours, and specialised centres. This will put the consortium in the position to successfully apply for research grants and finally establish the mentioned registry. It will also lead to the envisioned randomized trial, thanks to the potential access to more than 100,000 patients and, among them, thousands with rare adrenal tumours (ACC, PPGL). The Action also includes a partner from Canada, boosting the international reach of HARMONISATION and securing connection beyond the European network. Finally, the Action will involve other partners who can benefit from its activities, such as patient associations, health authorities, and pharmaceutical industries (see below).

### 2.2.2. INVOLVEMENT OF STAKEHOLDERS

This Action will establish an international network of stakeholders including health care professionals and their associations, scientists, patient associations, pharmaceutical industries, and health authorities.

**Health care professionals** will be involved in the Action through the participation of their University Hospitals and specialised centres. The Action will create a platform of networking activities for healthcare professionals: workshops, training courses, working groups, meetings, and global conferences. This will allow the professionals to benefit from the network knowledge and international collaboration. The consortium will also disseminate the activities via an Action website and scientific publications in peer-reviewed journals.

**Clinical and basic researchers** will be involved in all the scientific activities of the Action, with the aim of improving research on adrenal tumours. We will bring together clinical and basic researchers to encourage translational studies. These stakeholders will network to (i) develop research infrastructure (particularly in ITCs); (ii) standardise research methodologies; (iii) generate collaborative research projects and clinical trials with large cohorts of patients with rare tumours; and (iv) disseminate knowledge. The Action will also invite more scientists to join HARMONISATION throughout its lifetime, with a Working Group specifically dedicated to this task. Finally, the Action will hold training workshops in new technologies, including IT-related and bioinformatic analyses.

**Patients and patient associations** are already connected with many clinicians and researchers on a national level. In HARMONISATION, patient representatives will actively participate in defining the detailed goals of the future registry and registry-based trials, by research priority setting and contribution to the development of patient-reported outcome measures. Involving patient associations will make them be part of a process that will enable them to actively enter future trials, as they are conscious and involved in the clinical implication and impact of these trials. Furthermore, this COST Action will provide patients with a platform to connect with each other throughout Europe.

**European associations of health care professionals and researchers** will be invited to participate in the Action´s activities by WG5´s liaison officer. They can be invited as formal members through the "open door" policy, or by *ad hoc* participation in specific activities organised by the Action. External networks will also be invited to participate in communicating the socio-economic impact of adrenal

tumours, and the new treatment options to health authorities and policy makers. The latter include national and regional governments.

**The Pharmaceutical industry** will be invited to establish collaborative projects that foster the translation of scientific network activities into clinical practice. These stakeholders will benefit from using the Action's intellectual property to develop new diagnostic tools and treatment options. By the end of the third year of this Action, we envision that at least one pharmaceutical company will establish a randomised clinical trial based on a registry. Thus, this Action will serve as a basis for launching a new generation of clinical trials for treating adrenal tumours.

The Action will bring its achievements to the attention of **health authorities and policy makers** throughout Europe. These achievements include results of the joint research activities and possible new therapeutics (as a long-term benefit of this new network structure).

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

To further expand the Action´s global reach, and to provide access to expertise and patient cohorts beyond Europe, the Centre Hospitalier Universitaire de Montréal (CHUM) will join the Action as an International Partner Country (IPC) Observer. Considering their leading position in the management of adrenal tumours in Canada, experts from this centre will help strengthen the network at both clinical and research expertise levels. In addition, our information technology core team is contributing to an ongoing initiative of federated registry for rare diseases in Canada. This will be a unique opportunity for synergistic interaction with HARMONISATION.

# 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)

HARMONISATION will foster capacity building, the application of high-standards clinical practices, and the federation of tightly connected clinical centres throughout Europe, with various levels of impact. By standardising clinical practice and creating common treatment guidelines, the Action will harmonise patient care/collection of clinical data, and provide access to new biomarkers. This will have high impact even in the short term (1-5 years). It will also lay the groundwork for a new type of adrenal tumour registry that will accelerate the future goal of initiating federated registry-based real-time and real-life randomised trials (5-7 years). In the longer run, a new generation of adrenal experts will be created (10-15 years). With the help of the new artificial intelligence tools, these experts could lead the envisioned revolution in federated registry-based real-life and real-time randomized trials. These trials could even go beyond the field of adrenal tumours (15-20 years).

