

Brussels, 12 May 2023

COST 024/23

DECISION

Subject: Memorandum of Understanding for the implementation of the COST Action “Maternal Perinatal Stress and Adverse Outcomes in the Offspring: Maximising infants’ development” (TREASURE) CA22114

The COST Member Countries will find attached the Memorandum of Understanding for the COST Action Maternal Perinatal Stress and Adverse Outcomes in the Offspring: Maximising infants’ development approved by the Committee of Senior Officials through written procedure on 12 May 2023.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA22114

**MATERNAL PERINATAL STRESS AND ADVERSE OUTCOMES IN THE OFFSPRING: MAXIMISING
INFANTS' DEVELOPMENT (TREASURE)**

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, maintain and propel a synergetic and multidisciplinary international network of academics, researchers and clinicians working on maternal perinatal stress and adverse infant outcomes with an epigenetic, biomedical, psychological, socio-cultural, economic and neuro-endocrinological approach to scientific knowledge. 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

High levels of maternal perinatal stress are associated with negative effects in the offspring. The adverse impact maternal stress can have in the infants' health is 1) in the short term (prematurity, low infant birthweight); 2) the long-term (neuroinflammation, autism); 3) the very long-term (transgenerational effects). Previous studies have reported maternal stress can have transgenerational consequences. During pregnancy, high levels of maternal stress can cross the placenta and reach the fetus. Mediators responsible for the impact of maternal stress in the developing fetus include cytokines, tryptophan, cortisol, catecholamines, reactive oxygen species, oxidative stress and microbiota. These mediators, along with epigenetic mechanisms, are involved on the adverse consequences high levels of maternal stress can have in the offspring.

In order to improve fetal development and boost infant's health throughout their lifespan, the TREASURE project aims to consolidate a multidisciplinary and international network of scientists, clinicians, students, stakeholders, Non-Governmental Organisations (NGOs) and Enterprises to achieve impact through a three-fold main objective : 1) discovering, reviewing and disseminating scientific evidence on minimize, reduce and prevent the impact of maternal perinatal stress on fetal development, and to improve psychological, medical and neural development in the offspring during their life-span; 2) bridging knowledge, evidence and experience between scientific disciplines, and bringing international research groups together to increase knowledge exchange between countries. 3) forming international coalitions to efficiently translate scientific knowledge into clinical guidelines and best practices across Europe to improve the health of children, and reducing economic cost appearing from high levels of maternal perinatal stress.

Areas of Expertise Relevant for the Action	Keywords
• Health Sciences: Social biomedical sciences (including family planning, sexual health, psycho-oncology, political and social effects of biomedical research) • Health Sciences: Environment and health risks including radiation	• Fetal • Programming • Pregnancy • Women • Health

Specific Objectives

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

Research Coordination

- To build a common definition of maternal perinatal stress for use by researchers, clinicians, stakeholders and policymakers;
- To understand the risk factors involved in the development of high levels of maternal perinatal stress;
- To improve and further develop and consolidate measures that can be used to screen for and assess perinatal maternal stress;
- To create and unify global research collaboration by means of a well-balanced multidisciplinary and international network of academics, researchers and clinicians on perinatal mental health and child development;
- To intensify international collaboration to advance knowledge on the perinatal susceptibility periods and more vulnerable time-frames when maternal perinatal stress is more pernicious for fetal development;

- To increase the understanding of the economic cost of maternal perinatal stress in terms of adverse infant outcomes, and to inform stakeholders and policymakers to develop cost-effective strategies to prevent, reduce, assess, diagnose and treat such stress;
- To disseminate results among potential users, including academics, researchers, clinicians, the general public, industry and stakeholders, and to incorporate findings into public policymaking.

Capacity Building

- To create, unify and consolidate a pan-European and multidisciplinary network of academics, researchers and clinicians involved in maternal perinatal care, mental health, and fetal and child development;
- To promote Early Career Investigators to act as an incentive to streamline their career development internationally while boosting their leadership of newly created research groups;
- To foster knowledge for future generations of academics, researchers and clinicians through participation and involvement in Training Schools to broaden their research horizons and research network;
- To exchange knowledge on techniques and skills through Short-term Scientific Missions for experts, researchers and students while visiting a laboratory or institution in another country participating in the COST Action;
- To encourage gender-balanced representativeness in leadership positions through specific actions aiming to achieve at least 50% of female participants;
- To encourage geographically balanced representativeness in leadership positions through specific actions aiming to ensure that at least 50% of participants are from Inclusiveness Target Countries;
- To disseminate and use the results to translate research into practice and thus to reduce the impact of maternal perinatal stress on the offspring.

TECHNICAL ANNEX

1. S&T EXCELLENCE

1.1. SOUNDNESS OF THE CHALLENGE

1.1.1. DESCRIPTION OF THE STATE OF THE ART

Advancing scientific knowledge related to maternal perinatal stress can improve opportunities for women, families and their children. Stress is necessary for an optimal functioning of the organism, it is involved in inflammatory responses, metabolism and immunity, and is responsible for an optimal adjustment to challenges through the lifespan. Nevertheless, high levels of maternal stress during pregnancy have been associated with detrimental consequences in the offspring. Maternal perinatal stress is associated with adverse effects for the newborn such as stillbirth, low-birth weight and prematurity, and long-term effects on the child such as cardiovascular disease, reduced intelligence, autism spectrum disorder, neuroinflammation and asthma. These effects can also have intergenerational consequences. Recent developments in epigenetics have found that a complex interplay exists between exposure to prenatal stress, changes in miRNA expression and methylation of DNA in the placenta (epigenetic modifications), which may be linked with medical and mental disorders in the fetus and in subsequent generations. The scientific study of the key role of the prenatal environment for fetal development in humans has grown since the 1940s with the fetal programming hypothesis.

Evidence shows that high levels of stress during pregnancy can have detrimental effects on the fetus. However, there is insufficient evidence to explain the processes involved (biological, psychological, social) or to identify which women have a high risk of having a neonate with a maternal stress-related health and disease condition. Exposure to a stressful situation boosts the production of cortisol in humans. Cortisol is a glucocorticoid hormone that is released through arousal of the hypothalamic–pituitary–adrenal (HPA) axis as a response to stress. Cortisol regulates a wide range of physiological processes (e.g. metabolism, immunity, inflammation, memory, blood pressure) and facilitates adjustment to environmental changes. Cortisol is a key hormone that helps the organism to cope with stressors by coordinating the brain and rest of the organism. Cortisol increases energy availability by enhancing glucose levels, muscle strength and the pain threshold, helping the individual to face a stressful stimulus. When cortisol levels remain high over a period of time, health problems may arise (e.g. high blood pressure, obesity). Consistently elevated cortisol levels during pregnancy can have detrimental consequences for the fetus.

High maternal cortisol levels can reach the fetus through the placenta. During pregnancy, the placenta plays a two-fold function associated with stress: 1) the placenta produces placental-corticotropin-releasing hormone, which increases maternal cortisol levels; during the third trimester of pregnancy, the expression of placental-CRH increases 100 times; 2) the placenta contains 11 β -hydroxysteroid dehydrogenase type II (11 β -HSD2). This enzyme (11 β -HSD2) is a natural inhibitor that metabolizes cortisol to its inactive form, cortisone. Thus, 11 β -HSD2 protects the fetus from exposure to certain levels of cortisol. High levels of maternal stress have been associated with low levels of 11 β -HSD2, allowing more cortisol to be transferred from mother to fetus through the placenta. Maternal stress during pregnancy can be transferred to the fetus through a variety of mediators, including cortisol. A multiple stress-transfer mechanism is associated with trans-placental transfer of maternal stress to the fetus and involves catecholamines (indirectly via impaired uterine blood perfusion), cytokines, serotonin, oxidative stress, cortisol and the infant's gut–brain axis. Mediators may increase during maternal exposure to a stressful situation.

