Deliverable D6.5
Initial common work plan for scientific collaboration under the 'Diagnosis and treatment' cluster

Diagnosis & Treatment Cluster

Summary

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Abbreviations

D	Deliverable
DMP	Data Management Plan
DTC	Diagnosis and Treatment Cluster
PCT	Pragmatic Clinical Trial
WG	Working Group

1. Introduction

1.1. Horizon Europe - Mission Cancer[1]

According to Europe's Beating Cancer Plan, the Horizon Europe Cancer Mission has set an important goal: to improve the lives of more than 3 million people by 2030. Its overall goal is to address the need not only to prevent and treat cancer, but also to improve the quality of life of those affected by the disease and their families.

The overview shows the huge social impact of cancer, with 2.7 million people diagnosed with cancer and 1.3 million dying from the disease every year. Factors contributing to this increased burden include ageing populations, poor lifestyles and the impact of the COVID-19 pandemic. In particular, the pandemic affected the basic functions of the fight against cancer, causing delays in treatment and an increase in cancer diagnoses and deaths in the coming years.

In this context, the healthcare system in Europe is under a great economic burden: cancer costs were estimated at €199 billion in 2018. The EU Beating Cancer Plan highlights the need for a coordinated approach to research and policy development in Europe. It underlines the urgent need to standardise and streamline processes to ensure that everyone, regardless of their circumstances, has equal access to effective cancer treatment.

Constant dialogue and collaboration with patients and representative Associations, Member States, relevant stakeholders as healthcare and pharma companies and the citizens are the basis for creating new solutions.

By combining care, research, education and experience, the European Community aims to improve the overall quality of care and close existing gaps.

This Cluster “Diagnosis and Treatment”, representing a fundamental component of the Mission on Cancer, strategically connects projects funded under the Horizon Europe Funding Programme. Functioning as a collaborative hub, it will amplify the impact of individual projects by promoting synergy among consortia. Doing this, this Cluster will work to maximise the value of research investments through shared best practices, fostering collective learning, and accelerating progress in cancer diagnosis and treatment.

Fostering collaboration, knowledge exchange, and engagement with stakeholders will serve the European Community advancing the overarching goals of the Horizon Europe Mission on Cancer.

[1] https://research-and-innovation.ec.europa.eu/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-europe/eu-missions-horizon-europe/eu-mission-cancer_en

1.2. Pragmatic clinical trials to optimise treatments for patients with refractory cancers (HORIZON-MISS-2022-CANCER-01-03)[2]

Recognizing the imperative for more effective and patient-centred interventions, particularly in the context of a complex and fragmented oncology healthcare system, the Horizon Europe call-for-funding that enabled the creation of this Cluster "Diagnosis and Treatment" places pragmatic clinical trials (PCTs) at the forefront of innovation and progress.

The text underscores that PCTs offer a unique avenue to evaluate real-world effectiveness, addressing the need for different clinical trial designs with fewer inclusion and exclusion criteria. By focusing on care options and assessing the impact of treatments in routine clinical practice, PCTs are positioned as powerful tools to drive better and more affordable solutions, ensuring wider accessibility across EU regions, Member States, and Associated Countries. Projects funded under this call are specifically tasked with designing and conducting randomised or cluster-randomised academic investigator-initiated pragmatic clinical trials. These trials are expected to deliver not only effective and evidence-based treatment interventions but also to adapt these interventions to the diverse needs of the target population and the specificities of care provision at local, regional, or national levels. Moreover, the call places a premium on the affordability and accessibility of chosen treatment interventions, underlining the importance of justifying these choices based on robust evidence. The primary and secondary endpoints of the pragmatic clinical trials are directed towards overall survival, patient-preferred clinical benefit, patient-reported outcomes, and quality of life – all of which are defined in collaboration with patients and their caregivers.

The trials aim to provide practical solutions to the needs of patients with difficult-to-treat cancer, contributing to the overall goal of effective cancer treatment and becoming more accessible and affordable across Europe.

2. Diagnosis and Treatment Cluster composition

2.1. Overview of the projects involved

CARE1

In 2020, Europe saw over 138,000 new cases of clear cell renal carcinoma, the most common form of kidney cancer, resulting in 50,000 deaths (source: GLOBOCAN). To define research priorities in academia and launch dedicated clinical trials for this tumor, European oncologists have joined forces under the CARE group. This consortium brings together 14 partners, including four from Cancer Core Europe, representing 8 European countries (France, Germany, Spain, the Netherlands, Italy, Austria, the Czech Republic, and the United Kingdom). CARE1 also includes two patient associations.