**Improving Clinical practice:** this Action will enable more efficient clinical management of adrenal tumours in Europe through the implementation of guidelines and best practices that reflect the highest available standards. Indeed, homogenizing clinical procedures is mandatory to run federated clinical trials, and centres with less expertise will be the main beneficiaries, especially in ITCs. A main improvement will be the access for all patients to the analysis of biomarkers derived from genomic characterization of tumours.

**Improving adrenal tumour research:** this Action will assemble the broadest European network on rare adrenal tumours (ACC, PPGL) to date. Clinical practice will be standardised by establishing SOPs for biomaterial collection (blood, urine, and tumour samples). These SOPs will ensure the usability of samples, thus enlarging the effective size of biobanks. Samples will first be used for studying the diagnostic, prognostic, and theranostic value of biomarkers. Moreover, they may be used for future research, by implementing the proper ethical and regulatory requirements. HARMONISATION will therefore help connect basic sciences with the healthcare system. In addition, the Action will train a new generation of ECIs (PhD and post-docs), and this will have direct and long-term positive consequences on adrenal tumour research.

**Providing direct benefits to patients, especially for rare adrenal tumours:** HARMONISATION will establish a framework for rapid translation of experimental results into improved clinical practice and guidelines for patient management. As mentioned earlier, this will provide access to the analysis of new generations of biomarkers for all patients, even in the short term. In the longer term, patients will benefit from the smart and solid results derived from registry-based trials, for which HARMONISATION will set the stage. This type of future randomized trial will assess treatment efficiencies, management strategies (e.g. implementing prognostic molecular classes determined by omics), and surveillance. The success of this Action will also shed additional light on adrenal tumours, with the potential global impact of better “advertising” and earlier detection of these rare diseases.

**Towards a new generation of clinical trials:** HARMONISATION will establish a multidisciplinary network, unprecedentedly associating artificial intelligence specialists and lawyers, along with the more “classical” translational research experts. Therefore, this network will bring together the essential ingredients for setting up an ambitious evolution of clinical trials. Indeed, HARMONISATION could lead adrenal tumour research to serve as a use-case for an ambitious evolution of registry-based trials. AI tools could serve to collect real-time and real-life data, feeding a federal registry that would be compliant with national and European regulations on randomizing and running clinical trials. If successful, this Action may have a huge impact on clinical trials in general, beyond the field of adrenal tumours in terms of costs, technical, ethical, and legal relevance.

**Promoting the European ideal through a common ethical and regulatory framework federating different countries:** it is necessary to implement federated registry-based real-life and real-time randomized trials. To this aim, it is essential to comply with current ethics and legal standards at the national level across different European countries. The shared framework aims to build the local actions that each centre will have to lead by addressing local ethical committees and regulatory agencies with a high-quality project. The Action strategy is inspired by the FAIR principles, which will facilitate global integration with other research programs. In addition, technical and regulatory initiatives will be individually carried out by each centre and coordinated between countries. This will greatly promote the idea of federated clinical research at European level. If successful, it could also promote pan-European research programs. Finally, the European Community could create tools and agreements between countries for promoting these types of federations.

## 3.2. MEASURES TO MAXIMISE IMPACT

### 3.2.1. KNOWLEDGE CREATION, TRANSFER OF KNOWLEDGE AND CAREER DEVELOPMENT

**Knowledge creation:** HARMONISATION will maximize knowledge creation by several means. First, the large size of this federation on adrenal tumour research will help combine efforts instead of competing. The Action will have the opportunity to combine the largest cohorts and the most advanced expertise to address the major questions in future research programs. This will serve for both rare and common adrenal tumours. In addition, AI experts and specialists in ethical and legal issues will be involved, creating a unique momentum to establish the framework for a new generation of clinical trials. If successful, HARMONISATION will help accelerate such future trials, with the long-term perspective of advancing clinical and translational research on adrenal tumours. Involving patient groups will ensure the pursuit of relevant patient-related outcomes of these studies.

