Brussels, 19 May 2025

COST 024/25

DECISION

Subject: Memorandum of Understanding for the implementation of the COST Action “Connecting an INternational Network of Academic Manufacturers of ONcoimmunotherapies” (CINNAMON) CA24115

The COST Member Countries will find attached the Memorandum of Understanding for the COST Action Connecting an INternational Network of Academic Manufacturers of ONcoimmunotherapies approved by the Committee of Senior Officials through written procedure on 19 May 2025.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA24115
CONNECTING AN INTERNATIONAL NETWORK OF ACADEMIC MANUFACTURERS OF ONCOIMMUNOTHERAPIES (CINNAMON)

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 set up a collaborative and interconnected network of centres dedicated to standardizing, expanding, and optimising CAR-T cell therapy expertise. This network will promote equitable access to CAR-T therapies, foster innovation in ATMPs, and provide comprehensive training programmes for scientists and clinicians. 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
CAR-T cell therapy represents a breakthrough in cancer treatment but faces challenges in accessibility, standardization, and expertise across Europe. Improvement of health outcomes and addressing inequalities in advanced therapy medicinal products (ATMPs) are major European challenges according to European Medicines Agency (EMA). Currently, CAR-T manufacturing, regulatory, research and clinical capabilities are unevenly distributed, particularly in Inclusiveness Target Countries (ITCs). The urgency stems from the growing demand for cutting-edge therapies.

The main aim of CINNAMON is to establish a collaborative network of European centres to standardize, expand and optimise CAR-T cell therapy expertise. This involves promoting equitable access to these therapies, fostering innovation in ATMPs, and providing comprehensive training programs for scientists, innovators and clinicians, particularly in (but not limited to) ITCs. CINNAMON will assemble a multidisciplinary team that will bridge gaps in knowledge and technology, thereby improving the overall quality and reach of CAR-T cell therapies.

Areas of Expertise Relevant for the Action	Keywords
● Medical biotechnology: Gene therapy, stem cell therapy, regenerative medicine for medical biotechnology ● Clinical medicine: Adaptive immunity ● Clinical medicine: Oncology ● Clinical medicine: Hematology ● Basic medicine: Adaptive immunity	● CAR-T therapy ● Immunotherapy ● Oncology ● Cell manufacturing ● Regulatory

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

Research Coordination
● To build the foundation for sustainable collaboration and foster cross-border partnerships that will accelerate the development of CAR-T cell therapies
● To adopt common standards to streamline manufacturing practices, reduce variability and ensure high-quality treatments for patients across Europe
● To address manufacturing bottlenecks, thus expanding the availability of CAR-T therapy and reducing production costs
● To promote the joint development of novel CAR-T cell therapies among academic researchers by encouraging the preclinical development of novel products for diverse clinical conditions
● To develop common guidelines to facilitate regulatory approvals. This could potentially reduce delays in market authorization, enabling faster patient access to innovative therapies
● To facilitate clinical data sharing and collaborative research among clinicians. This will enhance research capabilities and foster continuous improvements in patients' care and outcome

Capacity Building
● To enhance collaborative research infrastructure and resource access, addressing disparities in infrastructure and building a robust network by facilitating resource sharing and technical capacity across European institutions

● To promote public awareness and patient engagement, emphasizing the importance of public/patient involvement in the scientific process, thus promoting trust and ensuring that CAR-T therapies meet societal needs and expectations
● To promote knowledge exchange and training, by providing regular opportunities for networking and specialized training, ensuring the workforce remains at the forefront of innovation
● To encourage young researchers and innovators (YRI) participation by creating a supportive ecosystem for career development, ensuring long-term growth and innovation in the field

TECHNICAL ANNEX

1. S&T EXCELLENCE

1.1. SOUNDNESS OF THE CHALLENGE

1.1.1. DESCRIPTION OF THE STATE OF THE ART

Chimeric Antigen Receptor T-cell (CAR-T) therapy represents a groundbreaking advancement in cancer treatment, particularly for (but not limited to) haematological malignancies such as leukaemia, lymphoma and multiple myeloma[1]. This innovative therapy involves genetically modifying a patient's own T-cells to express receptors targeting cancer cell antigens, enabling the immune system to target and destroy cancer cells with high precision[2]. Clinical trials and real-world applications have shown remarkable remission rates, especially in patients with relapsed or refractory cancers who have exhausted conventional treatments[3]. The significance of CAR-T therapy lies in its personalized approach, offering targeted treatment that minimizes damage to healthy tissues and reduces side effects compared to traditional therapies. Its success has spurred further innovations in advanced therapy medicinal products (ATMPs), highlighting the potential of personalized medicine in oncology and other pathologies. However, challenges remain in terms of accessibility, affordability, standardization and patient stratification, which need to be addressed to ensure equitable access and maximize the therapy's benefits across diverse patient populations[4].

Despite these challenges, CAR-T therapy continues to represent a transformative leap forward in the fight against cancer[5]. Recent technological and clinical developments in CAR-T cell therapy have significantly enhanced its efficacy and safety[6]. Additionally, advances in manufacturing processes, including automated and scalable production methods, have increased the consistency and availability of CAR-T products. Clinically, CAR-T therapies have demonstrated impressive outcomes, with key trials showing high remission rates in patients with advanced haematological malignancies. This has led to a positive scientific recommendation from the European Medicines Agency (EMA), and approval of the European Commission (EC)[7] and the U.S. Food and Drug Administration (FDA)[6]. In 2018, the European Commission approved Norvartis' Kymria® (Tisagenlecleucel), and Kite/Gilead's Yescarta® (Axicabtagene ciloleucel) as the first two treatments. In December 2020, Kite/Gilead's Tecartus® (KTE-X10) was also approved by the EC, followed by BMS' Abecma® (Idecabtagene Vicleucel) in August 2021, and BMS' Breyanzi® (lisocabtagene maraleucel) in April 2022[7].

Academic institutions have also played crucial roles in pioneering research and clinical trials, developing CAR-T products that are currently available for patients under the hospital exemption regulation and compassionate use programmes[8]. This regulation implies that the product is prepared on a non-routine and non-market basis, and can only be administered within one member state, in a specific hospital, and for a specific patient. This hospital exemption clause enables the member state to provide provisory access to the treatment without the EC marketing authorization, hence, these CAR-T products are not intended for marketing and are often manufactured by hospitals themselves. Hospital exemption is useful, for example, in a scenario where there are high unmet medical needs, yet no product is available on the market. In fact, some Western Europe countries offer these academic CAR-T therapies exceptionally providing patients treatment options and access to new medicinal products[9].

However, CAR-T products cannot be used by every hospital, as it requires advanced practical skills and expertise, as well as specific equipment and facilities for it to become a qualified treatment centre. In fact, the distribution of CAR-T expertise and manufacturing capabilities across Europe paints a picture of uneven progress. While Western European nations boast major research centres and hospitals with advanced CAR-T programs, access in Eastern and Central European countries is often limited, highlighting disparities in healthcare infrastructure and resources across the continent[10]. This disparity stems from several factors, with funding availability playing a major role. Wealthier Western nations can dedicate more resources to research and infrastructure development, fostering expertise and infrastructure unavailable in their Eastern counterparts. Additionally, limited clinical trial participation in Eastern and Central Europe restricts access to the latest treatments and hinders the development of local expertise. Moreover, patient accessibility remains a challenge due to several factors. The exorbitant cost of these commercial therapies (approx. 320.000€/patient)[11], as result of the personalized nature of the treatment, the complex manufacturing process, and the current centralised production model adopted by pharmaceutical companies has severely restricted patient access globally. Numerous EU member states (such as Bulgaria, Estonia, Latvia, Lithuania, and Romania, among others) lack access to commercial CAR-T cell products[12]. Reimbursement policies further complicate access, and in the case that these commercial therapies will become available in the aforementioned countries, they will be extremely expensive for healthcare systems. Moreover, regulatory approval processes for CAR-T therapies vary widely across countries. Limited or slow approvals can restrict patient access, even where therapies are available. Additionally, the current manufacturing infrastructure for CAR-T

therapies might not be sufficient to handle a significant increase in demand. This limited capacity creates waiting lists and further restricts access for patients in need, therefore, representing a serious bottleneck in many EU countries. These geographical disparities within Europe and the associated accessibility challenges highlight the **need** for **initiatives that promote advanced skills for manufacturing decentralisation, standardization, the overcoming of regulatory hurdles, knowledge and technology transfer, as well as infrastructure development**. Achieving equitable access to this life-saving therapy requires a concerted effort to bridge the gap between different regions in Europe. This Action, ***CINNAMON**: **C**onnecting an **IN**ternational **N**etwork of **A**cademic **M**anufacturers of **ON**coimmunotherapies*, will actively contribute to these efforts by fostering collaboration, facilitating knowledge exchange, and promoting capacity building across Europe and beyond.