Sources of maternal stress during pregnancy that can have a detrimental effect on the fetus include a wide range of events. Highly negative perinatal stressors include the death of a relative, terrorism, violent conflicts, natural disasters, intimate partner violence, nuclear accidents, life events stress, famines, work and financial stress, assisted reproductive techniques and exposure to a pandemic. Evidence on maternal stress and infants' detrimental consequences has shown an association between the death of a relative and a higher risk of having an infant with attention deficit hyperactivity disorder (ADHD), bipolar syndrome, schizophrenia, cerebral palsy and an increased risk of suicide. Moreover, maternal exposure to a war or a natural disaster has been reported to be associated with psychosis, hypertension and epilepsy. An additional source of maternal stress during the perinatal period is pregnancy-specific stress (PSS). PSS refers to specific worries and concerns pregnant women have related to medical symptoms, social relationships, prematurity, attachment with the neonate, the health of the fetus and fear of labour. PSS is a better predictor of negative infant outcomes (poor neurodevelopment, altered HPA axis functioning, low head circumference) than general stress.

Evidence on the prevention, reduction and treatment of perinatal maternal stress is scarce. A few studies have been conducted using cognitive-behavioural therapy and mindfulness, with inconsistent results and low sample sizes. Little research has focused on reducing and preventing maternal stress and how this can be modified to potentially mitigate against negative and traumatic consequences in the offspring. The impact partners have on maternal stress and its link with negative neonatal consequences must also be taken into consideration as a potential changeable risk factor. Given infants' adverse outcomes associated with exposure to prenatal stress while in the maternal womb, it is mandatory to take a family-centred and social-centred approach, as maternal perinatal stress can be modified within the family and social system. Thus, partner relationship quality and social support are critical factors that can buffer maternal stress during highly vulnerable situations. Research on treatment is also sparse. Interest among researchers and clinicians in maternal perinatal stress is increasing. For this reason, screening women for perinatal stress and referral for treatment at the earliest opportunity is widely recognised by health care providers and academics. Nevertheless, there are no studies on screening for maternal stress and very few studies have focused on effective treatments and therapeutic options for women during the perinatal period.

The adverse consequences that maternal perinatal stress can have in the offspring have severe economic costs for health systems and governments. These costs are mostly associated with the intergenerational effects on neonates and infants, but also transgenerational consequences on child development. In Europe, the total 2-year cost of caring for a premature infant is €104,635. Half a million neonates are born prematurely every year in Europe. Untreated perinatal mental health issues can cost more than €9 billion (each cohort of births per year), more than 70% of which is associated with its detrimental effect on the offspring. For this reason, adequate prevention, reduction and treatment strategies should be implemented. A priority must be to inform health policymakers to help them address this important public health problem.

1.1.2. DESCRIPTION OF THE CHALLENGE (MAIN AIM)

The World Health Organization (WHO) regional office for Europe task force recommends the promotion of maternal mental health in order to result in positive early childhood development. In line with "the fetal origins of adult disease hypothesis", WHO/Europe states that a healthy environment during the perinatal period is associated with a healthy infancy, childhood and adulthood. High levels of stress while still in the womb may last a lifetime. Every year there are 4 million live births across Europe. Evidence suggests that approximately 25% (1 million) of women in Europe experience high levels of perinatal stress each year. It is likely that the prevalence of high levels of stress during pregnancy is underestimated. The National Institute for Health and Care Excellence (NICE) guidelines developed in the UK reported that maternal mental health problems during the perinatal period can have a severe impact on the fetus/baby, including infanticide. A recent meta-analysis and systematic review based on more than 65 million women and their children revealed a clear association between maternal stress during pregnancy and the development of medical and psychopathological diseases in the offspring (e.g. autism, obesity). However, the majority of European countries offer no screening or treatment to pregnant women suffering from high levels of stress. Qualitative evidence on maternal stress clearly reflects the importance of the issue. It has a dramatic impact on pregnant women and the offspring as indicated by the following accounts: *"I am prone to be really judgmental on how much stress I can tolerate. And I should be like superwoman" "I feel so bad... I'm afraid I'm affecting her. From being just, you know, so frustrated, and angry, and angry at myself, and then melting down right there, and crying while I'm holding her... I don't want that to go into her psyche."*

Recent studies have highlighted the need to better understand the hormonal and other biological mechanisms involved in the transfer of maternal stress to the fetus. Most of these studies have focused mainly on the HPA axis as the main biological mechanism underlying the effects of perinatal maternal stress on the fetus. Dysfunction of the HPA is associated with behavioural problems and the susceptibility to short-, long- and very long-term effects on the offspring. There is strong evidence on the association between maternal stress and prematurity and low birth-weight (short-term consequences). Nevertheless, the proportion of maternal perinatal stress responsible for infants' later psychopathological and medical diseases (long- and very long-term consequences) remains unclear. The HPA axis is critically associated with preserving physical well-being and preventing inflammatory responses under stressful situations. Chronic activation of the HPA axis is associated with the development of diseases and health issues. Studies on animals have discovered that maternal activation of the HPA axis is accompanied by the downregulation of glucocorticoid receptors (GRs) in some brain areas (i.e. hippocampus, hypothalamus) and upregulation of GRs and corticotropin- releasing-hormone (CRH) in the amygdala in the fetus. A potential epigenetic mechanism may underlie the link between perinatal maternal stress and adverse infant outcomes. A prospective study showed that maternal stress predicted the methylation of the promoter region of the glucocorticoid receptor (NR3C1) in neonates, which in turn predicted a cortisol stress response among infants. The magnitude of prenatal cortisol exposure surrounding the fetus in the womb may have an impact on the neonate's cortisol levels and the stress response of infants, especially in those born prematurely, with low birth-weight or fetal growth restriction. The underlying biological mechanisms involved in the association between maternal perinatal stress and the programming and reprogramming of the HPA remain unclear. The specific role of the placenta and mediators (e.g. cytokines, serotonin) should be further explored to better understand the biological mechanism involved in maternal perinatal stress and the development of health and disease in the offspring.

The timing and the method of assessing maternal stress are key factors. Some studies have reported that high levels of maternal psychological stress during the first and second trimester of pregnancy were associated with low head circumference, low biparietal diameter and low neurodevelopment in the neonate. Controversial findings have been reported with respect to high levels of cortisol during the third trimester. A study found that high maternal cortisol levels may be beneficial for infant neurodevelopment. Vulnerable periods of time should be identified to better understand the role of maternal stress in adverse infant outcomes. While acute levels of cortisol can be measured in saliva, blood, amniotic fluid or urine, these samples are usually painful to obtain and can be modified by situational variables. Chronic stress can be measured using hair cortisol levels, which offers information on the level of stress during the previous 3 to 6 months. Hair cortisol samples from neonates inform about the level of fetal stress while in the womb and can be used as a time-travelling biomarker.

Perinatal maternal stress impacts infants differently depending on the sex of the fetus and can increase the possibilities of having either a male or a female infant. Controversial results have been reported in this respect. While some studies have reported that a certain amount of maternal stress was associated with having a male neonate, another study reported that high maternal hair cortisol levels (due to the COVID-19 pandemic) increased the odds of having a female neonate. Other evidence suggests that males are more greatly impacted by maternal perinatal stress, having a higher rate of autism spectrum disorder and dyslexia following exposure to perinatal stress than females. Other studies have found a higher prevalence of low birth-weight, prematurity and low head circumference among female neonates that were exposed to high maternal perinatal stress before birth. No consensus exists on the effects of maternal stress on infants depending on whether it is a female or a male.