Its goal is to assist oncologists in selecting the best treatment combination for each patient. Focused on pragmatic clinical trials, it aims to improve the first-line treatment for patients with metastatic kidney cancer by implementing a routine biomarker, leveraging a unique academic network in Europe.

The treatment of clear cell renal carcinoma relies on a combination of two classes of agents: anti-angiogenic targeted therapy (VEGFR TKI - vascular endothelial growth factor receptor tyrosine kinase inhibitor) and immunotherapy (immune checkpoint inhibitors targeting PD-1/PD-L1 or CTLA-4). However, there has been

[2] https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/horizon-miss-2022-cancer-01-03

no direct comparison between these two approaches as first-line treatments, and patients have been treated based on the physician's decision, without clinical or biological factors guiding the treatment choice.

CARE1 was designed to determine the optimal combination for patients using a routine implementable biomarker. This prospective randomized phase III study aims to recruit 1,250 treatment-naive patients with clear cell metastatic renal carcinoma from 8 European countries to compare the combination of two immunotherapies versus the combination of targeted therapy + immunotherapy, based on the tumor's PD-L1 status. PD-L1 status for each patient is determined through immunohistochemistry conducted by the pathology laboratory at the patient's treatment center. If the tumor expresses the PD-L1 marker, it's PD-L1+, otherwise, it's PD-L1-. The primary endpoint of the study is overall survival in the PD-L1+ population, with a co-primary endpoint of overall survival and progression-free survival in the PD-L1- population.

CARE1 will establish a large-scale platform to define the best standard of treatment based on a routine biomarker to enhance treatment efficacy.

In the long term, a data collection effort, including the creation of a pathological and blood biobank, will be conducted on a European scale.

Website: https://www.gustaveroussy.fr/en/care1-european-study-first-line-treatment-metastatic-kidney-cancer

DE-ESCALATE

Prostate Cancer is the most common cancer in European men. Despite dramatic improvements in early diagnostic and local treatment, one out of five prostate cancer patients will die from their disease. Despite progress in the past years, it remains critical to improve on the present strategy for advanced and metastatic prostate cancer. Within the proposed project, we will evaluate whether intermittent intensified androgen deprivation treatment (iADT) in prostate cancer is not inferior to continuous treatment in terms of oncological benefit while minimizing side effects and resource utilization and improving patient quality of life. The proposed clinical trial is designed to detect early if iADT has a negative impact on overall survival compared to continuous therapy. If successful, the outcomes of the project will define a new evidence-based standard of care for metastatic hormone sensitive prostate cancer. The proposed research could lead to improved patient survival and quality of life but also improve health system sustainability. This is a multidisciplinary and multistakeholder consortium involving clinical oncologists, surgeons, health economists and patient representatives. The study design was successfully discussed with patients.

The DE-ESCALATE consortium is composed by six partners: the European Organisation for Research and Treatment of Cancer (project coordinator and legal sponsor of the clinical trial), the Syreon Research Institute (Health Economics and communication), the Spanish Oncology GenitoUrinary Group (clinical research group), Cancer Trials Ireland (clinical research group), Unicancer (clinical research group) and Europa Uomo (patient organisation). In addition, 80 clinical sites from eight countries will join the study.

Website: https://deescalate-horizon.eu/

IMPACT- AML

In IMPACT-AML, a multidisciplinar R/R AML represents a model of high-impact disease, in which no standard of care exists, and where we have an urgent need for new evidence on possible therapies; AML offers the setting in which methodological innovation will combine powerful instruments of clinical trials with personalized medicine through academic efforts. Hereby, we propose to create an inclusive master framework for relapsed or refractory acute myeloid leukemia (STREAM) to include patients with R/R AML across Europe proficiently acquire an unselected population for clinical trials and

monitor outcomes including neglected cohorts. Thereafter, we will conduct a prospective randomized pragmatic clinical trial (RPCT) that will compare the classical "high intensity" rescue chemotherapy with biology-driven, "low intensity" rescue to obtain "real world" data on the benefit of one of the two different strategies in term of survival also considering patients and caregivers preferences, patient-reported outcomes (PRO), accessibility, affordability, and social cost.