1.1.2. DESCRIPTION OF THE CHALLENGE (MAIN AIM)

Currently, the commercial manufacturing of CAR T-cells by pharmaceutical companies is organized in a centralised manufacturing setup that presents significant obstacles to the efficient implementation and scale-up of CAR-T products (**Figure 1**, left)[13]. This production model involves apheresis collection of patient peripheral blood mononuclear cells (PBMCs) at the treating hospital. These PBMCs are then cryopreserved and shipped to a central manufacturing facility for CAR vector transduction and T-cell expansion. The final CAR T-cell product is then cryopreserved again and shipped back to the hospital for patient infusion. Consequently, products often have extended lead times, making it difficult for critically ill patients to access these life-saving treatments in a timely manner. Additionally, centralised production limits the pace of innovation and has a substantial environmental impact due to frequent shipments. Moreover, each manufacturer has its own requirements, certification procedures and shipping methods, increasing complexity and bureaucracy and placing an undue burden on healthcare providers. The high costs associated with centralised production also place a heavy burden on European healthcare systems, even for the few conditions currently approved for CAR-T treatment. Consequently, some countries do not offer CAR-T therapies as part of their standard public healthcare options. Moreover, developing medicines for rare diseases poses limited commercial incentives due to challenges in scale up production and serving a small patient group. The substantial upfront costs and complex registration and reimbursement procedures further discourage big pharmaceutical companies investment.

In order to address some of the limitations of the centralized model there is a growing focus on developing academic point-of-care (PoC) manufacturing[14], and academic research centres are increasingly leading ATMP research and development (**Figure 1**, right). In contrast to the centralised model where CAR T-cell therapy is manufactured in a dedicated facility, **point-of-care manufacturing brings production directly to hospitals**. This eliminates the need to transport patient's cells to a central location, potentially leading to a faster turnaround time for treatment. Additionally, it could allow for more flexibility in CAR T-cell design, potentially enabling a more personalized approach to treatment. However, this approach faces its own challenges.

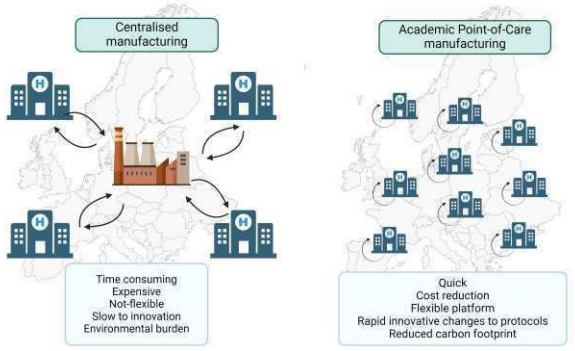

***Figure 1.** Centralised vs Point-of-Care manufacturing.*

To accomplish the point-of-care (PoC) model for CAR-T cell therapy, several key elements need to be established and integrated seamlessly. Securing funding from governmental bodies, private investors, and public-private partnerships is essential for the development of PoC facilities and related infrastructure. Hospitals and academic institutions must develop or upgrade facilities to support CAR-T cell production, including specialized clean rooms, bioreactors, and other essential equipment for cell processing and genetic modification. The implementation of advanced manufacturing technologies, such as automated and scalable systems, is necessary to ensure efficient and consistent production of CAR-T cells within the hospital setting. Regulatory compliance is also a significant factor. Establishing a clear and supportive regulatory framework at EU and country level that permits PoC production while ensuring patient safety and product efficacy is critical. This includes compliance with Good Manufacturing Practices (GMP) and other relevant regulations. Collaboration with regulatory bodies such as the EMA can help streamline the approval process for PoC-produced CAR-T therapies. Another regulatory challenge is the ambiguity surrounding the regulation of next-generation CAR-T therapies based on mRNA approaches. The EU regulation of RNA-based medicinal products is complex and is likely to become more pronounced with the continuous evolution of this innovative technology in the

CAR-T space. According to EU legislation, these mRNA-based products can currently be categorized into different regulatory statuses depending on their target—whether for infectious diseases or other indications—and the method of production, which can be either chemical or biological. For instance, therapies that involve ex vivo electroporated T-cells with mRNA CAR or in vivo targeting of T-cells with mRNA CAR can be classified as either a somatic cell therapy medicinal product (sCTMP) or a gene therapy medicinal product (GTMP). This variability means that different regulatory pathways must be followed for marketing authorization, which complicates the process for developers and manufacturers. Moreover, training programmes for scientists, clinicians, nurses, and technical staff are needed to equip them with the skills required for the complex processes involved in CAR-T cell production and administration. Developing and disseminating standardized protocols for CAR-T cell production, quality control, and patient care will help maintain uniformity and high standards across different PoC facilities. Furthermore, educating patients on the benefits and risks of CAR-T cell therapy is critical, ensuring they fully understand the treatment process, possible side effects, and the rigorous follow-up required. Such education empowers patients to make informed decisions and prepares them for the emotional and physical challenges of the therapy. Additionally, fostering collaborative networks is vital. Building partnerships between academic institutions, hospitals, and research centres will facilitate the sharing of knowledge, resources, and best practices. Additionally, collaboration with biotech companies and technology providers can provide access to advanced manufacturing technologies and expertise. Finally, it is also important to raise awareness among patients, clinicians, and healthcare authorities (including local, regional, national authorities setting healthcare policies and funding) about the availability of CAR-T cell therapies. By addressing these elements, the transition to a PoC production model for CAR-T cell therapy can be achieved, leading to more efficient, cost-effective, and accessible treatments for patients across Europe.

The main aim of CINNAMON, is **to set up a collaborative and interconnected network of European centres dedicated to standardizing, expanding, and optimising CAR-T cell therapy expertise and capabilities** (**Figure 2**). This collaborative network will seek to promote equitable access to CAR-T therapies, foster innovation in ATMPs, and provide comprehensive training programmes for scientists and clinicians. Specific objectives include developing standardized protocols for CAR-T cell production and clinical application, addressing regulatory hurdles, expanding manufacturing capabilities, increase public awareness, and implementing training programs to build expertise across Europe, particularly in widening countries. Through these efforts, CINNAMON seeks to **bridge gaps in knowledge and technology**, ultimately improving the quality and reach of CAR-T cell therapies across Europe.

In the long-term, addressing these challenges will have significant impact on public health, including improved cancer treatment outcomes and reduced health disparities across Europe. By enhancing CAR-T cell therapy expertise and capabilities, CINNAMON will not only foster more effective and accessible treatment options for patients with haematological malignancies but also eventually expand to other conditions. Moreover, in the long term, CINNAMON will create a unique network of expertise and excellence, ready to assist industrial and academic developers of CAR-Ts by enabling access to translatable, scalable, quality-controlled, and robust technologies. This will reduce timeframes, lower costs, and accelerate clinical development. This initiative will position Europe as a leader in CAR-T cell therapy. By creating a collaborative network of centers, Europe will enhance its global competitiveness in the biopharmaceutical sector. This leadership will not only benefit European patients but also contribute to global advancements in cancer treatment, solidifying Europe's role as a pioneer in healthcare innovation.