Pregnancy is a very important time in a woman's life. During the perinatal period, a range of situations, such as assisted reproductive techniques (ART), intimate partner violence, feelings of intense isolation or financial stress, may lead to high levels of maternal stress. It has been reported that few women actually discuss psychological stress with antenatal health care providers. High levels of psychological stress in women undergoing ART are associated with a developmental impact in neonates. The COVID-19 pandemic and the 1918 Spanish flu pandemic have also highlighted the impact of deprived social support on maternal stress levels and its potential impact on infant health. Social support from partners, family and friends can apparently mitigate the effects of maternal stress. The presence of supportive partners can mitigate maternal perinatal stress. A family-centred, partner-centred and social-centred approach should be used when developing strategies and treatments to reduce maternal perinatal stress. Studies have reported that enrichment of the postnatal environment can mitigate the effects of maternal perinatal stress. In this regard, resilience has been presented as a protective factor when women confront the negative effects of perinatal stress. The potential utility of resilience to enhance the health of neonates should be exploited. Evidence has demonstrated that psycho-educational programmes

addressing couples' and parents' empowerment and focused on mutual co-parental support reduced the incidence of adverse birth outcomes in women exposed to high levels of stress, and countries should thus include such programmes in their health systems to help women and their babies. Improvements in neonatal outcomes could mean substantial cost reductions.

A multidisciplinary and international approach to exploring maternal perinatal stress is fundamental. Researchers and clinicians from a range of cultural backgrounds need to collaborate jointly to advance scientific knowledge and best practices. This perspective will empower women, partners and families to reduce the impact of maternal stress on the health and disease of the offspring. Further studies are required to explore the links between maternal perinatal stress and adverse impacts on the offspring. Research is also necessary to discover the most sensitive periods during the perinatal period in terms of the impact of maternal perinatal stress. The precise period during which maternal perinatal stress impacts the developing fetus remains unclear. Furthermore, the extent to which infants are affected by previous traumatic experiences and maternal perinatal stress appears to vary from individual to individual. The recognition that individual differences exist in the response to maternal stress has supported the search for biological and genetic explanations. Improving knowledge on epigenetics, neurotransmitters and hormones associated with the HPA axis and the placenta may offer a clearer understanding of how maternal stress reaches the fetus and impact the development of its organs and systems. Measures of assessing maternal perinatal stress are needed to predict negative infant outcomes. Societal and economic benefits might arise if we could anticipate which infants will develop a certain disease during their life, depending on the levels of stress they were exposed to before birth. Given the impact maternal perinatal stress may have on infants' psychological, medical and neural development (from fetal development to adulthood), improvements must be made to reduce the prevalence of certain diseases (e.g. autism spectrum disorder, schizophrenia, heart failure, premature death). Consequently, economic costs will be reduced.

The COST framework offers the opportunity to implement an integrated evidence-based model of perinatal health in order to boost maternity care and ensure adequate fetal development and the best health for future generations. The main aim of this Action is three-fold. The Action will create and consolidate an international network of multidisciplinary researchers, clinicians, non-governmental organizations (NGOs), stakeholders and small- and medium-sized enterprises (SMEs) to accomplish a real and long-term impact on: 1) discovering, reviewing and disseminating scientific evidence on minimizing, reducing and preventing the impact of maternal perinatal stress on fetal development, and improving psychological, medical and neural development in the offspring during their life-span; 2) bridging knowledge, evidence and experience between scientific disciplines, and bringing international research groups together to increase knowledge exchange between countries; and 3) forming international coalitions to efficiently translate scientific knowledge into clinical guidelines and best practices across Europe to improve the health of children, and reducing economic costs stemming from high levels of maternal perinatal stress.

PROGRESS BEYOND THE STATE OF THE ART

1.1.3. APPROACH TO THE CHALLENGE AND PROGRESS BEYOND THE STATE OF THE ART

Evidence shows that 1:4 women in Europe have high levels of stress during the perinatal period. The prevalence of maternal perinatal stress may be higher during exposure to a pandemic or an armed conflict. Stakeholders and policymakers are becoming more concerned about the psychological, clinical and economic effects of high levels of maternal perinatal stress in the offspring on population health. Creating and consolidating a pan-European network of multidisciplinary experts will improve the health of the offspring by reducing the prevalence of perinatal maternal stress and its impact on children. This Action will advance beyond the state of the art through a joint collaboration between researchers, health clinicians and interested parties. Advances can be achieved by conceptualising maternal perinatal stress and developing a standardised tool to assess perinatal stress. Furthermore, a comprehensive understanding of the neuroendocrine, social and psychological factors involved in the development of perinatal maternal stress will optimise infants' outcomes. This Action will be the first time that a wide range of disciplines and pan-European countries will work together to reduce the adverse impact of maternal perinatal stress on the offspring. This innovative approach will involve the following activities: 1) Systematic reviews to gather and summarise scientific information on the maternal perinatal stress framework, including risk factors, moderators and mediators of its adverse impact on the offspring, along with effective reduction, prevention and treatment strategies. An adequate review of the available

knowledge will reduce current gaps in most European countries regarding clinical guidelines, professional training and the provision of health services associated with the impact maternal stress can have on the offspring. These systematic reviews will guide the development of adequate standardised assessment measures, clinical guidelines, prevention programmes and treatments throughout pan-European countries and beyond. 2) Clarification of the neuroendocrine and biological factors associated with the development of high levels of maternal stress and its impact on the offspring. This will include the sharing of valuable information on epigenetics, neurophysiology, neuroimaging, neuroendocrinology and the placenta to identify and characterise potential neurobiological mediators involved in the transfer of maternal stress to the fetus. Moreover, information on maternal responses in terms of the expression of genes, immunity and metabolism associated with maternal perinatal stress and infant outcomes at birth and development will be collected and reviewed. 3) Identification of studies exploring maternal psychological variables involved in the development of maternal perinatal stress, along with social factors that can reduce maternal stress. How partners and social support can help decrease maternal stress and the impact this has on the offspring will also be reviewed. Partners' mental health during the perinatal period may be crucial for adequate fetal development. Partners and support people should be included in policies and guidelines after consensus statements are produced. 4) Coordination of information regarding adverse infant outcomes associated with maternal perinatal stress. This procedure will classify adverse infant outcomes as short- and long-term outcomes (intergenerational), and very long-term outcomes (trans-generational). Child development is shaped by maternal perinatal stress and environmental factors. Postnatal moderators will be explored to successfully coordinate the development of guidelines aiming to improve child development. In this respect, the sex of the children and time-frame of exposure to maternal stress should be taken into consideration. 5) Detection of current research projects in the field to pinpoint potential gaps, which will enable the implementation of research on reducing, preventing and treating maternal perinatal stress across a range of cultural backgrounds. Moreover, the socioeconomic impact perspective will be included as a key factor in the identification of personalised and innovative treatments. 6) This Action will inform policymakers, stakeholders and interested parties on the benefits that reducing, preventing and treating maternal perinatal stress may have for healthcare costs. Moreover, this Action will enable the study of the postpartum mechanisms that influence optimal infant development. By exploring the contextual factors that positively and negatively influence child health, sustainable health services could be developed across pan-European countries.