RPCT will aim to evaluate the effectiveness of real-world clinical alternatives in routine care. In addition to retaining the high internal validity of traditional randomized trials, it will maximize external validity, i. e. generalizability of results to many settings. In this context, the inclusion of an RPCT in the master framework will allow a dynamic inclusion and the collection of the excluded population as an instrument to predict the real-life applicability of clinical trial results. We will offer Europe results from an ambitious project, that will go beyond the state of the art in R/R AML demonstrating the superiority of a strategy in a first-of-his-kind clinical trial, providing strong data that will be delivered to national health care providers, policymakers, and health authorities data on optimized and affordable treatment for R/R AML and promoting the implementation of the selected better option.

Website: https://impactaml.eu/

IMPORTANT

IMPORTANT study is a multicentred, open-label, prospective, randomized-controlled, non-inferiority trial with a pragmatic approach involving older patients (female and male ≥ 70 years old) with advanced hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer, not amenable for curative treatment and without prior therapy for advanced disease, who are suitable to receive CDK 4/6-inhibitors plus endocrine therapy as first line therapy. The study implements two approaches with high level of evidence, namely the use of comprehensive geriatric assessment (CGA) approach in treatment decision making and the use of CDK 4/6-inhibitors as the initial treatment of choice, to investigate whether a common clinical practice (starting dose reduction of CDK 4/6-inhibitors in older patients) with evidence of low certainty can be standardized using a more individualized-based approach.

On the basis of baseline CGA assessment, patients will either receive full dose of CDK 4/6-inhibitors plus endocrine therapy (if patients are fit according to CGA) or be randomized to full dose vs. reduced initial dose of CDK 4/6-inhibitors (if vulnerable or frail according to CGA). The study hypothesis is that adjusting the dose according to vulnerability will allow patients to tolerate treatment better without jeopardizing the treatment efficacy.

Aiming at implementing a pragmatic clinical study, the IMPORTANT consortium includes 19 organizations with 8 clinical sites in six European countries (Region Örebro County and Region Uppsala in Sweden, University Hospital Akershus in Norway, Helsinki University Hospital in Finland, Azienda USL Toscana Centro and University of Florence in Italy, Hospital Clinic of Barcelona in Spain and Hellenic Cooperative Oncology Group in Greece), and four from the cancer medical domain (Care Across, Institute for Medical Technology Assessment, Phaze Clinical Research & Pharma Consulting, and Swedish Breast Cancer Association).

The IMPORTANT study has been registered with clinicaltrials.gov with ID number NCT06044623.

Website: https://important-project.com/

IntReALL 2020

The IntReALL 2020 project addresses the treatment of children with relapsed acute lymphoblastic leukemia (ALL) in Europe. It includes 18 member states of the EU and 3 non-member countries (Israel, Switzerland and Norway). ALL is the most frequent malignancy of childhood and, with conventional combinatorial chemotherapies, can be cured in approximately 85% of the patients. However, about 15% of the patients suffer a relapse of the disease that is a relatively chemotherapy-resistant disease and requires much more intensive combination chemotherapy, including allogeneic hematopoietic stem-cell transplantation in roughly 2/3 of the patients. The previous experience of treatment of these patients enabled to stratify the risk of further relapse according to the timing of occurrence of the relapse, site of relapse, ALL immunephenotype and cytogenetic characteristics and to distinguish standard-risk, high-risk (HR) and very-high-risk (VHR) relapses. For patients with standard-risk and HR relapse of B-cell precursor (BCP)-ALL, a large randomized trial, IntReALL BCP 2020, will be set up with the aim to improve survival and reduce toxicity by replacing toxic chemotherapy elements with very promising targeted immunotherapeutic approaches. For patients with VHR features or those with T-ALL relapse, non-randomized, novel experimental treatment strategies will be developed and offered. For patients with refractory or subsequently relapsed disease, individualized treatment approaches or allocation to appropriate phase I/II trials with promising new compounds will be provided upon recommendation of a federated relapsed/refractory acute leukemia (FEDRRAL) expert board.