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 formation of a collaborative network of European centres (**Figure 2**) is a cornerstone of CINNAMON. This network will consist of leading academic institutions, hospitals, research centres, SMEs, patient organisations and NGOs across Europe and beyond, each contributing their unique expertise and resources. Key participants will include centres of excellence in Western Europe, which have advanced academic CAR-T programs, as well as emerging centres in Eastern and Central Europe, as well as institutions in Near Neighbour Countries (NNC) to further expand the scope beyond Europe. The intended collaborations will focus on **sharing knowledge, best practices, and technological advancements**, ensuring a cohesive and synergistic approach to CAR-T cell therapy development. This network will facilitate **regular workshops and meetings, new joint R&D inititiatives and clinical trials**, to promote innovation, standardization and advancement in CAR-T therapy. To ensure consistency in CAR-T cell production and clinical application across countries, the Action will **develop**

and implement standardized protocols. These protocols will cover all aspects of CAR- T cell therapy, from manufacturing processes to patient stratification and care guidelines. A dedicated task force within the collaborative network will be responsible for drafting and refining these protocols, incorporating feedback from all participating centres. This effort will not only streamline CAR-T therapy production but also facilitate regulatory approval and enhance patient safety across Europe.

Moreover, expanding CAR-T manufacturing capabilities will be crucial for meeting the growing demand for these therapies. Outcomes from this collaborative network may include agreements for **technology transfer** from leading centres to those in Inclusiveness Target Countries (ITC). Moreover, collaboration between centres will encourage **increased joint participation in EC funding programmes**, ultimately leading to funding acquisition, together with the financial contribution from healthcare authorities. This will foster **infrastructure development** and drive investment in state-of-the-art **facilities and equipment**, which will allow (in the long-term), the establishment of new local manufacturing facilities. Consequently, the overall capabilities of CAR-T cell therapy across Europe will be enhanced. Establishing new local manufacturing capabilities will also ensure that patients have access to these therapies, which would otherwise be unavailable in their countries. It is anticipated that regional or national nodes will serve as referral centres, ensuring efficient patient access and smooth patient pathways.

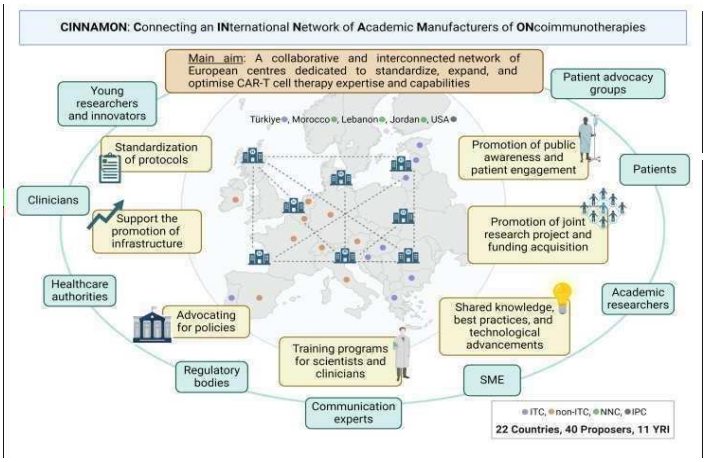

Figure 2. *CINNAMON main aim (orange square), approach (yellow squares), stakeholders (green squares), and countries involved at the time of submission.*

A critical pillar of this Action will be the development of comprehensive **training programmes for scientists and clinicians**, which are essential for building and sustaining CAR-T expertise. These programmes will target ITC, non-ITC and NNC, ensuring a broad distribution of knowledge and skills. The training will include workshops, training schools and short-term scientific missions (STSM), focusing on various aspects of CAR-T cell therapy, from laboratory techniques to clinical management. By fostering a well-trained workforce, the Action aims to create a sustainable pipeline of skilled professionals capable of advancing CAR-T therapies. Additionally, **advocating for policies** that promote equitable access to CAR-T therapies will be a critical component of this COST Action. This will involve active engagement with policymakers (including patient advocacy groups, healthcare authorities, regulatory agencies, and other stakeholders) to highlight the importance of making CAR-T treatments available to all patients, regardless of geographic location. Efforts will focus on streamlining regulatory pathways, ensuring fair pricing, and integrating CAR-T therapies into national healthcare systems. By influencing policy, the initiative aims to remove barriers to access and create a more inclusive healthcare landscape, with a central focus on improving safety and efficacy. This COST Action will also lead to **new R&D initiatives** focusing on the development of novel CAR-T therapies, improving CAR-T cell efficacy, reducing side effects, and expanding the range of treatable cancers. Moreover, incorporating emerging technologies such as novel CAR designs and scalable manufacturing platforms using cheaper consumables will be pivotal in advancing the field. The Action will support the exploration and integration of cutting-edge technologies that optimise the functionality and safety of CAR-T cells. Partnerships with biotech companies will facilitate the translation of research findings into clinical applications, accelerating the development of next-generation CAR-T therapies. In the long- term, clinical trials will be conducted to test new CAR designs and therapeutic strategies. The Action will push the boundaries of current CAR-T cell therapy practices, setting new standards for excellence and innovation. By developing standardized protocols, fostering collaborations, and incorporating emerging technologies, the Action will lead to groundbreaking advancements in CAR-T therapy. The focus on point-of-care production will further revolutionize the field, making treatments more accessible and efficient. The unparalleled capacity of CINNAMON lies in uniting CAR-T-specialized organizations, including research and clinical centres, patient advocacy groups, regulatory and standards experts, and industry and manufacturing companies. Together, CINNAMON is committed to delivering lasting impact on the CAR-T development landscape in Europe and beyond, driven by patients' needs and

empowered by cutting-edge, standardized technological advancements.

1.2.2. OBJECTIVES

1.2.2.1. Research Coordination Objectives

The following objectives and KPIs are proposed to ensure the project achieves its mission of fostering collaboration, advancing CAR-T cell manufacturing, and improving access to therapies across Europe. These objectives are designed to be Specific, Measurable, Achievable, Relevant, and Time-bound (SMART), ensuring clear goals with defined outcomes:

RCO1. To set up a collaborative network of centres.

This objective aims to build the foundation for sustainable collaboration and foster cross-border partnerships that will accelerate the development of CAR-T cell therapies.

- Specific: Form a unique and non-existing collaborative network that includes leading and emerging CAR-T cell therapy centres across Europe.
- Measurable: Establish a network of **≥ 30** European centres and engage **≥ 80%** of ITCs.
- Achievable: Set up a coordination team to manage the network, recruit new members, and engage with potential partner centres in Europe and beyond.
- Relevant: Enhance collaboration and knowledge sharing among centres to accelerate research and improve patient outcomes.
- Time-bound: Consolidate a widespread European network of 30 centres within the first **3 years** of CINNAMON.

RCO2. To establish common manufacturing and quality control standards.

The adoption of common standards will streamline manufacturing practices, reduce variability, and ensure high-quality treatments for patients across Europe.

- Specific: Develop and implement harmonized protocols for CAR-T cell manufacturing across network centres.
- Measurable: Create standardized manufacturing and quality control protocols and have them adopted by **≥ 60%** of network centres.
- Achievable: Utilize existing expertise in manufacturing, quality control and regulatory compliance within the network to develop the protocols.
- Relevant: Consistent manufacturing and quality control processes are essential for ensuring the safety and efficacy of CAR-T cell therapies.
- Time-bound: Develop the protocols within the first **24 months** and achieve 60% of adoption within **3 years**.

RCO3. To promote collaboration on addressing manufacturing challenges.

By addressing manufacturing bottlenecks, the network aims to expand the availability of CAR-T therapies and reduce production costs.

- Specific: Facilitate joint research efforts among network members to address CAR-T cell manufacturing challenges.
- Measurable: Develop **≥ 4** new collaborative proposals focused on manufacturing.
- Achievable: Leverage the expertise and resources of participating centres to initiate and support these projects.
- Relevant: Overcoming manufacturing challenges is crucial for making CAR-T therapies more widely available and affordable.
- Time-bound: Submit ≥ 4 new collaborative proposals within **2 years** and launch ≥ 2 research projects within **3 years**.