1.1.4. OBJECTIVES

1.1.4.1. *Research Coordination Objectives*

This Action will consolidate multidisciplinary global research, enhancing interconnectedness and advancing innovation in the research community across Europe and beyond. This COST Action has several research coordination objectives that will help prioritise the support, prevention and treatment of maternal perinatal stress and reduce its detrimental impact on the offspring. This Action has the following specific objectives:

- 1) to build a common definition of maternal perinatal stress for use by researchers, clinicians, stakeholders and policymakers. This common definition will support the development of guidelines, preventive statements and effective treatments;
- 2) to understand the risk factors involved in the development of high levels of maternal perinatal stress;
- 3) to improve and further develop and consolidate measures that can be used to screen for and assess perinatal maternal stress;
- 4) to create and unify global research collaboration by means of a well-balanced multidisciplinary and international network of academics, researchers and clinicians on perinatal mental health and child development. In order to achieve this goal, neuroendocrinological, epigenetic, economic, socio-cultural, psychological, biomedical and bio-psycho-social perspectives will be addressed to better understand maternal perinatal stress and reduce its adverse impact on the offspring;
- 5) to intensify international collaboration to advance knowledge on the perinatal susceptibility periods and more vulnerable time-frames when maternal perinatal stress is more pernicious for fetal development. This should maximise the production of new knowledge related to how maternal perinatal stress differentially affects female and male fetuses;
- 6) to increase the understanding of the economic cost of maternal perinatal stress in terms of adverse infant outcomes, and to inform stakeholders and policymakers to develop cost-effective strategies to prevent, reduce, assess, diagnose and treat such stress;
- 7) to disseminate results among potential users, including academics, researchers, clinicians, the

general public, industry and stakeholders, and to incorporate findings into public policymaking.

1.1.4.2. Capacity-building Objectives

This Action will build a global research network of professionals to reduce the adverse impact of maternal perinatal stress on the offspring. Creating and consolidating a network of academics, researchers, clinicians, policymakers and stakeholders with a multidisciplinary approach to maternal perinatal stress and child development will increase and ease the sharing of up-to-date information, knowledge, best practices and awareness of scientific developments in the field, through stimulating international mobility and organising and attending workshops, events, conferences, meetings, Short Term Scientific Missions (STSMs) and Training Schools. This COST Action includes various overarching capacity-building objectives. This Action has several specific objectives to assist in driving scientific knowledge forward:

- 1) to create, unify and consolidate a pan-European and multidisciplinary network of academics, researchers and clinicians involved in maternal perinatal care, mental health, and fetal and child development. This broad network will actively use a neuroendocrinological, epigenetic, economic, socio-cultural, psychological, biomedical and bio-psycho-social perspective to address maternal perinatal stress and its adverse psychological and medical impacts on the offspring;
- 2) to promote Early Career Investigators (ECIs) to act as an incentive to streamline their career development internationally while boosting their leadership of newly created research groups;
- 3) to foster knowledge for future generations of academics, researchers and clinicians through participation and involvement in Training Schools (TSs) to broaden their research horizons and research network;
- 4) to exchange knowledge on techniques and skills through Short-term Scientific Missions (STSM) for experts, researchers and students while visiting a laboratory or institution in another country participating in the COST Action;
- 5) to encourage gender-balanced representativeness in leadership positions through specific actions aiming to achieve at least 50% of female participants;
- 6) to encourage geographically balanced representativeness in leadership positions through specific actions aiming to ensure that at least 50% of participants are from Inclusiveness Target Countries (ITCs);
- 7) to disseminate and use the results to translate research into practice and thus to reduce the impact of maternal perinatal stress on the offspring.

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 goal of this Action is to create, maintain and propel a synergetic and multidisciplinary international network of academics, researchers and clinicians working on maternal perinatal stress and adverse infant outcomes with an epigenetic, biomedical, psychological, socio-cultural, economic and neuro-endocrinological approach to scientific knowledge. The innovative initiative of this COST Action aims to build a network of experts and end users to synergistically achieve a reduction in the impact of maternal perinatal stress on children. The objectives will be accomplished through a collaborative exchange of knowledge and practice, standardisation of definitions, translation of scientific evidence into best practices and guidelines and by promoting the implementation of any recommendations. This Action will unify the currently fragmented academic and clinical expertise to increase our understanding of maternal perinatal stress and its medical and psychological impact on the offspring. This Action will build on the previous work of two COST Actions on perinatal mental health, one to be completed in April 2023 and the other in October 2023.

The added value of this COST Action in relation to previous or existing efforts is that this Action will be the first to address the adverse impact of maternal perinatal stress on the offspring through an international and multidisciplinary network of coordinated experts in the field. Collaborative work within this Action will increase the progress of knowledge in this field across Europe. This Action aligns with The Regional Office for Europe of the World Health Organization Sustainable Development Goal target

3.1 of eliminating avoidable maternal and perinatal mortality and morbidity, the European strategic approach for making pregnancy safer, the European Perinatal Health Report (Health and care of pregnant women and babies in Europe in 2010), and the new publication on improving the quality of care for mothers and neonates and improving the quality of care for reproductive, maternal, neonatal, child and adolescent health in the WHO European Region, a regional framework to support the implementation of Health 2020. This Action will establish the first multidisciplinary and global cooperative network of experts to reduce the detrimental consequences of maternal perinatal stress on the offspring. The Action is in line with United Nations International Children's Emergency Fund (UNICEF) Data: Monitoring the situation of children and women, entitled "Healthy Mothers, Healthy Babies". Thus, the Action aims to establish an international scientific environment of pre-doctoral and post-doctoral students, Early-Stage Researchers (ESRs), senior experts and invited scientists, which will enhance competitiveness across Europe and beyond. This Action will work on the following topics: 1) developing maternal/infant surveys to benchmark perinatal health across Europe and internationally; 2) conducting longitudinal studies to follow up vulnerable infants (e.g. premature infants); 3) understanding the perinatal molecular mechanisms involved in the environmental control of infant phenotype development with a special focus on the HPA axis, the immune system and high-risk epigenetic changes; 4) biological, neuroendocrine and biomedical mechanisms involving intergenerational and transgenerational transfer of maternal perinatal stress to the developing fetus; 5) focusing on the impact the maternal environment has on negative fetal and infant outcomes; 6) focusing on clinical practice that may influence maternal perinatal stress and mediate consequences in the offspring; 7) understanding and improving the prevention and treatment of maternal perinatal stress; and 8) fostering the health of new generations of children and adults. This Action will ensure a balanced network of ECIs and senior researchers to promote mentorship and new leadership of prospective researchers who will contribute to the short-, long- and very long-term goals of Horizon Europe pillar 1 (Excellent Science), pillar 2 (Global Challenges and European Industrial Competitiveness) and pillar 3 (Innovative Europe), and the horizontal focus area (Widening Participation and Strengthening the European Research Area). This Action is in line with goal 3 of the Council of Europe to ensure a healthy life and promote well-being for everybody at all ages.

2.2. ADDED VALUE OF NETWORKING

2.2.1. SECURING THE CRITICAL MASS, EXPERTISE AND GEOGRAPHICAL BALANCE WITHIN THE COST MEMBERS AND BEYOND

A critical mass working together towards a joint objective promotes the more effective and efficient achievement of goals and boosts the dissemination and exploitation of health results by networking. This network aims to become an important research community for knowledge on maternal perinatal stress and adverse infant outcomes. This COST Action will be the largest international network in this field composed of academics, researchers and clinicians with a multidisciplinary approach to the subject. This pan-European network will have the necessary expertise to achieve the aims and activities proposed in this COST Action. This initial network was composed of 37 proposers (researchers, academics, clinicians and innovators) from 24 Full Member countries, 13 (52%) Inclusiveness Target Countries, one Cooperating Member (Israel), one Partner Member (South Africa) and one Near Neighbour Country (Jordan) and 3 International Partners Countries (Australia, Canada, United States). Additional members, including researchers and clinicians affiliated to a legal entity in a COST Full/Cooperating Member, Inclusiveness Target Countries, COST Partner Member, Near Neighbour Country and International Partner Countries will be invited to join the COST Action through the Action website and established collaborations across Europe and beyond. Some of the proposers have ongoing collaborations with contacts from Chile, Brazil, Egypt and New Zealand, who will be approached to potentially join the COST Action. The sampling technique that will be used to promote and collect participants to join the Action will be chain-referral sampling. This technique involves a primary participant nominating additional potential participants and is based on referrals. The critical mass of researchers, clinicians and SMEs working on maternal perinatal stress and adverse infant outcomes will increase and facilitate the exchange of knowledge, information and expertise. This multidisciplinary and international network is composed of midwives, obstetricians, psychiatrists, psychologists, neurobiologists, epigeneticists, neurologists, epidemiologists, social workers, nurses, pediatricians, pharmacists, biochemists, sociologists, health economists, mathematicians and statisticians, all of them experts in their field. The participants will have wide research experience related to methodological processes and expertise in project management, analytical practices, team management, resource planning, preparing timelines and milestones and dissemination. This COST Action aims to create and consolidate a multidisciplinary network that will promote the progress of international and collaborative research projects on maternal perinatal stress and fetal development in Europe and beyond.