Website: https://intreall2020.eu/

LEGATO

Recurrent glioblastoma is an invariably fatal refractory cancer with dismal prognosis. Patients suffer from low quality of life and very burdensome symptoms. This project is proposing an investigator-initiated phase III randomised pragmatic clinical trial. We will assess whether the addition of radiation treatment to lomustine chemotherapy has superior efficacy as compared to lomustine chemotherapy alone for treatment of patients with recurrent glioblastoma. The study will apply minimal patient eligibility criteria, and thus be as close as possible to the routine clinical setting. Cost-effectiveness analysis will be performed to investigate the economic value of adding radiation treatment to lomustine chemotherapy in different countries to support evidence-informed policy decisions. If successful, the outcomes of the project will define a new evidence-based standard of care for recurrent glioblastoma. The proposed research could lead to improved patient survival and quality of life but also improving health system sustainability. This is a multidisciplinary and multistakeholder consortium involving clinical oncologists, radiation oncologists, health economists and patient representatives. The study design was successfully discussed with patients.

The consortium is composed by five partners: the European Organisation for Research and Treatment of Cancer (project coordinator and legal sponsor of the clinical trial), the Syreon Research Institute (Health Economics and communication), Medical University of Vienna (clinical lead), Sapienza University of Rome (clinical coleader), and Brainstrust (patient organisation). In addition, some 40 clinical sites from 10 countries will join the study.

Website: https://legato-horizon.eu/

LIVERATION

LIVERATION is an ambitious, pragmatic multicenter clinical trial in 7 different countries and 20 Hospitals to determine whether in liver surgery to resect cancer, additional ablation of tumor margin produced by scalpels that coagulate with radiofrequency can decrease the cancer recurrence rate and improve patient survival.

Radiofrequency is a high-frequency alternating polarity, where electrical current is applied to biological tissue with the intention to cut, coagulate, desiccate, or fulgurate tissue. Its benefits include the ability to make precise cuts with limited blood loss and its ability to deeply coagulate the tissue. Radiofrequency devices are frequently used during surgical operations helping to prevent blood loss in hospital operating rooms and their indications are being investigated and enlarged each year.

Colorectal Cancer (CRC) ranks fourth in cancer deaths worldwide. Between 20% and 30% of patients with advanced CRC have Liver Metastases. Liver cancer ranks second in cancer deaths worldwide, including hepatocellular carcinoma. Despite recent advances, liver resection offers the only chance of cure for patients with liver metastases and liver cancer.

However, the recurrence rate of these liver tumors is high even after resection. The presence of positive (with malignant cells) margins in the remaining liver after resection correlates with increased local recurrence and decreased overall survival. So this is the only factor where expectation of survival could be influenced by the performance of surgery.

Currently, there are radiofrequency ablation studies that, based on preliminary retrospective human clinical studies, able to correlate an additional coagulation of tumor margins with a reduction on local recurrence. However, there is no prospective and controlled or comparative trial that accurately measures this additional margin and its impact on oncological outcomes. We hope to confirm this expectation with Liveration.

The LIVERATION project is led and coordinated by surgeons from Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), experts on surgical ablative techniques for CRC and CRLM resection. The project is backed by the expertise in clinical trial development of the European Clinical Research Infrastructure Network (ECRIN) and its affiliated entities (specially the lead Clinical Trial Unit (CTU) Fundación para la Investigación Biomédica del Hospital Universitario La Paz), and complemented by the expertise on ablative medical devices from Vecmedical. The project statistical power is provided by the University of Ioanina (UOI), which will also collaborate with the Social Science entities focused on patient experiences evaluation or conducting systematic reviews, SHINE 2Europe (SHINE) and The Avedis Donabedian Research Institute (FAD). The project will also count on the expertise of the Society for the Improvement of Science (SACSIS), on Communication and Dissemination of the novelties and results of the LIVERATION project. Also, the European Liver Patients Association (ELPA) will reach the main stakeholders and policy makers.

Website: https://liveration.eu/

PragmaTIL

The Pragmatic approach to Adoptive Cell Therapy (ACT) using Tumor Infiltrating Lymphocytes (TIL) in selected solid tumors (PragmaTIL) is a project that received funding from the European Union's Horizon Europe research and innovation program under grant agreement No. 101104684 and started in 2023 with 12 partners across 6 countries.

Other PragmaTIL objectives are focused on the comparison of quality of life of patients during their hospitalization period, as well as to provide relevant information to participant member states regarding the possibility of implementing optimised and affordable treatments via the development of the health technology assessment of TIL-ACT using ANV419 together with a social return of investment analysis.

Website: https://pragmatil.eu/

PRIME-ROSE

PRIME-ROSE (Precision Cancer Medicine Repurposing System Using Pragmatic Clinical Trials) is a Horizon Europe Mission on Cancer project with 24 partners from altogether 18 European countries.