RCO4. To promote joint development of novel CAR-T cell therapies among academic researchers.

This objective will foster innovation within the network by encouraging the preclinical development of novel CAR-T therapies for diverse clinical conditions.

- Specific: Encourage collaboration between researchers to develop new oncological CAR-T cell therapies.
- Measurable: Develop **≥ 4** collaborative sustainability strategies focused on developing novel CAR-T cell therapies.
- Achievable: Leverage the research capabilities and innovative potential of the network's members.
- Relevant: Developing new and more effective CAR-T therapies will address various cancers.
- Time-bound: Elaborate collaborative sustainability strategies within **2 years** and launch joint initiatives within **3 years**.

RCO5. To develop common guidelines to facilitate regulatory approvals.
The harmonization of regulatory processes will reduce delays in market authorization, enabling faster patient access to innovative therapies.

- Specific: Harmonize regulatory pathways for CAR-T cell therapies across Europe.
- Measurable: Formulate a comprehensive set of regulatory guidelines that incorporates feedback from **≥ 5** regulatory experts.
- Achievable: Collaborate with regulatory experts and stakeholders within the network to draft the guidelines.
- Relevant: Streamlined regulatory approval processes will expedite patient access to CAR-T therapies.
- Time-bound: Complete the guidelines within **2 years** and update them in **4 years**.

RCO6. To facilitate clinical data sharing and collaborative research among clinicians.
Knowledge and data sharing will enhance research capabilities and foster continuous improvements in patient care and therapy outcomes.

- Specific: Organize meetings, conferences and workshops focused on sharing clinical trial data, patient outcomes and best practices.
- Measurable: Conduct **≥ 4** events and ensure **≥ 50%** of network centres actively participating in these events; **> 50%** of CINNAMON partners using **> 5** open databases.
- Achievable: Coordinate with centres to organize events and internally disseminate databases.
- Relevant: Sharing knowledge, data and experiences through these events and databases is crucial for advancing research and improving patient outcomes.
- Time-bound: Hold the first event within **12 months** and the remaining events within the next **3 years**, and achieve **≥ 50%** participation from network centres, and the use of databases.

1.2.2.2. Capacity-building Objectives

Building capacity is essential to the success and sustainability of CAR-T cell therapy across Europe. These objectives aim to strengthen infrastructure, foster public awareness, enhance knowledge exchange, and empower the next generation of researchers and innovators. Through targeted initiatives, the Action will ensure that institutions, professionals, and communities are equipped with the resources and expertise needed to accelerate CAR-T cell development and accessibility. The following capacity-building objectives are defined using the SMART framework to ensure their effective implementation and measurable impact:

CBO1. To enhance collaborative research infrastructure and resource access.
This objective addresses disparities in infrastructure and aims to build a robust research and production network by facilitating resource sharing and technical capacity across European institutions.

- Specific: Share access, improve and/or establish CAR-T cell manufacturing facilities in European countries.
- Measurable: Build a network connecting **≥ 15** countries, which will enable institutions to access shared resources and attract funding for infrastructure improvements.
- Achievable: Identify key partners, secure funding through new collaborative R&D initiatives, and provide technical support for facility development.
- Relevant: Enhance Europe's capability to conduct CAR-T cell research and production.
- Time-bound: Initiate collaboration efforts within the first **2 years** and have established and/or improved facilities within **4 years**.

CBO2. To promote public awareness and patient engagement.
This objective emphasizes the importance of engaging the public and patients in the scientific process, promoting trust, and ensuring that CAR-T therapies meet societal needs and expectations.

- Specific: Develop and distribute educational materials and organize outreach events annually.
- Measurable: Distribute **3** types of educational materials and organize **1** outreach event annually to reach **≥ 5,000** people.
- Achievable: Create a workforce for content creation, program planning, and outreach activities.
- Relevant: Increase public understanding of CAR-T cell therapy and involve patients in research activities.
- Time-bound: Begin developing educational materials within **12 months** and roll out the first outreach event within **18 months**.

CBO3. To promote knowledge exchange and training.
This objective promotes continuous professional development by providing regular opportunities for networking and specialized training, ensuring the workforce remains at the forefront of innovation.

- Specific: Organize networking activities, workshops, training schools, and STSM for researchers, clinicians, and stakeholders involved in CAR-T cell therapy.
- Measurable: Organize **≥ 2** networking activities, **≥ 2** workshops, **≥ 1** training school and **≥ 10** STSM annually. Track the number of events held and aim for **≥ 50** participants in networking activities, **≥30** participants per workshop, **≥ 30** per training course and **≥ 10** participants per STSM.
- Achievable: Strengthened partnerships within CINNAMON will facilitate knowledge exchange and training.
- Relevant: Focus on enhancing the skills and knowledge of professionals in the CAR-T cell therapy field.
- Time-bound: Conduct on average 5 events **per year**.

CBO4. To encourage young researchers and innovators (YRI) participation.
This objective focuses on empowering the next generation of researchers and innovators by creating a supportive ecosystem for career development, ensuring long-term growth and innovation in the field.

- Specific: Create opportunities for YRI to participate in network and mentorship activities with established experts.
- Measurable: Organise **≥ 20** tailored trainings and meetings with senior experts annually and track the number of YRI involved.
- Achievable: Develop a structured mentorship and support program with clear guidelines and objectives.
- Relevant: Support the career development of YRI in the field of CAR-T cell therapy.
- Time-bound: Launch the mentorship program within **18 months** and review its impact annually.

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 advanced therapies field is key for Europe, as evidenced by the multiple calls for proposals from the European Commission (EC). Under Horizon Europe, 8 calls in the field of advanced therapies have been published to date, highlighting the clinical need's relevance and urgency and underscoring its priority for the EC. There are very relevant ongoing projects funded under these topics and other European programs, aiming at improving the effectiveness of CAR-T cell therapy. For example, projects such as **T- FITNESS**, **Synthetic T-rEX** and **Exh-Res-CART** aim to understand the mechanisms of T-cell exhaustion and design strategies to overcome them. Another relevant project is **T^{2}EVOLVE**, working to overcome obstacles in engineered T-cell cancer therapy. They are creating tools for predicting treatment outcomes, standardizing therapy production, and improving patient education to accelerate the therapy's clinical use. Regarding CAR-T cell manufacturing, initiatives such as **SMARTER**, **PAT4CGT** and **InnoCAR-T** aim to enhance the manufacturing process of cell-based therapies to make them more efficient, scalable, and accessible to patients. Also, **AIDPATH** aims to advance personalized medicine in EU hospitals by integrating AI technology with CAR-T cell therapy, optimizing patient-specific data integration and resource planning to reduce costs and improve efficiency. Another relevant project is **JOIN4ATMP**, which aims to overcome regulatory obstacles and streamline processes to make ATMPs more accessible to patients across Europe.

While all these projects have significantly contributed to the development and manufacturing of novel CAR-T cell therapies, their efforts primarily address specific aspects of CAR-T therapy. This Action takes a broader perspective by emphasizing the integration of research findings into clinical practice, the standardization of protocols, and the capacity building of a wide range of European centres. There remains a critical gap in translating these advancements into widespread clinical practice and ensuring equitable access across all Europe, including countries where CAR-T therapy is not yet available. The fact that **only 20%** (3 out of 16) of the countries participating in the aforementioned projects and other CAR-T-related initiatives are a COST Inclusiveness Target Country (ITC) underscores the urgent and unmet need to create a network that includes these countries as well. Furthermore, CINNAMON initiative aligns with EU health goals and policies aimed at improving health outcomes and reducing disparities in the availability of advanced therapy medicinal products (ATMPs)[15]. Tackling these challenges supports the EU's commitment to advancing healthcare innovation and ensuring equitable access to cutting-edge therapies for all citizens.