Based on the policy on COST inclusiveness and excellence, this Action will secure a geographical, gender and age balance across operations and activities in order to strengthen excellence. For this reason, this Action will secure collaborative opportunities for researchers, clinicians and innovators from Full Member countries, Inclusiveness Target Countries, a Cooperating Member, a Partner Member, Near Neighbour Countries and International Partner Countries, offering equal access to knowledge and resources to the different research communities, even those with restricted access to funding and/or infrastructure. This Action will foster balanced access to leadership and induce structural modifications in the national health and research systems of COST Members, non-COST members and Specific Organisations (e.g. Near Neighbour Countries (NNCs)). The initial network of proposers has a high female representativeness, with 73% of participants being women, reflecting the nature of the professional disciplines involved (midwifery, nursing, psychology, social workers). Nevertheless, this Action will work towards the suggest focus on gender balance. The Management Committee (MC) of this COST Action will ensure compliance to gender balance by increasing the number of males collaborating. Mentoring ECIs, researchers from ITCs and NNCs and including collaborators of all ages and seniority will support the spread of excellence across Europe. The acceleration in progress on the issue of maternal perinatal stress and its detrimental consequences for the offspring through this multidisciplinary and well-balanced network will boost the health of current and future generations of pregnant women and their children.

2.2.2. INVOLVEMENT OF STAKEHOLDERS

The benefits of engaging and involving stakeholders in this Action are wide, including organisational commitment, improved support for the outcomes and scientific literacy. Nowadays, stakeholders are located in universities, research centres, professional organisations, technological associations, SMEs and end-users' organisations. Involving stakeholders will reduce and close the existing gap between research output and its practical application. Stakeholders in this COST Action will become instruments for transferring knowledge to the scientific community, policy-makers and the public and will facilitate the implementation of assessment and treatment. Members will invite new national and international stakeholders to join this COST Action who will be involved in all the steps and phases planned for this Action. The Management Committee (MC) will constantly review the involvement of stakeholders through an organisational plan and dedicated meetings. In order to improve communication between stakeholders and members, the Action will develop an Action website. The Action website will be an innovative and user-friendly environment to facilitate the exchange of knowledge and the generation of new research questions. The Action website will have two components: 1) an intranet only accessible to members of the COST Action, a place where WGs can communicate, explore new alternatives and generate solutions. The intranet will also host outputs from Training Schools (TS), conferences, workshops, meetings, scientific papers and clinical practice guides, which will improve the spread of knowledge among members, including stakeholders. To maximise open access to knowledge and visibility of information, similar information regarding the COST Action will be placed on OpenAIRE; 2) a public space open to all visitors to explore and learn about the Action, to serve as an invitation to join and find out about the network. Moreover, the use of social media and artificial intelligence will serve as an additional way to develop strategic connections with policymakers, stakeholders, women, partners and families.

3. IMPACT

3.1. IMPACT ON 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)

The advantages of this COST Action rest in the multidisciplinary and international network of experts and stakeholders advancing the study of maternal perinatal stress and its detrimental consequences for the offspring. This Action has been designed to expand knowledge in this field, and to promote the prevention, assessment, diagnosis and treatment of maternal perinatal stress and adverse consequences in children. Training Schools across Europe will foster and establish evidence-based knowledge among young researchers that can be translated into good clinical guidelines to improve maternal care. The outputs resulting from this Action will have a positive impact on women, partners, families and their children, while decreasing the socio-economic cost of maternal and paediatric health care, including indirect costs (e.g. maternal absence from work). Based on 'the fetal origins of adult

disease hypothesis' and given that high levels of maternal perinatal stress have adverse consequences for the offspring (short-term, long-term and very long-term), this Action will have a strong and constructive impact on society. This Action aims to reduce maternal perinatal stress and improve fetal development. Consequently, the health of society will improve.

The potential for innovation lies in the publishing of open access scientific papers, clinical guidelines, consensus statements, whitepapers and toolkits and the production of additional results through secondary analyses of data hosted on open access platforms. This procedure will maximise the impact and value of this Action while making the outputs of this Action freely available for researchers, stakeholders and citizens. Moreover, this method will expedite the progress of knowledge, research, innovations, assessment, diagnosis and intervention more rapidly. Data-driven models and artificial intelligence techniques could also be used to develop neurobiological models of maternal perinatal stress and epigenetic predictors of infant adverse outcomes. Future projects could improve these prediction models. One of the resources that this Action will build is an international archive within the Action website of perinatal maternal stress and infant outcomes. This international database will constitute a valuable resource for future research in this field. Technological approaches to prevention, assessment, diagnosis and treatment will benefit from the use of mobile applications and virtual reality (VR) in order to achieve better communication between women, health care providers and researchers. The Action network will promote synergetic progression towards a healthier society.

In the short-term, this COST Action will have a variety of scientific impacts originating from its multidisciplinary and international approach. This Action aims to build and promote knowledge through:

- 1) Creation of an integrated network of disciplines to accelerate scientific understanding of maternal perinatal stress and its adverse consequences in the developing fetus;
- 2) Production of scientific evidence through systematic reviews to gather current knowledge and practices;
- 3) Dissemination of knowledge to research and academic institutions and health care practitioners;
- 4) Innovation and development of alternative research questions to guide prospective projects;
- 5) Supporting and guiding ECIs and young researchers to achieve new skills that will facilitate the production of new leaders for the future;
- 6) Encouraging the participation of male experts in this female-dominated area from a range of disciplines;
- 7) Increasing access to information to women and families;
- 8) Upgrading less research-intensive countries through collaborative projects in order to stimulate the scientific production of knowledge across different nations.

In the long-term, the impact of this Action will focus on society and economic costs in the following ways:

- 1) Production and transfer of knowledge based on scientific information;
- 2) Networking of researchers, clinicians and end-users regarding maternity care, fetal development and birth outcomes;
- 3) Development of clinical guides, whitepapers and toolkits that can be used by health care practitioners and policymakers, in order to implement the best practices that will reduce maternal perinatal stress and its negative impact on the developing fetus and child.
- 4) Establishment of training strategies for clinicians (midwives, obstetricians, nurses, psychologists, psychiatrists, pediatricians);
- 5) Development of clinical consensus documents on how clinicians in maternity care services (e.g. preconception care, assisted reproductive technologies) and infant health services (e.g. neonatal intensive care units) can reduce maternal perinatal stress and its detrimental impact on the offspring.
- 6) Exploring the economic costs of intergenerational transfer of maternal perinatal stress on child health by reviewing direct costs (e.g. prematurity) and indirect costs (e.g. hospital admissions).
- 7) Facilitate the implementation of technologies (e.g. apps, bots) to reduce the levels of maternal perinatal stress and lower its detrimental consequences for the offspring (e.g. neurodevelopment delay).
- 8) Accelerate the publication of high impact scientific papers, development and validation of assessment tools, and establishment of best practices across Europe and beyond.

In the very long-term, this Action will have a positive impact on the health of society through the generation of knowledge, social values and public policy. This Action will also promote the developing of future Actions/Horizon funding.