**Knowledge transfer:** it is vital that the knowledge created by HARMONISATION reaches all its stakeholders. Within the Action, the consortium will train and mobilise physicians and researchers, especially from ITCs, through educational initiatives and by hands-on collaboration between the various disciplines. A specific aim is to implement molecular biomarker analysis in ITCs, by transferring the knowledge of generating and interpreting these markers through training in molecular biology and bioinformatics. Similarly, the Action will implement common AI, legal, and ethical frameworks to promote a rapid development of numerous clinical applications. This will be an innovative approach for reciprocal knowledge transfer between clinicians and researchers, while symposiums and workshops will help to spread the knowledge to the rest of the partners. Regarding external stakeholders, including the public, the Action will use the targeted dissemination plan described in section 3.2.2, which will be continuously updated throughout the Action's lifetime.

The consortium considers it important to sustain these activities beyond the scope of this COST Action. Therefore, it will implement future organisational measures, like securing alternative funding.

**Career development:** HARMONISATION will create unique opportunities for career development in contemporary and future cross-topic medicine, including AI. ECIs will be specifically targeted through master classes and schools, and will be engaged by internationally renowned researchers. This will promote their careers by acquiring new skills, running original research, and building/expanding their international networks. The Action will also actively help ECIs to pursue alternative funding, such as fellowships and junior leadership projects, through personalized coaching and workshops on funding application.

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

The Action will define an overall strategy for dissemination and activities in the first three months, as part of the deliverable "plan for exploitation and dissemination of results". This document will be revised and updated throughout the lifetime of the Action. The plan will describe the Action's target groups and its specific objectives. The Action will define quantitative and qualitative key performance indicators (KPIs) to monitor the activities and ensure that their impact and outcome will be measurable. Below, we provide a summary of identified target groups and specific activities.

**Multidisciplinary workshops:** multi-disciplinarity is the landmark of HARMONISATION. The Action will foster multidisciplinary exchanges at various levels, as follows:

- **Between basic researchers and clinicians:** the Action will organise discussions on translational research with the aim of harmonising practices to easily exchange data, materials, and techniques. The Action will identify a limited number of priority research topics gathering efforts and contributions from everyone in the consortium. The Action will lead annual web-based workshops and an in-person workshop during the annual HARMONISATION meeting.
- **Between ethics and legislative representatives of each country:** there will be a core legal and ethics expert team specialized in AI in health. This team will progressively disseminate a common European ethics and legal framework. This will be applicable in each country through dedicated workshops and regular meetings using web-based solutions. Local ethics and legal experts in each country will also have the opportunity to conduct/receive short-term scientific missions. This will serve to review and discuss specific aspects with the core legal and ethics team, with the aim of locally transposing the European goal.
- **Between artificial intelligence experts, methodologists, and clinicians:** these workshops will focus on the operational implementation of AI-based tools. Such tools will allow the simple, automated, and reliable extraction of key clinical features from real-life unstructured medical records. This will imply defining the items to be extracted and methods to extract them. The Action will organise dedicated workshops to define these items through regular meetings using web-based technologies (4 times a year). Another dissemination activity will concern the local implementation of these technologies in each participating centre. For that aim, the Action will propose workshop sessions on

inter-operable computing solutions for information technology specialists in each centre, starting from the core AI-expert team. There will be an absolute need for local adaptation; therefore, involving local IT experts is mandatory. For instance, the Action will need to adapt natural language processing tools to each language. These workshops will finally make a link between local experts.

- **Between patients and researchers:** This will facilitate a two-way exchange and the co-creation of clinical trials with patient-driven priority-setting and outcome measures reporting.

**Training programs:** the Action proposes several training programs within HARMONISATION. Such programs will be specific for different categories of experts listed below.