Recently, a newly funded project (**PRECISEU**: PeRsonalised medicine Empowerment Connecting Innovation ecoSystems across EUrope) funded under European innovation ecosystems, has included a relevant list of ITCs, including Romania, Bulgaria, Lithuania, Greece and Ukraine. While PRECISEU

takes a broad approach, including ATMPs, working to scale a wide range of healthcare innovations in personalised medicine, CINNAMON narrows its scope to the challenges and clinical applications of CAR-T therapy. PRECISEU focuses on addressing various needs within personalized medicine, whereas CINNAMON is deeply rooted in overcoming the specific barriers to implementing CAR-T therapies across Europe.

A significant gap in the field of ATMPs is the lack of a united multidisciplinary network, which efficiently addresses the creation of new treatments and diagnostics, including clinical trials, by allowing customization based on **standardized manufacturing processes, clinical protocols, regulatory pathways** which streamlines development, reduces costs, and increases efficiency. In 2021, the NIH and the FDA, along with several pharmaceutical companies and non-profits, launched the Bespoke Gene Therapy Consortium (BGTC) to establish standards for faster development of tailored gene therapies for rare diseases. Similarly, European initiatives like **RESTORE** and **RARE-IMPACT** contributed to gaining a better understanding of the complex ATMP landscape, showcasing Europe's potential for innovation while highlighting the challenges in healthcare delivery and treatment processes. CINNAMON aims to replicate such initiatives within the CAR-T field in the future, and this Action is an initial step towards building and consolidating a capable network that can address the manufacturing, regulatory and patient stratification challenges.

Moreover, up to date, a COST Action specifically addressing the CAR-T field does not exist. A related, but with a very different scope, COST Action is **IMMUNO-model** (CA21135), which aims to foster research and innovation in preclinical immuno-oncology models (e.g. organoids, organ-on-chip, animal models) through a collaborative network that promotes the sharing, standardization, and application of these models across Europe. In contrast, CINNAMON is specifically dedicated to CAR-T cell therapy, aiming to standardize and expand its capabilities across European centres. CINNAMON emphasizes comprehensive training for scientists and clinicians, particularly in ITC and NNC, to ensure equitable access to CAR-T therapies and streamline regulatory processes for integrating new protocols into clinical practice. This focused approach seeks to directly impact clinical outcomes and healthcare systems by advancing CAR-T cell technology and its application.

2.2. ADDED VALUE OF NETWORKING IN IMPACT

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

To address the critical challenge of expanding and standardizing CAR-T cell therapy across Europe, the Action is designed to secure the necessary critical mass, expertise, and geographical balance. This wide network will ensure that the objectives of CINNAMON are achieved effectively and equitably. The Action comprises a diverse array of stakeholders, including leading academic institutions, hospitals, research centres, SMEs, large enterprise and patient organizations. Key participants include centres of excellence in Western Europe, which have advanced CAR-T programs and significant experience in clinical application and manufacturing. Additionally, emerging centres in COST Inclusiveness Target Countries (ITC) will be integral members, ensuring that expertise and capabilities are spread across the continent. The Action is also designed to ensure representation and participation from COST Near Neighbour Countries (NNCs) and Third States (IPC) in order to foster broader collaboration and share knowledge and expertise beyond Europe, thereby enhancing the global impact of our efforts. Furthermore, the Action includes investigators, clinicians, representatives from patient associations and biotech companies, this secures the critical mass and diversity of input required for the implementation of the aims of this Action. However, to further reinforce this critical mass, the network will be open to all experts with interest in the field and from all regions of Europe and outside Europe.. In the short term, the inclusion of more patient associations from different European regions, EU and national regulatory agencies (e.g. EMA, AEMPS, AIFA), and international (non-European) partners will be pursued. The recruitment of new members will be an important task of this Action, with a focus on ensuring geographic, age, and gender balance. Special emphasis will be placed on enrolling YRI at early and mid-stages of their scientific careers. Additionally, the Action will leverage the resources and expertise provided by key European research infrastructures and platforms such as **ECRIN** (European Clinical Research Infrastructure Network), **ELIXIR** (European Life Sciences Infrastructure for Biological Information), **BBMRI** (Biobanking and BioMolecular Resources Research Infrastructure) and **EATRIS** (European Infrastructure for Translational Medicine). These infrastructures offer valuable resources in clinical trial support, data management, biobanking and translational research, which will enable the Action to accelerate clinical development, enhance cross-border collaboration, and ensure the robust standardization of CAR-T cell therapy across Europe.

2.2.2. INVOLVEMENT OF STAKEHOLDERS

Different stakeholder groups can participate and benefit from CINNAMON activities as well as to contribute to the long-term sustainability of the network. The following groups, with specific roles, have been identified:

Patient advocacy groups and **patients**. Role: Patient advocacy groups represent the interests of patients and their families. They provide valuable input on regulatory guidelines and educational materials and advocate for patient-centric policies. Involvement plan: (1) Participation in advisory boards; (2) Invited participation to the annual Action meetings; (3) Patients' input on educational materials and outreach events.

Academic researchers. Role: Academic researchers are involved in all stages of development, from preclinical development and testing to clinical trials. Potential target fields of research are, but not limited, to molecular and cell biology, immunology, bioinformatics, biotechnology, and bioengineering. Their roles will include conducting literature reviews, developing standard operating procedures (SOPs) for manufacturing and quality control, and developing preclinical testing guidelines. Involvement plan: (1) Definition of a joint research agenda; (2) Participation in expert meetings; (3) Being part of consortiums to submit proposals for funding acquisition and collaborating on new research projects.

Clinicians. Role: Clinicians, including medical doctors and nurses, are involved in the clinical management of patients receiving CAR-T therapies. Their roles will include conducting literature reviews on clinical trials and develop clinical management guidelines, advocate for market access, distribute educational materials and engage with patients during outreach events. Involvement plan:
(1) Participation in expert meetings; (2) Being part of consortiums to submit proposals for funding acquisition and collaborating on new research projects; (3) Interact with regulatory bodies.

SME. Role: SMEs provide essential technological support and innovations for CAR-T therapy development. Involvement plan: (1) Collaborate with academic researchers and clinicians in research projects; (2) Contribute to the manufacturing of CAR-T cells and scale-up processes.

Regulatory bodies. Role: Regulatory bodies will ensure that protocols meet regulatory standards. Involvement plan: (1) Participation in expert meetings; (2) Provide guidance on regulatory frameworks;
(3) Collaborate on developing common guidelines.

Healthcare authorities. Role: Healthcare authorities are crucial enablers for implementing CAR-T therapies into the clinics. They will set healthcare policies and strategic agendas. Involvement plan: (1) CINNAMON will develop tailored dissemination material targeting healthcare authorities; (2) Invited participation to key Action meetings.

Communications experts. Role: Communication experts are responsible for developing educational materials and organizing outreach events to raise public awareness about CAR-T therapies. Creating public awareness is a top priority of this Action, as effectively communicating the benefits and potential of CAR-T therapies is critical for fostering understanding and support among the general public. Involvement plan: (1) Collaborate with patient advocacy groups to ensure messages are patient- centric, which involves crafting tailored educational content that resonates with diverse audiences, including patients, families, and the wider community; (2) Participate in communication and dissemination actions.

Young researchers and innovators. Role: YRI are the future leaders in CAR-T therapy field. They bring fresh perspectives and innovative ideas to CAR-T therapy development. They are essential for driving forward new research and innovation initiatives and embracing cutting-edge technologies. Their roles will include data collection and analysis, contributing to the writing and publication of research papers and performing laboratory experiments. Involvement plan: (1) Participation in training programs, workshops, STSM and mentorship opportunities with experienced researchers; (2) Involvement in collaborative research projects; (3) Active participation in conferences and symposiums to present their findings.

3. IMPACT

3.1. IMPACT TO SCIENCE, SOCIETY AND COMPETITIVENESS, AND POTENTIAL FOR INNOVATION/BREAKTHROUGHS

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

Scientific Impact. The collaborative network will have profound scientific implications, driving innovation and knowledge sharing in CAR-T cell therapy.

Short-term Impact

- **Promotion of collaborative research:** Establishing joint R&D initiatives and academic clinical trials that enhance cooperation among network centres.
- **Innovation in CAR design:** Incorporating emerging technologies for gene editing, leading to

improved efficacy and safety of CAR-T cells.