- 1) Maternal perinatal stress can be transferred to the developing fetus (inter-generational effects) and to future generations (trans-generational effects).
- 2) This COST Action aims to reduce, prevent and treat high levels of maternal perinatal stress and its adverse consequences in the offspring. With this in mind, the benefits of this Action will also be observed in future generations of children and adults.
- 3) Implementing this COST Action will improve the production of scientific knowledge and the creation of new leaders in the field who will shape the future of clinical practice, the state of the art and optimize best practice, expertise and competitiveness.
- 4) This Action will reduce the multigenerational adverse effects of ongoing maternal perinatal stress on children.

3.2. MEASURES TO MAXIMISE IMPACT

3.2.1. KNOWLEDGE CREATION, TRANSFER OF KNOWLEDGE AND CAREER DEVELOPMENT

This COST Action will contribute to knowledge creation through the development of scientific publications, clinical guidelines and recommendations, consensus statements, toolkits and whitepapers that will be easily accessible to researchers, clinicians, stakeholders and policymakers. The international network will promote and ease the distribution of information and expertise between the scientific community and end-users. The multidisciplinary network will comprise a range of experts and scientists from different disciplines including midwifery, obstetrics, pediatrics, psychology, psychiatry, epigenetics, epidemiology, social disciplines, neuroscience, mathematics, informatics, biochemistry and health economics. The variety of disciplines involved in this Action will facilitate the creation of knowledge and the development of future projects aiming to understand and reduce the detrimental consequences of maternal perinatal stress in the offspring. Collaboration between members will promote transfer of knowledge to national and international experts, stakeholders, policy-makers and families. Transfer of knowledge between public research institutions and third parties will improve associations with industry while also improving good practices. Collaborative interactions will increase the socio-economic impact of the research by creating new products and new career development, especially of ECIs and members of ITCs. Career development of young researchers and ECIs will help spread their excellence in maternal perinatal stress and adverse infant outcomes. Finally, the development of an international network of experts will increase the possibilities of members accessing research funds by enhancing their visibility and expertise in the field.

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

Dissemination and exploitation activities will be performed through, but not limited to the Action Website, social media, mailing lists, conferences, presentations, scientific publications and press releases. The dissemination activities will have key beneficiaries that include health care professionals and students (e.g. medicine, nursing, midwifery, psychology, psychiatry, biology), researchers, academics, policymakers, health agencies and stakeholders. Dissemination activities will benefit from a multimodal strategy that will include both online and face-to-face deliverables. Dissemination of knowledge in this Action aims to maximise the public impact of the network research outcomes. In order to improve the dissemination strategy, a Science Communication Coordinator (SCC) will manage the organisation and communication of scientific events through the Action Website, social media platforms, Open Access scientific publications, conferences and workshops. A dissemination strategy will be defined including the content and structure of the key messages to be disseminated, the appropriate recipients and the most suitable channels of communication. In this respect, the critical elements will include: 1) What to communicate (e.g. specific project outcomes, skills, recommendations, guidelines). 2) To whom to communicate (e.g. stakeholders, media, researchers, academics, institutional interlocutors). 3) Why communicate (e.g. publicise the funding source, raise awareness, continuity of the project). 4) How to communicate (e.g. social channels, public events, online and offline tools, multimedia products). 5) When to communicate (e.g. before, during and after the project). A plan for dissemination is a valuable tool for assessing results against the Action objectives while generating recommendations for future projects. Exploitation of results refers to the use of outputs in providing a service to members of the public and society through the open availability of results. This Action will facilitate the specific use of the generated results through PhD theses, policy changes and activities within society, which will in turn facilitate further use of the results. The exploitation of results will be achieved by 1) Identifying specific areas and stakeholders that may use the Action's results; 2) Using appropriate channels to engage users (e.g. networks, platforms); and 3) Collecting feedback from users to further develop the Action. In addition, implementing an open dialogue with the public including women, partners and families will enable a mutual learning process aimed at increasing insights into maternal perinatal stress research. Sharing knowledge with the public will help the public better understand science so that they will be more receptive to the Action's results while producing a positive societal impact. Dialogue with the general public and policy will contribute an open mind-set and will be supported by active listening, guidelines and the use of dialogue techniques such as brainstorming, metaplanning and future visioning. Patient and public involvement will be encouraged through an innovative model named Researchers' Café (a free-to-attend public meeting and discussion on scientific topics related to the Action). Finally, liaising with other chairs and vice-chairs in the field and linking with the science communication department of COST will improve the dissemination plan.

4. IMPLEMENTATION

4.1. COHERENCE AND EFFECTIVENESS OF THE WORK PLAN

4.1.1. DESCRIPTION OF WORKING GROUPS, TASKS AND ACTIVITIES

The Action Management Committee (MC) is responsible for the adequate allocation of the grant to achieve the Action's scientific objectives. The MC will hold two meetings annually, with at least one face-to-face meeting per year. The MC will be established during the first Action meeting with participating countries. During the first MC meeting, the election of leadership roles, including the Action Chair (AC) and the Action Vice Chair (AVC) of the network, Grant Holder, Working Group Leaders (WGLs) and WG Vice Leaders (WGVL) will be addressed. In addition, the Grant Awarding Coordinator, the Science Communication Coordinator, and Early Career coordinator will be elected, reserving up to 50% of these roles for members from NNCs or ITCs. The MC Chair will describe deliverables so that the WGs can achieve the Action goals. The kick-off meeting will focus on the election of the Action Chair (AC) and the Action Vice Chair (AVC). The AC will be responsible for coordinating the MC's activities. The MC, along with the WGLs and WGVLs, will coordinate and organise the WGs' activities while designing a detailed plan for each individual WG. Each member of the MC will also be a member of a minimum of one WG. The MC will regularly present a report to the COST office and annually at the face-to-face MC meeting. The Core Group (CG) will be composed of the Action Chair, Action Vice-Chair and five WG Leaders. The CG will be responsible for day-to-day management and urgency cases as per delegation of the MC. It will meet face-to-face annually and online meetings will be organised when necessary. Gender balance will be an issue in the MC agenda. The MC will be responsible for approving (or rejecting) the decisions made at the CG. The Working Groups will be established. At the first MC meeting, WG Leaders and WG Vice-Leaders will be appointed. A detailed Work Plan will be developed during the first MC meeting regarding the first Grant Period (GP). WGLs will put forward their plan of action at a MC meeting, including planned activities, model of network and potential synergies. The Action will focus on making outputs open access and widely available. Reports, guidelines, toolkits and papers will be disseminated to the research community, members of the public, policymakers and stakeholders. The Action will have an Early Career Coordinator (ECC) that will closely support WGLs in their plan of action.

Working Groups:

WG1: Maximising our understanding of maternal perinatal psychological and physiological stress. WG1 aims to conceptualise maternal perinatal stress along with the psychological and biological factors involved.

TASKS/ACTIVITIES:

T1.1 Application of a multi-method perspective through quantitative and qualitative research methods to develop clear definitions of maternal perinatal stress (see Deliverable 1.1)

T1.2 Exploration of women's psychological experiences of maternal perinatal stress through secondary data analysis (see Deliverable 1.2), and development of a validated tool (see Deliverable 1.3)

T1.3 Analysis of the biological factors that can predict maternal perinatal stress in order to better understand the biomarkers influencing the development of high levels of maternal stress in the perinatal period (see Deliverable 1.4)

WG2: Exploring intergenerational and transgenerational impact of maternal perinatal stress on the offspring through epigenetic and biomedical research. WG2 aims to increase knowledge on the biological predictors associated with short-, long- and very long-term adverse consequences in the offspring.