- **Clinicians**: the Action will propose a series of masterclasses with the aim to cover the whole spectrum of adrenal tumours over the course of this Action. Masterclasses will be organised twice a year; one will be in-person (adjacent to the HARMONISATION meeting), and one will be online. The Action will record these masterclasses and make them available for educational purposes through the HARMONISATION website. Finally, the Action will consider the specific needs of ITCs as a priority.
- **Researchers:** the Action will train researchers in new techniques for adrenal tumour studies. A prototypical example of training programs will be a series dedicated to handling genomic data. These programs will be especially focused on bioinformatics courses. The Action plans to organise two sessions per year: one in an online virtual classroom and one in-person at the time of the annual HARMONISATION meeting.
- **Information technology experts**: the Action will conduct training on AI tools for local IT experts. This will be held through a specific session (on demand) using web-based tools.
- **Legal and ethical experts**: the Action will conduct training on legislative and ethical issues related to AI in health for experts in each country. This will be held through a specific session (on demand) using web-based tools.
- **Patients**: to provide timely information on the Action development and empower them to provide input into the research process

**Annual HARMONISATION meetings:** the adrenal tumours symposia will be held once a year, in-person, and will include physicians, researchers, AI experts, ethics/legal experts, and patients' representatives. These symposia will have a particular focus on different topics indicated below.

- **Scientific exchanges:** the Action will present main clinical and basic research achievements through symposia. A series of scientific communications will also take place, including oral communications and live poster sessions. The Action will encourage young researchers to present their work to senior investigators.
- **Informal exchanges promoting multi-disciplinarity:** the Action will run workshops to foster networking and exchanges between the different disciplines involved in this Action.
- **Meetings with patients' representatives:** these meetings will be a useful platform for representatives of patients and their relatives. They will be able to give their feedback on patients' needs and a personal perspective to globally direct adrenal tumour research.

**Communication and dissemination:** the Action will use several tools to communicate and disseminate the aims and outcomes of the Action, as follows:

- An **Action website:** the Action will build a website to communicate and promote information on ongoing research and other activities. This task will be assigned to a partner as a dedicated web-site coordinator. The website will have a password-protected intranet to exchange information and unpublished data between partners and an open section accessible to the general public. The website will contain information on the adrenal tumour research activities, links to publications by participants and related institutions and organisations, job announcements, and material and presentations from the training and teaching activities.
- **Open Access Scientific publications:** the Action will publish in specialized and peer-reviewed journals. We foresee such publications at a late stage to disseminate the findings to the scientific

community. To increase its visibility, the Action will publish the **proceedings of WG meetings** as special issues in international journals.

- **Advocacy towards public/healthcare authorities**, both at national and federal/European levels: ethics and legal experts will have to convince the public representatives of the legitimacy and necessity of implementing artificial intelligence-based tools for promoting research. A long-term aim will be to promote federal research programs in Europe, especially based on modern technologies.
- **Exchanges with patients' representatives:** such exchanges will occur during the annual symposium. In addition, the Action will be presented to patient associations in each country through local experts.
- **Exchanges with industry**: when the federated framework for AI-based randomised trial initiative is in place, this framework will be presented to industry through targeted meetings. The aims will be to identify partners for developing specific trials with this framework, and to evaluate the framework itself from a broader perspective, since it might deeply impact clinical trials.
- **Reporting:** HARMONISATION will provide the deliverables along with the administrative justification of the costs. This activity will be assisted by a dedicated administrative structure.
-