- **Enhanced understanding of T-cell biology:** Pooling resources and expertise to investigate mechanisms of T-cell exhaustion, persistence, and function.
- **Development of standardized protocols:** Implementation of standardized protocols for CAR-T cell manufacturing and quality control, which will improve research reliability and reproducibility.
- **Training programs:** Initiating training programs for scientists and clinicians to develop a skilled workforce in CAR-T research and clinical applications.
- **Research publications:** Publication of multiple scientific research and review papers stemming from the activities of WG 1–4.

Long-term Impact

- **Major scientific breakthroughs:** Continued collaborative efforts are likely to yield significant advancements in CAR-T therapy, expanding its application to solid tumours and autoimmune diseases.
- **Improved therapeutic strategies:** A deeper understanding of T-cell biology will lead to the development of more effective therapeutic strategies.
- **Sustainable research ecosystem:** Establishing a long-lasting ecosystem for CAR-T research that encourages ongoing innovation and improvement.
- **Next generation of experts:** Opportunities for young researchers will ensure a robust future generation of CAR-T specialists.

Technological Impact. The technological advancements facilitated by this network will significantly enhance CAR-T manufacturing processes and infrastructure.

Short-term Impact

- **Funding acquisition for infrastructure:** The Action will elaborate collaborative sustainability strategies for the development of infrastructure, together with the financial contribution from healthcare authorities.
- **Point-of-Care (PoC) manufacturing:** Initial advancements in PoC manufacturing capabilities will decentralize CAR-T production and reduce reliance on centralized facilities.
- **Improved local facilities:** Enhancements to existing facilities and establishment of new ones in hospitals and academic institutions to support CAR-T cell production.
- **Investment in essential equipment:** Upgrades in bioreactors, clean rooms, and other critical equipment to ensure high-quality production of CAR-T cells.

Long-term Impact

- **Decentralized manufacturing:** Widespread decentralization of CAR-T manufacturing, leading to reduced production costs and improved patient access.
- **Sustainable infrastructure:** Development of a network of PoC manufacturing facilities across Europe, enabling local production to meet patient demand.

Socioeconomic Impact. The economic implications of this initiative are substantial, with a focus on reducing costs and improving patient access to CAR-T therapies.

Short-term Impact

- **Reduction in healthcare costs:** CAR-T therapy can replace years of expensive chemotherapy for patients with relapsed or refractory B-cell malignancies, significantly reducing overall healthcare expenditures.
- **Cost-effective manufacturing models:** Non-profit academic institutions demonstrating the ability to manufacture CAR-T products at a significantly lower cost compared to for-profit pharmaceutical companies.
- **Strengthened interaction with biotech companies:** Enhanced innovation in CAR-T manufacturing processes, logistics, and delivery systems.

Long-term Impacts

- **Affordability of CAR-T therapies:** Establishing a network focused on PoC CAR-T manufacturing will enhance the affordability of therapies, ultimately making them accessible to more patients.
- **Reduction of health inequalities:** By improving access to CAR-T therapies across Europe, the network will help to reduce disparities in healthcare.
- **Increased treatment accessibility across borders:** When regulatory frameworks are aligned across multiple jurisdictions, approved CAR-T therapies can more easily be marketed and distributed across different regions. This improves patient access to these treatments, even in smaller or less-developed healthcare markets.
- **Improved patient safety and health outcomes:** Standardized clinical guidelines will enhance

patient safety by providing clear recommendations for patient selection, administration protocols, monitoring, and management of adverse effects and enhance the delivery of care, offering clinicians evidence-based recommendations that support decision-making. Enhanced CAR-T cell therapy expertise will lead to better cancer treatment outcomes, including faster treatment for critically ill patients and higher survival rates.

3.2. MEASURES TO MAXIMISE IMPACT

3.2.1. KNOWLEDGE CREATION, TRANSFER OF KNOWLEDGE AND CAREER DEVELOPMENT

Creation of knowledge: CINNAMON will advance knowledge by formulating a joint research agenda and synchronizing diverse research activities in various areas of CAR-T cell therapy, including CAR design, innovative gene transfer technologies, and manufacturing processes. CINNAMON will foster cooperation among stakeholders from academic, clinical, industrial, and regulatory sectors to expedite the clinical translation process. Additionally, various tasks are aimed at generating articles and other academic outputs such as conference presentation and guidelines. The Action will also support open-access publications and datasets by allocating specific funds for this purpose, ensuring that the research findings are widely accessible and can further drive advancements in the field. ***Impact metrics***: ≥4 reviews published, ≥4 protocols or clinical guidelines, ≥20 citations per publication, ≥10 conference presentations, ≥3 types of educational materials. **Transfer of knowledge**: CINNAMON will facilitate knowledge transfer by establishing a collaborative environment where participants can share their expertise. Additionally, knowledge will be shared from experienced researchers through various activities such as short-term scientific missions (STSMs), meetings, training schools, and workshops. This exchange will occur between countries with varying levels of research intensity, collaborating biotech companies, and through engagement with stakeholders, patient associations, and healthcare professionals. ***Impact metrics***: ≥8 workshops, ≥4 training schools, ≥30 STSMs. **Career development**: CINNAMON will create a Working Group on "training and dissemination", with the specific aim of supporting the career development of participating young and established researchers and clinicians by fostering the acquisition of knowledge, research-based training, and transferable skills. This will be achieved by short-term scientific missions (STSMs), attendance to conferences, and participation in Action meetings and training schools. Moreover, CINNAMON will design and launch a mentorship program for YRI, including meetings with senior experts together with clinical and laboratory trainings and workshops on regulatory requirements for CAR-T therapies, advanced gene editing techniques in CAR-T development, good manufacturing practices, etc. Additionally, the Action will promote gender equality by fostering the participation and leadership of women. ***Impact metrics***: ≥20 mentorships established.

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

A Science Communication Plan including an appropriate Communication, Dissemination and Exploitation strategy will be developed by WG6 and approved by the Management Committee (MC) within the first six months of the Action. It will be reviewed annually by the MC to ensure its alignment with the Action's objectives and to incorporate any necessary amendments based on the progress and developments in the field. **Dissemination**: The Action will follow the principles of **Open Science** and **Open Access** in dissemination. The goals are to increase awareness of CAR-T cell therapies, foster engagement and dialogue with key stakeholders, and inform and influence policy and clinical practice. The dissemination formats include review articles, clinical guidelines, and other tailored materials. Events such as conferences, symposiums, workshops, training schools will be organized. Online platforms like the CINNAMON website together with webinars will be utilized. **Exploitation plan**: The Action will seek the **valorisation of its results,** with the support from the Technology Transfer Offices of the involved institutions. *Exploitation for further use:* Training materials developed within CINNAMON (guidelines, best practices documents, etc) will be used by healthcare providers to improve patient care. Policy makers will be provided with evidence-based recommendations to inform healthcare policy decisions. *Commercial exploitation:* To maintain a balance between medical and social usefulness and financial profitability, the Action will work with a multidisciplinary team, including health economists, social scientists, technological developers and ethicists, to evaluate the broader impact of commercial applications. This will help ensure that while economic viability and commercial exploitation is considered, the primary focus remains on enhancing public health and patient care. In case new products or services are generated, an exploitation agreement will be set-up among the concerned members. Incubators and innovation hubs will be engaged to provide additional expertise in scaling up

relevant solutions and accelerating the translation of research outcomes into real-world clinical applications. Collaboration with biotech companies will aim to translate research findings into commercial applications. Collaborative partnerships and licensing agreements will facilitate the future transfer of technology to other organizations. **Dialogue with the general public or policy**: The Action will prioritize the dissemination of public health information directed to general public in formats that are easy to understand for all audiences to effectively communicate the benefits of CAR-T therapy to the public. Visual content such as infographics and video explainers, brochures, posters as well as interactive formats such as Q&A sessions, public webinars tailored to diverse communities, and publications in social media such as X, LinkedIn will maximize public awareness. Materials will be translated into multiple languages, considering different literacy levels, and collaborations with experts in public communication will ensure that messaging is accessible and impactful, especially to non-specialist audiences.