TASKS/ACTIVITIES:

T2.1 Secondary data analysis from Birth Cohort studies and maternity registries to identify potential medical and neurodevelopmental negative outcomes in neonates (see Deliverable 2.1)

T2.2 To create and develop a mathematical model to predict adverse outcomes that can be used to increase the medical and psychological health of future generations (see Deliverable 2.2)

T2.3 Systematic review of the transgenerational impact maternal perinatal stress can have in human populations (see Deliverable 2.3)

T2.4 Based on T2.1 and T2.2 (and Deliverables 2.1 and 2.2), to develop future projects exploring adverse outcomes in the offspring (intergenerational outcomes) and future generations (transgenerational outcomes) from a biological and psychological perspective (see Deliverable 2.4).

WG3: Improving assessment approaches in perinatal maternal stress through psychological and biological measures. WG3 aims to stimulate knowledge on which measures better predict adverse outcomes in the offspring

TASKS/ACTIVITIES:

T3.1 Systematic review and meta-analysis of the maternal perinatal stress biomarkers that can predict negative outcomes in neonates (see Deliverable 3.1)

T3.2 Secondary data analysis from Birth Cohort studies on pregnancy-specific stress and general psychological stress associated with negative outcomes in the offspring to support appropriate health decisions (see Deliverable 3.2)

T3.3 Feasibility and acceptability study among clinicians from a sample of countries on biological and psychological measures to assess perinatal maternal stress (see Deliverable 3.3)

T3.4 Write a guideline/position paper for researchers and clinicians on the psychological and biological predictors of adverse infant outcomes (see Deliverable 3.4).

WG4: Optimising the perinatal period to reduce the adverse impact on the offspring. WG4 aims to stimulate the healthy development of the fetus in order to improve positive outcomes

TASKS/ACTIVITIES:

T4.1 Synthesise the best practices for reducing maternal perinatal stress through non-pharmacological treatments (see Deliverable 4.1)

T4.2 Qualitative interviews of partners and families across a sample of countries to identify potential social, cultural and psychological factors (e.g. resilience) associated with a reduction of maternal perinatal stress (see Deliverable 4.2) in order to develop a toolkit for partners and families (see Deliverable 4.3)

T4.3 Critical appraisal of methods to improve the mother-baby dyad, the father-baby dyad and the mother-father dyad (see Deliverable 4.4)

WG5: Analysis of health economics. WG5 aims to study the economic burden of adverse infant outcomes due to maternal perinatal stress and the cost-effectiveness of identified interventions.

TASKS/ACTIVITIES:

T5.1 Analysis of the economic cost of adverse infant outcomes as a consequence of maternal perinatal stress (see Deliverable 5.1)

T5.2 Position/theoretical paper on current methodological perspectives and development of an analytical framework for assessment (see Deliverable 5.2)

T5.3 Protocol for a health economic assessment (see Deliverable 5.3)

WG6: Communication, dissemination and knowledge transfer. WG6 aims to communicate, disseminate and transfer outputs from this COST Action to the scientific community, clinicians, policymakers, stakeholders, women, partners and families.

TASKS/ACTIVITIES:

T6.1. Draft and implementation of the Science Communication Plan (see Deliverable 6.1)

T6.2 Organise two International Conference (see Deliverable 6.2)

T6.3 Review and gather the current scientific advances into an informative essay (see Deliverable 6.3)

T6.4 Organise open access events for the general public (see Deliverable 6.2)

T6.5 Write a guideline/position paper for policymakers and stakeholders on maternal perinatal stress and the adverse consequences in the offspring, in order to promote healthy neonatal development across the lifespan (see Deliverable 6.4)

4.1.2. DESCRIPTION OF DELIVERABLES AND TIMEFRAME

WG1: Maximising our understanding of maternal perinatal psychological and physiological stress. Major deliverables for WG1: Three scientific papers and one standardised and validated measurement tool.

D1.1: Scientific paper on quantitative perception of maternal perinatal stress (M24)

D1.2: Scientific paper on qualitative perception of maternal perinatal stress (M28)
 D1.3: Development of a standardised and validated tool to measure psychological maternal perinatal stress (M39)
 D1.4: Publication of biological and neuroendocrine predictors involved in the development of physiological maternal stress during the perinatal period (M42)

WG2: Exploring intergenerational and transgenerational impact of maternal perinatal stress on the offspring through epigenetic and biomedical research. Major deliverables for WG2: Two scientific papers and one systematic review.

D2.1: Scientific paper on adverse neurodevelopmental and medical outcomes in neonates (M20)
 D2.2: Scientific paper on predictors of negative outcomes (M28)
 D2.3: Systematic review (M40)

WG3: Improving assessment approaches in perinatal maternal stress through psychological and biological measures. Major deliverables for WG3: One scientific paper, one systematic review, a feasibility and acceptability study and a guideline/position paper

D3.1: Systematic review and meta-analyses on biomarkers predicting adverse outcomes in neonates (M21)
 D3.2: Scientific paper on psychological stress measures (pregnancy-specific stress and general psychological stress) (M27)
 D3.3: Feasibility and acceptability paper on clinicians across countries (M36)
 D3.4: Guideline/position paper for researchers, clinicians, stakeholders and policymakers (M42)

WG4: Optimising the perinatal period to reduce the adverse impact on the offspring. Major deliverables for WG4: A theoretical paper, a scientific qualitative paper, a toolkit and a critical appraisal.

D4.1: Theoretical/Expert consensus/Position paper on the best non-pharmacological interventions to reduce maternal perinatal stress (M24)
 D4.2: Scientific qualitative paper on partners and families (M33)
 D4.3: Development of an educational toolkit for partners and families (M42)
 D4.4: Critical assessment of methods to improve neonates' attachment (M45)

WG5: Analysis of health economics. Major deliverables for WG5: an analysis of economic burden, a protocol and a theoretical paper.

D5.1: Analysis of the impact of maternal stress on health economics: report on the economic burden (M39)
 D5.2: Protocol for a health economic assessment (M45)
 D5.3: Position/theoretical paper (M48)

WG6: Communication, Dissemination and knowledge transfer deliverables for WG6: Two International Conferences, an informative essay, a series of workshops and a guideline.

D6.1: Science Communication Plan
 D6.2: Disseminating and transferring knowledge to society: Conference proceedings (M33 & M48)
 D6.3: Development of an informative brochure for families and members of the public (M42)
 D6.4: Guideline/position paper for policymakers and stakeholders (M36)

4.1.3. RISK ANALYSIS AND CONTINGENCY PLANS

In this section are identified the main risks associated to the Work Plan of this COST Action. The contingency plan included in this section will ensure the successful competition of this Action. More precisely, the risk analysis and contingency plans included below represent the potential risk that may be present during the development of this Action, along with the solutions proposed to achieve the objectives.

Risk analysis	Contingency plan (solution)
Members of the COST Action do not complete proposed tasks (e.g. scientific publications, protocols, etc.) on time	Agree due dates in advance. Reminders. Provide clear templates. Assistance. Identify difficulties and propose alternative solutions.
Lack (or difficulty) of engagement with researchers, clinicians, service user representatives or policymakers	Increase effective communication. Identify relevant stakeholders early on. Promote transfer of knowledge and dialogue with stakeholders. Discussion of good participation. Promote the value of health outputs.
Data availability challenges (e.g. differences across countries in terms of captured data)	Focus on common data across databases (nationally and internationally).
Low involvement of PhD students and ECIs	Clarify the benefits of their involvement. Emphasis of mentorship. Prioritise career development.
Low communication with stakeholders and policymakers	Use of COST Action Website, OpenAIRE, social media and mobile phone applications for modes of science communications (e.g. via press releases, webinars).
Low impact of dissemination activities	Generate collaborative strategies across STSMs focusing on ECIs and students. Produce information leaflets aimed at different stakeholders.
Difficulties achieving full gender balance	Improve dissemination strategies among researchers and clinicians in the field.
Issues related to the Ukrainian war (additionally affected countries, energy crisis, travel restrictions, visa issues)	Face-to-face meetings will be implemented as online meetings while focusing on prioritising outcomes.
Pandemic re-establishes itself impacting on travel for meetings	Establish alternative meeting and collaboration strategy from outset including alternative calendar of online meetings, online workshops and online collaborator engagement sessions.
Competitor group establishes research findings before the COST Action collaborative	The form, function and operationalisation of the COST Action is multimodal, comprising broad workgroups and goals. The risk of a competitor group is intrinsically low in terms of the scope of the COST activity but low-medium in terms of the scientific goals and contribution. The Action will establish a leading group in this field scientifically and the risk mitigation strategy will focus on robust science delivered at an efficient pace.
Complex interactions between disciplines in which a number of areas of cutting-edge science within the area intersect, thus the goals of the group are contingent on all key members delivering. This is analogous to a chain only being as strong as its weakest link.	The Action advocates a layered approach in terms of the overall scientific mission to mitigate against any 'single point of failure'. Thus, the Action network will be mindful from the outset to ensure overlap and contingency across areas and themes to ensure no single adverse event, for example, laboratory non-delivery of key assay results, impacts deleteriously or catastrophically on the overall goals, aspirations and ultimately the scientific achievements of this COST Action.