<table>
<tr><th colspan="2">Activities</th><th>Multidisciplinary Workshops</th><th>Training</th><th>Congress</th><th>Communication & dissemination</th><th>Reporting</th></tr>
<tr><td colspan="2">Working Groups</td><td colspan="2">WG1 - WG4</td><td>WG1 - WG5</td><td colspan="2">WG5</td></tr>
<tr><td rowspan="6">TARGET GROUPS</td><td>1. Clinicians</td><td rowspan="4">- Promote translational research<br><br>- Implement AI-based tools to prepare a future registry<br><br>-Create ethical & legal frameworks adapted to each country<br><br>- Meetings twice a year (one virtual, one in-person)</td><td>Courses covering all adrenal tumours<br><br>Priority to ITCs</td><td rowspan="5">Scientific presentations<br><br>In-person workshops<br><br>Informal exchanges<br><br>Exchanges with patients' representatives<br><br>Once a year</td><td>Consensus statements<br><br>Methodological strategies<br><br>Best practice clinical guidelines</td><td rowspan="6">Deliverables<br><br>COST administrative reports</td></tr>
<tr><td>2. Researchers</td><td>New technologies (eg. "omics)<br><br>Funding application workshops</td><td>Open source scientific publications<br><br>SOPs</td></tr>
<tr><td>3. IT & AI experts</td><td>AI and data management tools required</td><td>Technical notices<br><br>SOPs</td></tr>
<tr><td>4. Ethics & legal experts</td><td>AI and data management framework required</td><td>Legal and scientific publications</td></tr>
<tr><td>5. Patient representatives</td><td></td><td></td><td>Target newsletter</td></tr>
<tr><td>6a. National Healthcare authorities</td><td></td><td></td><td></td><td>Advocacy</td></tr>
</table>

| | | | | | | |
|---|---|---|---|---|---|---|
| | **6b. EU Healthcare authorities** | | | Participation | | |
| | **7. Industry** | Targeted meetings | | Exchanges | Targeted meetings | |
| **KPIs** | | # exams<br># attendants<br># accredited students | # sessions<br># attendants | # oral/poster<br># lectures | # socials<br>Type of socials<br># followers & website accesses | # briefs<br># reports |

*Table 2: HARMONISATION activities, target groups and KPIs*

*Abbreviations: IT: information technology; AI: artificial intelligence; #: number*

# 4. IMPLEMENTATION

## 4.1. COHERENCE AND EFFECTIVENESS OF THE WORK PLAN

### 4.1.1. DESCRIPTION OF WORKING GROUPS, TASKS AND ACTIVITIES

HARMONISATION is divided into five working groups (WG) that are strongly linked and that all contribute to the purpose of promoting a framework for future improved research on and clinical care of adrenal tumours.

**WG1. Harmonizing adrenal tumour clinical practice:** the main aim of this WG is to improve the standard of clinical practice, specifically targeting ITCs. This WG will be composed of adrenal tumour experts who will help disseminate state-of-the-art practices on adrenal tumour management through masterclasses. A first step will be to advertise this training effort in clinical structures throughout Europe, especially in ITCs, to maximise the knowledge dissemination among as many clinicians as possible (Task 1.1). Clinicians wishing to attend the masterclasses will be identified. The Action will propose masterclasses covering the entire clinical spectrum of adrenal tumours, both in person (at the time of the yearly Action meetings), and using online virtual classrooms (Task 1.2). ECIs will be targeted and prioritised.

In addition to the masterclasses, adrenal tumour experts will also create consensus statements, methodological strategies including common diagnostic algorithms, and best-practice clinical guidelines for managing adrenal tumours, which will be endorsed by national, European and international professional and specialist societies and patient associations (Task 1.3).

**WG2. Harmonizing adrenal tumour research and -omics practice:** this WG will mainly focus on training researchers on modern research techniques relevant to the field of adrenal tumours, and to the perspective of next generation trials. We will organise masterclasses specifically targeting ITCs and young researchers. A dedicated theme will be generating and managing “omic” data (genomic, metabolomic, proteomic, radiomic) on adrenal tumours, with the aim of helping to implement molecular biomarkers. The Action will run master classes twice a year, either in person (at the time of the yearly meeting) or using online virtual classrooms (Task 2.1).

A second activity will be to identify and analyse state-of-the-art tools and technologies available in the more advanced groups, and make these available to groups with less experience and resources, again prioritising ITCs to help provide access to and training on such tools (Task 2.2). A prototypical example is the genomic screening of 20 genes in pheochromocytoma, which is currently not available to some of the partners, but is routinely used by many of those located in COST countries. Ultimately, this will enable all centers to access the most advanced technologies.