4. IMPLEMENTATION

4.1. COHERENCE AND EFFECTIVENESS OF THE WORK PLAN

4.1.1. DESCRIPTION OF WORKING GROUPS, TASKS AND ACTIVITIES

During the kick-off meeting the Management Committee (MC) will be instituted and will address the election of representatives to key leadership roles: Action Chair, Action Vice Chair, Grant Holder Scientific Representative; and if possible, as well at that meeting, Working Group Leaders and Working Group Vice Leaders, Grant Awarding Coordinator, Science Communication Coordinator, Gender equality coordinator and STSM Coordinator. At the first Action MC meeting additional committees will be created: The Training Committee (TC), Dissemination and Website Committee (DWC) and Ethics Committee.

The Management Committee (MC) will be responsible for oversee the coordination and management of the Action, define an annual joint research agenda, create and update a General Plan for the implementation of Action activities, define and update the stakeholder engagement plan.
The MC will aim for a diversity target that includes: 50% of members ITC to ensure geographic diversity, 25% representation by YRI to promote age inclusivity, 50% male/female membership to achieve gender balance. The MC members will follow the principles of good governance, financial soundness and efficiency, and will enact transparent decision-making and conflict resolution processes.
The MC will meet annually and will be responsible for direct and daily business of the Action. The committees will submit annual reports to the MC to monitor and ensure progress in line with the Action objectives. Working Groups will report directly to the MC. The number of members within the WGs will not be restricted, and targeted recruitment of new members will be pursued. The work plan will be structured in 6 Working groups (WG) that are designed to operate within and achieve the Research Coordination Objectives (see section 1.2.2.1) and Capacity-building Objectives (see section 1.2.2.2) of the Action as follows:

Research Coordination Objectives	
RCO1. To set up a collaborative network of centres	MC, all WGs
RCO2. To establish common manufacturing and quality control standards	WG1
RCO3. To promote collaboration on addressing manufacturing challenges	WG1
RCO4. To promote joint development of novel CAR-T cell therapies	WG2
RCO5. To develop common guidelines for regulatory approval	WG3
RCO6. To facilitate clinical data sharing and collaborative research	WG4
Capacity-building Objectives	
CBO1. To enhance collaborative research infrastructure and resource access	WG1
CBO2. To promote public awareness and patient engagement	WG5
CBO3. To promote knowledge exchange and training	WG6
CBO4. To encourage young researchers and innovators participation	WG6

The specific objectives and detailed tasks, activities, milestones and stakeholders involved for each WG is detailed as follows:

WG1: Manufacturing, scale-up, standardization and quality control (M1 – M36)
Objectives: (O1.1) To develop and implement standardized protocols for CAR-T cell manufacturing across network centres; **(O1.2)** To stablish a common quality control protocol; **(O1.3)** To address challenges in manufacturing scale-up; **(O1.4)** To build new collaborative projects on addressing manufacturing hurdles.
Tasks: (T1.1) Literature review on current CAR-T cell manufacturing and quality control processes and manuscript preparation; **(T1.2)** Develop and update Standard Operating Procedures (SOPs) guideline document for production, quality control (QC) and release; **(T1.3)** Establish sustainability strategies.
Activities: (A1.1) Expert meeting to review T1.2 output and agree on the guideline document and follow-up meetings to refine and update protocols based on feedback; **(A1.2)** Networking meetings to establish sustainability strategies focused on scalability and affordability; **(A1.3)** Training school on cell manufacturing; **(A1.4)** Annual WG meetings to review progress, share insights, and plan future research directions.
Milestones: (M1.1) collaborative strategies focused on manufacturing prepared(M24); **(M1.2)** Adoption of standardized manufacturing and quality control protocols by at least 60% of network centres (M36); **(M1.3)** Launch I of new collaborative initiatives (M36).
Stakeholders involved: Academic researchers, SME, Regulatory bodies, Healthcare providers
WG2: Preclinical development of novel CAR-T therapies (M1 – M36)
Objectives: (O2.1) To promote the development of next-generation CAR-T cell therapies targeting various cancers and pathologies; **(O2.2)** To incorporate emerging technologies to enhance CAR-T cell efficacy and safety; **(O2.3)** To initiate new collaboration to develop novel CAR-T therapies.
Tasks: (T2.1) Literature review on next-generation CAR-T cell therapies and emerging technologies and manuscript preparation; **(T2.2)** Develop guidelines for preclinical testing of CAR-T cell therapies; **(T2.3)** Establish a sustainability strategies .
Activities: (A2.1) Expert meeting to review T2.2 output and agree on the guideline document. **(A2.2)** Networking meetings to establish sustainability strategies to develop novel CAR-T cell therapies; **(A2.3)** Training school on recent advances in CAR-T; **(A2.4)** Annual working group meetings to review progress, share insights, and plan future research directions.
Milestones: (M2.1) new collaborative strategies focused on developing novel CAR-T cell therapies submitted (M24); **(M2.2)** Launch of new collaborative initiatives (M36).
Stakeholders involved: Academic researchers, clinicians, Biotech companies
WG3: Regulatory affairs and market access (M1 – M48)
Objectives: (O3.1) To develop common guidelines for regulatory approval; **(O3.2)** To facilitate market access and ensure equitable availability of CAR-T therapies.
Tasks: (T3.1) Literature review on current regulatory frameworks and approval processes for CAR-T therapies across Europe and manuscript preparation; **(T3.2)** Develop and update a comprehensive set of common guidelines for regulatory approval in collaboration with regulatory experts; **(T3.3)** Conduct a market analysis to identify barriers to market access and propose solutions to ensure equitable availability of CAR-T therapies; **(T3.4)** Engage with healthcare providers and policymakers to advocate for the inclusion of CAR-T therapies in national healthcare systems.
Activities: (A3.1) Expert meeting to discuss and review T3.2 output and finalize the guideline document; **(A3.2)** Expert meeting to discuss and review T3.3 output and finalize the analysis report; **(A3.3)** Workshops with regulatory bodies to discuss and refine common guidelines; **(A3.4)** Organize policy forums to discuss fair pricing strategies and reimbursement policies; **(A3.5)** Annual working group meetings to review progress, share insights, and plan future research directions.
Milestones: (M3.1) Publication and update of common guidelines for regulatory approval (M24, M48); **(M3.2)** Completion of the market analysis report identifying barriers to market access (M30).
Stakeholders involved: Regulatory bodies, Healthcare authorities, Patient advocacy groups, Clinicians, Biotech companies
WG4: Clinical research (M1 – M48)
Objectives: (O4.1) To promote collaborative clinical research to enhance CAR-T cell therapy outcomes, including the identification of robust biomarkers that predict efficacy and toxicity; **(O4.2)** To facilitate clinical data sharing through databases, meetings, conferences, and workshops to improve understanding of patient variability and clinical outcomes.