4.1.4. GANTT DIAGRAM

Bellow these lines it is displayed the diagram representing the network timetable. This timetable offers an overview of this COST Action milestones, including COST Action years (1-4), calendar dates, quarters, management activities and Working Groups 1-6 Deliverables and Milestones.

Regarding the management activities, the timetable displays information related to Management Meetings, Action Website, MC meetings, WG Meetings, Workshops for WGs, Training Schools, Short term Scientific Missions, Progress reports (PR) and Final Assessment Report (FR).

Activities related to Working Groups 1-6 are also included in this diagram.

The graphical illustration represented bellow highlights the wide range of activities and deliverables included, according to the structure of this COST Action.

To sum up, the structure is divided into 6 Working Groups (WG1: Conceptualisation; WG2: Intergenerational and transgenerational impact; WG3: Assessment approaches; WG4: Reduce the adverse impact; WG5: Dissemination; WG6: Health economics) aiming to focus on the impact maternal perinatal stress can have on the offspring.

COST Action Treasure Network	COST Action Year 1				COST Action Year 2				COST Action Year 3				COST Action Year 4			
Calendar dates	Start date-												End date-			
Quarters	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Milestones (M)																
Management Activities																
Kick off meeting-Management Committee meet and coordination of WGs	M															
Action Website			M													
MC/TC/DC/WC/SC/CC meetings		M				M				M				M		
WG Meetings and minutes		M		M		M		M		M		M		M		M
Workshops for WGs		M		M		M		M		M		M		M		M
Training Schools							M				M				M	
Short term Scientific Missions				M				M				M		M		
Progress reports (PR1, PR2), Final Assessment Report (FR)				PR1				PR2								FR
Work Groups 1-6 Deliverables and Milestones																
WG1: Three scientific papers and one standardized measurement tool								D1.1	D1.2					D1.3	D1.4	
WG2: Two scientific papers, systematic review and a grant application						D2.1		D2.2							D2.3	
WG3: Scientific paper, systematic review, a feasibility and acceptability study and a guideline/position paper							D3.1		D3.2			D3.3		D3.4		
WG4: A theoretical paper, a scientific qualitative paper, a toolkit and a critical appraisal								D4.1			D4.2			D4.3	D4.4	
WG5: Economic burden, protocol, theoretical paper													D5.1		D5.2	D5.3
WG6: Two International Conferences Proceedings, informative essay, series of workshops and guideline (including policymakers and stakeholders)		D6.2									D6.2			D6.3		D6.2

References

1. Szyf, M. (2022). The epigenetics of perinatal stress. *Dialogues in Clinical Neuroscience*.
2. Barrero-Castillero, A., Pierce, L. J., Urbina-Johanson, S. A., Pirazzoli, L., Burris, H. H., & Nelson, C. A. (2022). Perinatal and early childhood biomarkers of psychosocial stress and adverse experiences. *Pediatric Research*, 1-10.
3. Rakers, F., Schleußner, E., Muth, I., Hoyer, D., Rupprecht, S., Schiecke, K., ... & Ligges, C. (2022). Association between antenatal glucocorticoid exposure and the activity of the stress system, cognition, and behavior in 8-to 9-year-old children: A prospective observational study. *Acta Obstetrica et Gynecologica Scandinavica*.
4. Jahnke, J. R., Terán, E., Murgueitio, F., Cabrera, H., & Thompson, A. L. (2021). Maternal stress, placental 11 β -hydroxysteroid dehydrogenase type 2, and infant HPA axis development in humans: Psychosocial and physiological pathways. *Placenta*, 104, 179-187.
5. Spry, E. A., Letcher, P., Patton, G. C., Sanson, A. V., & Olsson, C. A. (2022). The developmental origins of stress reactivity: an intergenerational life-course perspective. *Current Opinion in Behavioral Sciences*, 43, 187-192.
6. Mahaffey, B. L., Tilley, J. L., Molina, L. K., Gonzalez, A., Park, E., & Lobel, M. (2022). "How am I going to make it through pregnancy?" A qualitative examination of prenatal maternal stress. *Birth*, 49(2), 253-260.
7. Barrero-Castillero, A., Pierce, L. J., Urbina-Johanson, S. A., Pirazzoli, L., Burris, H. H., & Nelson, C. A. (2022). Perinatal and early childhood biomarkers of psychosocial stress and adverse experiences. *Pediatric Research*, 1-10.
8. World Health Organization. (2022). Guide for integration of perinatal mental health in maternal and child health services.
9. Morris, A. R., Herzig, S. E., Orozco, M., Truong, V., Campuzano, V., Sridhara, S., ... & Saxbe, D. E. (2022). Delivering alone in a pandemic: Anticipated changes to partner presence at birth are associated with prenatal distress. *Families, Systems, & Health*, 40(1), 126.
10. Barker, D. J. (1995). Fetal origins of coronary heart disease. *Bmj*, 311(6998), 171-174.
11. Glover, V. (2015). Prenatal stress and its effects on the fetus and the child: possible underlying biological mechanisms. In *Perinatal programming of neurodevelopment* (pp. 269-283). Springer, New York, NY.
12. Van den Bergh, B. R., Mulder, E. J., Mennes, M., & Glover, V. (2005). Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: links and possible mechanisms. A review. *Neuroscience & Biobehavioral Reviews*, 29(2), 237-258.
13. Bowers, K., Ding, L., Yoltan, K., Ji, H., Nidey, N., Meyer, J., ... & Folger, A. (2021). Pregnancy and Infant Development (PRIDE)—a preliminary observational study of maternal adversity and infant development. *BMC pediatrics*, 21(1), 1-8.
14. Hoffman, M. C., D'Anna-Hernandez, K., Benitez, P., Ross, R. G., & Laudenslager, M. L. (2017). Cortisol during human fetal life: Characterization of a method for processing small quantities of newborn hair from 26 to 42 weeks gestation. *Developmental psychobiology*, 59(1), 123-127.
15. Lin, T. T., Zhang, C., Chen, L., Jin, L., Lin, X. H., Pan, J. X., ... & Wu, Y. T. (2021). COVID-19 Lockdown Increased the Risk of Preterm Birth. *Frontiers in medicine*, 8.
16. Al Wattar, B. H., Honess, E., Bunnewell, S., Welton, N. J., Quenby, S., Khan, K. S., ... & Thangaratinam, S. (2021). Effectiveness of intrapartum fetal surveillance to improve maternal and neonatal outcomes: a systematic review and network meta-analysis. *CMAJ*, 193(14), E468-E477.
17. Wu, H. (2021). Maternal stress and sex ratio at birth in Sweden over two and a half centuries: a retest of the Trivers–Willard hypothesis. *Human Reproduction*, 36(10), 2782-2792.