A third action of this WG will be to establish standard operating procedures (SOPs) for translational research, which each centre should follow to develop a biobank devoted to adrenal tumours (Task 2.3). These SOPs will guarantee the standardisation and quality of clinical data, biological material, and genomic analyses in agreement with all partners, and will be both feasible in all centres, as well as compatible with the best practices. This will be a prerequisite for future federated research including these centres.

A final activity of this WG will be to coordinate the identification of two to three research questions that could be addressed by a randomised trial (Task 2.4). This selection of the most relevant questions to address in priority will involve researchers and clinicians, but also patients' representatives. Such trials would be the first step towards a new generation research framework, based on a common registry and AI, which is the end goal of HARMONISATION. The Action will apply for a separate funding to this end.

**WG3. Harmonizing Information Technology / Artificial Intelligence tools towards a standardized registry:** the core of this WG is an expert IT/AI research team, specialised in implementing data warehouse solutions from unstructured medical records, using natural language processing (NLP) among other AI resources. This core team will provide a first generic solution for collecting a limited range of relevant clinical and biological data, feeding a registry dedicated to patient selections for trials on adrenal tumours (Task 3.1). This solution will respect anonymization and legal obligations related to handling such data. The originality is that this will be the semi-automated data collection. For each patient included in this registry (after obtaining ethics approval and patient consent), clinicians will provide the unstructured medical record locally to the computing solution, which will anonymize and automatically and instantly extract the relevant data. The clinician will validate the accuracy of these data.

A second task of this core expert group will be to spread the identified solution to the other centres for further testing, through exchange with local IT/AI experts (short term scientific missions) and by producing a Standard Operating Procedure. Local adaptation is mandatory in each centre. For instance, NLP adaptation to each language will be required. Local adaptations of this solution will then emerge, generating local registries (Task 3.2).

A third task will be the anonymized connection of all local registries to a centralized federal system (data will not be imported, but will remain local and be interrogated in their respective centres) through coordinated exchange between IT specialists (Task 3.3). This step will require specific authorization, which will be addressed in WG4.

Finally, towards the end of this Action, in the perspective of launching a first trial, the Action will design and implement a series of optimized variables necessary for running the trial (randomization, then running the trial) (Task 3.4). This will be performed through a networking activity that will also involve clinicians and researchers.

This Action will cover the networking activities (interdisciplinary exchanges between IT, clinicians and researchers, and connections between IT experts), while alternative funding will serve to implement computing solutions.

**WG4. Harmonizing the ethical and legal framework towards the advent of federated European trials:** the aim of this WG is to help all centres get local clearance from ethics committees, and from any other regulatory body, to implement its local registry based on semi-automated treatment of medical records. The core team is composed of an academic, as well as a citizen science figure who is already deeply involved in the legal and ethical aspects at the national level of one of the participating countries.

After analysing common areas of complexity, the first activity will be to create an initial document addressed to the ethical committee of one of the participating centres, allowing us to start the project (Task 4.1). This document will emerge from the networking of this core actor with clinicians and researchers specialized in adrenal tumours. The second activity will be to adapt this document for each centre in each country (Task 4.2). Significant networking activity will be needed between the core actor and the ethics/legal representatives of each centre.

The third activity, at the end of this Action, will be to advocate towards the European Commission the establishment of a federated tool for interrogating all local registries in different countries (Task 4.3).

This Action will be part of a broader advocacy action to promote European standards for clinical databases and software approval. This WG will also have to include ethical stakeholders involved by the initiative. We will especially promote the principle of "Human Guarantee of AI", which consists of applying regulatory principles immediately upstream and downstream of the AI algorithm itself, through points of human supervision. The goal is to ensure that algorithms adhere to standards of medical effectiveness and ethical responsibility. This key ethical feature is currently under discussion at the WHO.