Tasks: (T4.1) Literature review on current clinical trials in CAR-T therapy focusing on patient outcomes, biomarker applications, and associated risks, and manuscript preparation; **(T4.2)** Develop a document for clinical management and best practices, emphasizing the integration of biomarkers to improve patient stratification and therapy outcomes; **(T4.3)** Data sharing on clinical trials and patient outcomes.
Activities: (A4.1) Expert meeting to discuss and review T4.2 output and finalize the clinical management guidelines; **(A4.2)** Workshops for clinicians training on best practices; **(A4.3)** Expert meetings to share data and trial updates and coordinate research efforts; **(A4.5)** Annual working group meetings to review progress, share insights, and plan future research directions.
Milestones: (M4.1) Consensus document on clinical guidelines and best practices (M24); **(M4.2)** Identification of candidate biomarkers (M36); **(M4.3)** 50% of CINNAMON partners using >5 open databases (M36).
Stakeholders involved: Clinicians, Regulatory bodies, Patients, Healthcare authorities
WG5: Public awareness and patient engagement (M1 – M48)
Objectives: (O5.1) To increase public understanding and awareness of CAR-T cell therapies; **(O5.2)** To involve patients and advocacy groups in the research and development process.
Tasks: (T5.1) Development of educational material (brochures, posters, and online content) explaining CAR-T therapy; **(T5.2)** Distribute materials through hospitals, clinics and online platforms; **(T5.3)** Set up a patient advisory board to provide input on research priorities and clinical trial design.
Activities: (A5.1) Organize annual outreach events in various European countries to educate the public and gather feedback; **(A5.2)** Hold annual meetings with the advisory board to discuss progress and incorporate patient feedback; **(A5.3)** Annual working group meetings to review progress, share insights, and plan future research directions.
Milestones: (M5.1) Development and update of dissemination materials (M12, M48); **(M5.2)** Establishment of the patient advisory board (M12); **(M5.3)** First outreach event (M18).
Stakeholders involved: Clinicians, Healthcare providers, Patient advocacy groups, Patients, Communications experts
WG6: Training and dissemination (M1 – M48)
Objectives: (O6.1) To promote knowledge exchange and training among researchers, clinicians and stakeholders involved in CAR-T cell therapy; **(O6.2)** To ensure YRI participation and involvement **(O6.3)** To disseminate the Action activities and results.
Tasks: (T6.1) Recruitment of new members; **(T6.2)** Website development and maintenance; **(T6.3)** Develop a Science Communication Plan; **(T6.4)** Develop and implement the final plan for training; **(T6.5)** Create a mentorship programme for YRI.
Activities: (A6.1) Propose to the MC some activities and disseminate training schools, workshops, networking meetings, STSM program and conferences; **(A6.2)** Share insights, and plan future research directions.
Milestones: (M6.1) Launch the website (M6); **(M6.2)** First event scheduled (M9); **(M6.3)** Launch the mentorship program for YRI (M18).
Stakeholders involved: All

4.1.2. DESCRIPTION OF DELIVERABLES AND TIMEFRAME

WG	Deliverable (Date)
MC	**D0.1** Stakeholder engagement plan (M6)
1	**D1.1** Review paper on CAR-T cell manufacturing and quality control processes (M18); **D1.2** Standard Operating Procedures (SOPs) document (M24); **D1.3** Summary reports from each meeting/event (M12, M24, M36)
2	**D2.1** Review paper on next-generation CAR-T cell therapies and emerging technologies (M18); **D2.2** Guideline document for preclinical testing of CAR-T cell therapies (M24); **D2.3** Summary reports from each meeting/event (M12, M24, M36)
3	**D3.1** Review paper on regulatory frameworks (M18); **D3.2** Guideline document for regulatory approval (M24, M48); **D3.3** Summary reports from each meeting/event (M24, M36, M48); **D3.4** Market analysis report (M30)
4	**D4.1** Summary reports from each meeting/event (M12, M24, M36, M48); **D4.2** Review paper on ongoing clinical trials (M24); **D4.3** Clinical management guidelines (M24, M48).
5	**D5.1** Educational materials (M12, M24, M36, M48); **D5.2** List of participants in the patient advisory board (M12); **D5.3** Summary reports from each meeting/event (M18, M36, M48)

6	**D6.1** Website (M6); **D6.2** Science Communication Plan and possible updates (M6, M24, M48); **D6.3** Training plan and possible updates (M6, M24, M48); **D6.4** List of new members (M12, M24, M36 M48); **D6.5** Mentorship program structure and participant list (M18, M36, M48); **D6.6** Summary reports from each meeting/event (M24, M36, M48)

4.1.3. RISK ANALYSIS AND CONTINGENCY PLANS

WG	Description of risk [(i) likelihood, (ii) severity: Low/Medium/High]	Contingency plan
1	Delays in developing and adopting standardized protocols [M, H]	Set up a team to monitor progress, ensure regular updates, and facilitate communication among centres. Introduce interim deadlines to keep the project on track
3	Heterogeneous feedback from regulatory agencies and complex regulatory pathways [H, H]	Regular consultation meetings with key regulatory stakeholders can facilitate open dialogue and clarify expectations. Implementing a feedback loop mechanism will allow for the systematic collection and analysis of feedback from different regulatory bodies, helping to identify common themes and discrepancies
1, 2	Difficulty in establishing new research consortium [L, M]	Proactively reach out to potential partners and stakeholders. Organize networking events to foster collaboration and partnership opportunities
3	Investment resistance from healthcare authorities and policymakers [M, H]	Initiate advocacy and awareness campaigns. Provide evidence-based data to highlight the benefits of CAR-T therapies. Establish a liaison team from WG3–5 to maintain continuous dialogue with stakeholders. Involve communication experts
4	Limited participation of certain stakeholders in events [L, H]	Promote the participation through targeted communication and invitations. Ensure events are well-structured to maximise value and relevance for participants. Develop targeted training materials tailored for different stakeholders
5	Difficulty in establishing a patient advisory board [L, M]	Engage with existing patient advocacy groups to identify potential board members. Offer clear roles, responsibilities and benefits to attract participants
6	Low participation in training and mentorship programs [L, M]	Promote the benefits of these programs through various channels. Provide incentives and recognition for participation

4.1.4. GANTT DIAGRAM

Quartile / Month	Year 1				Year 2				Year 3				Year 4			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
	3	6	9	12	15	18	21	24	27	30	33	36	39	40	43	48
WG1: Manufacturing, scale-up, standardization and quality control																
T1.1 Literature review on current CAR-T cell manufacturing and QC processes and manuscript preparation						D1.1										
T1.2 Develop and update SOPs guideline document for production, QC and release								D1.2				M1.2				
T1.3 Establish sustainability strategies				D1.3				D1.3 M1.1				D1.3 M1.3				
WG2: Preclinical development of novel CAR-T therapies																
T2.1 Literature review on next-generation CAR-T cell therapies and emerging technologies and manuscript preparation						D2.1										
T2.2 Develop guidelines for preclinical testing of CAR-T cell therapies								D2.2								
T2.3 Establish sustainability strategies				D2.3				D2.3 M2.1				D2.3 M2.2				
WG3: Regulatory affairs and market access																
T3.1 Literature review on current regulatory frameworks and approval processes for CAR-T therapies across Europe and manuscript preparation						D3.1										
T3.2 Develop a comprehensive set of common guidelines for regulatory approval in collaboration with regulatory experts								D3.2 M3.1								D3.2 M3.1
T3.3 Conduct a market analysis to identify barriers to market access and propose solutions to ensure equitable availability of CAR-T therapies										D3.4 M3.2						
T3.4 Engage with healthcare providers and policymakers to advocate for the inclusion of CAR-T therapies in national healthcare systems								D3.3				D3.3				D3.3
WG4: Clinical research																
T4.1 Literature review on current clinical trials in CAR-T therapy focusing on patient outcomes, biomarker applications, and associated risks, and manuscript preparation								D4.2				M4.2				
T4.2 Develop a document for clinical management and best practices, emphasizing the integration of biomarkers to improve patient stratification and therapy outcomes								D4.3 M4.1								D4.3
T4.3 Data sharing on clinical trials and patient outcomes				D4.1				D4.1				D4.1 M4.3				D4.1

WG5: Public awareness and patient engagement																
T5.1 Development of educational material (brochures, posters, and online content) explaining CAR-T therapy				D5.1 M5.1				D5.1				D5.1				D5.1 M5.1
T5.2 Distribute materials through hospitals, clinics and online platforms						D5.3 M5.3						D5.3				D5.3
T5.3 Set up a patient advisory board to provide input on research priorities and clinical trial design				D5.2 M5.2												
WG6: Training and dissemination																
T6.1 Recruitment of new members				D6.4				D6.4				D6.4				D6.4
T6.2 Website development and maintenance		D6.1 M6.1														
T6.3 Develop a Science Communication Plan		D6.2						D6.2								D6.2
T6.4 Develop and implement the final plan for training		D6.3	M6.2					D6.3 D6.6				D6.6				D6.3 D6.6
T6.5 Establish a mentorship programme for YRI						D6.5 M6.3						D6.5				D6.5

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