**WG5. Communication, dissemination, and inclusiveness:** the main aim is to involve new stakeholders and to disseminate the achievements of the Action to ensure uptake in the broader community. This WG will involve clinicians and scientists working on adrenal tumours, who will assign a specific liaison officer to actively promote the inclusion of new researchers and other reference networks (Task 5.1), as well as communication professionals. These partners will develop a dedicated HARMONISATION website (Task 5.2), coordinate and publish the WG's results (Task 5.3), translate scientific efforts into public dissemination (Task 5.4), and also help coordinate and promote research proposals to fund future collaborative research promoted by this COST Action (Task 5.5).

### 4.1.2. DESCRIPTION OF DELIVERABLES AND TIMEFRAME

**D1.1.** Plan for educational activities to harmonise adrenal tumours clinical practice (M6).

**D1.2.** Proceedings for clinician training schools (M12, M24, M36, M48).

**D1.3.** Consensus statement on the management of adrenal tumours (M39).

**D2.1.** Proceedings for researcher training schools (M6, M12, M18, M24, M30, M36, M42, M48).

**D2.2.** Action plan to complement technological limitations in some centres (M12).

**D2.3.** Standard operating procedures for translational research (M21).

**D2.4.** Report on key research questions, (M24, M48) and plan for future research projects (M45).

**D3.1.** Concept for data registry (M24).

**D3.2.** Report on the Short-Term Scientific Missions (STSMs) output (M12, M24, M36, M48).

**D3.3.** Report on the activities related to connecting local patients' registries into the central system (M33).

**D4.1.** Document on ethical and legal requirements for running the patient registry (M24).

**D4.2.** Report on ethical issues clearance by countries (M36).

**D4.3.** Advocacy action plan and reports on activities (M12, M24, M36, M48).

**D5.1.** Plan for exploitation and dissemination of results (M3).

**D5.2.** HARMONISATION Action website (M3).

**D5.3.** Report on WG activities (M12, M24, M36, M48).

**D5.4.** Report on Action effectiveness (M24, M48).

**D5.5.** Poster presentations, scientific papers, (M18-M48)**,** newsletters for stakeholders (M24, M48).

**D5.6.** Report on research proposals and available funding instruments (M24, M48).

**Milestones:**

**M1.** HARMONISATION kick-off meeting (M1).

**M2**. MC meeting (M1, M12, M24, M36, M48).

**M3.** Annual HARMONISATION meeting (M12, M24, M36).

**M4.** Final HARMONISATION meeting (M48).

**M5.** WGs meeting (M6, M12, M18, M24, M30, M36, M42, M48).

**M6.** Meetings with stakeholders (M12, M36).

**M7.** Training school for clinicians (M6, M12, M18, M24, M30, M36, M42, M48).

**M8.** Training school for researchers (M6, M12, M18, M24, M30, M36, M42, M48).

**M9.** Consensus group meeting (M12, M24, M36).

**M10.** STSMs for IT/AI experts (M12, M24, M36, M48).

**M11.** Pharmaceutical company contracted for building randomized clinical trial registry-based (M36).

### 4.1.3. RISK ANALYSIS AND CONTINGENCY PLANS

The following contingency plan will be set up to mitigate potential risks that can arise at several levels. The MC will evaluate the outcomes and deliverables of the Action every 6 months and will set up an action plan if any of the Action activities is in danger of being unsuccessful.

| RISK | WG | PROBABILITY | MITIGATION PLAN |
|---|---|---|---|
| Delay in the tasks' execution. | 1-5 | Low | Monitoring the release of deliverables on a regular basis. At the first indication of possible delay, WG leaders will take action to enhance members' commitment and, if needed, allocate additional resources to the task. |
| Failure in initiating collaborative projects arising from the network. | 1-5 | Low | Involving clinicians and scientists with high level of expertise in all WGs and MC.<br>Proposing and discussing ideas for new collaborative projects at WG meetings and at scientific meetings & conferences organized by the Action. |
| Lack of stakeholder engagement. | 5 | Low / medium | Promoting active involvement of the relevant stakeholders and ensuring that they will benefit from the Action's activities. The only potentially critical one is the pharmaceutical industry, which often does not focus on rare disease. With this proposed network, even rare adrenal tumours as ACC and PPGL will become targetable and attractive for industry partners. |
| Inability to physically attend WG meetings, training courses, and conferences. | 1-5 | High | Organising online meetings, audio conferencing, video conferencing and webinars. Due to the ongoing Covid19 pandemic, it is foreseeable that they will be of utmost importance. |
| Ethical and regulatory issues regarding the patient registry and data privacy. | 4 | Medium | Involving experts in ethics and legal clearance issues into the Action activities.<br>Providing support to each participating centre in adapting the general ethical and legal framework to local regulations. |
| Language barrier in communication with patients and their associations. | 5 | Medium | Translating newsletters for patients into several major languages. In each country, HARMONISATION will appoint/elect an individual clinician/researcher, who will serve as contact person to patients to mediate language-induced communication problems. |
| Insufficient quality of the deliverables. | 1-5 | Low | Implementing an internal quality control procedure which includes revising each deliverable by at least two MC members |

## 4.1.4. GANTT DIAGRAM

| | Year 1 | | | | Year 2 | | | | Year 3 | | | | Year 4 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| Kick-off meeting | M1 | | | | | | | | | | | | | | | |
| MC meeting | M2 | | | M2 | | | | M2 | | | | M2 | | | | M2 |
| WGs meeting | | M5 | | M5; D5.3 | | M5 | | M5; D5.3 | | M5 | | M5; D5.3 | | M5 | | M5; D5.3 |
| Annual Action meeting | D5.1 | | | M3 | | | | M3; D5.4 | | | | M3 | | | | M4; D5.4 |
| Consensus group meeting | | | | M9 | | | | M9 | | | | M9 | | | | |
| WG1. Harmonizing adrenal tumour clinical practice | | | | | | | | | | | | | | | | |
| Plan for educational activities | | D1.1 | | | | | | | | | | | | | | |
| Consensus/guidelines for patients' management | | | | | | | | | | | | | D1.3 | | | |
| Training school for clinicians | | M7 | | M7; D1.2 | | M7 | | M7; D1.2 | | M7 | | M7; D1.2 | | M7 | | M7; D1.2 |
| WG2. Harmonizing adrenal tumour research and -omics | | | | | | | | | | | | | | | | |
| SOPs for translational research | | | | | | | D2.3 | | | | | | | | | |
| Training school for researchers | | M8; D2.1 | | M8; D2.1 | | M8; D2.1 | | M8; D2.4 | | M8; D2.1 | | M8; D2.1 | | M8; D2.1 | | M8; D2.4 |
| WG3. Harmonizing Information Technology/Artificial Intelligence tools towards a standardized registry | | | | | | | | | | | | | | | | |
| Connecting local patients' registries to the central system | | | | | | | | | | | D3.3 | | | | | |
| STSMs | | | | M10 | | | | M10 | | | | M10 | | | | M10 |
| WG4. Harmonizing the ethical and legal framework towards the advent of federated European trials | | | | | | | | | | | | | | | | |
| Ethical and legal framework for running the registry | | | | | | | | D4.1 | | | | | | | | |
| Advocacy action | | | | D4.3 | | | | D4.3 | | | | D4.3 | | | | D4.6 |
| Report on Ethical Issue | | | | | | | | | | | | D4.2 | | | | |
| WG5. Communication, dissemination and reporting | | | | | | | | | | | | | | | | |
| Website | D5.2 | | | | | | | | | | | | | | | |
| Newsletters for stakeholders | | | | | | | | D5.5 | | | | | | | | D5.5 |
| Meetings with stakeholders | | | | M6 | | | | | | | | M6; M11 | | | | |
| Scientific dissemination | | | | | | D5.5 | D5.5 | D5.5; D5.6 | D5.5 | D5.5 | D5.5 | D5.5 | D5.5 | D5.5 | D5.5 | D5.5 D5.6 |

**M: milestone; D: deliverable**