The PRIME-ROSE vision is access to affordable Precision Cancer Medicine (PCM) that prolongs life at the best quality possible for all cancer patients. PCM is an approach that depends on access to adequate molecular diagnostics and drugs to have impact and move towards implementation in the national healthcare systems. Today there is inequality in access to PCM between and within EU countries, and while the promise of PCM is clear, implementation remains a challenge. This in particular affects cancer patients with the poorest prognosis who have exhausted all lines of standard of care treatment, those with tumours carrying rare mutations and patients with carcinoma of unknown primary.

The PRIME-ROSE project builds on a bottom-up, clinician-initiated family of PCM clinical trials which have been particularly successful in bringing up inclusion rates to offer additional lines of treatment and in providing patient benefit. These trials share the pragmatic clinical trial design of the original Dutch DRUP trial, with broad inclusion criteria and a limited set of endpoints. However, the trials are still anchored into national context and are funded independently. The result is a distributed DRUP-like clinical trial network that addresses local priorities while collaborating internationally for scale and impact.

The consortium will use these existing adaptive and pragmatic clinical trial platforms to answer key questions regarding clinical effectiveness, provide health-economic evaluations, and contribute to scientific progress across cancers. In particular, the cross-country collaboration provided by PRIME-ROSE will build capacity as well as enable cross-trial data aggregation and analysis, initiate shared cohorts across borders and provide health-economic evaluations. To ensure successful implementation, the consortium will work together with regulators, policymakers, payers, healthcare providers and patient advocacy groups to implement evidence-based PCM in routine practice and address inequalities in access.

Website: www.matrix-fkb.no/en/prime-rose/home

Sagittarius

A precision medicine trial leveraging blood-based tumor genomics to optimize treatment in operable stage III and high-risk stage II colon cancer patients - The Sagittarius trial (SAGITTARIUS) is a project that received funding from the European Union's Horizon Europe research and innovation program under grant agreement No. 101104657. It started on July 1st, 2023, and involves 8 partners from 5 European countries (Italy, Spain, Germany, Belgium, Estonia), including universities, hospitals, research institutions, an SME, a private foundation for cancer research and knowledge spreading, and an umbrella organization representing the community of patients with digestive cancer.

SAGITTARIUS aims to optimize the clinical management of stage II high-risk and stage III colon cancer. Approximately half of patients at these disease stages relapse within two or three years from surgery because of imaging-undetectable minimal residual disease. Given the lack of reliable predictors of individual risk, these patients are treated with a one-fits-all adjuvant chemotherapy. This gunshot approach results in either over- or under-treatment. We will measure circulating tumor DNA (ctDNA) in the patients' bloodstream to diagnose minimal residual disease. Retrospective studies show that ctDNA detection after surgery predicts cancer recurrence with high sensitivity and specificity. SAGITTARIUS will deploy a ctDNA assay to detect the absence, presence, or persistence of the micro-metastasis in individual patients and personalize therapeutic interventions. Real-world patients will be treated in two parallel trials based on their ctDNA status and the genomic landscape of their tumors. ctDNA positive patients will be randomized to conventional or personalized targeted therapy. ctDNA negative patients will be randomized to a physician-driven therapy or a Wait&See strategy. The efficacy and effectiveness of this new strategy of care will be measured via multiple

outcomes, including safety and time to events variables, patient-reported outcome measures, and health-economics evaluation.

Website: https://sagittarius-horizon.eu/

Social Media: LinkedIn, Facebook, X, Instagram, YouTube

SALVOVAR

The standard medical-and-surgical treatment of ovarian carcinoma patients relies on a systemic chemotherapy (carboplatin-paclitaxel), a tumor debulking surgery meant to be complete (no post-operative residual lesion), and a subsequent maintenance treatment with modern targeted agents. Recent studies identified a patient population (~14,000 patients / year in Europe), whose prognostic is poor (5 year-overall survival (OS) <20%) due to a refractory cancer, characterized by a poor chemosensitivity (assessable online with the numeric CA-125 KELIMTM score <1.0), and by a disease found non-resectable disease after 3-4 cycles of chemotherapy. In these patients, there is a high uncertainty about the best treatment adjustments to apply.

SALVOVAR is a European project led by HCL, meant 1) to raise the physician awareness, and propose practical and affordable diagnostic tools for identifying these patients, and 2) to assess the utility (OS benefit), acceptability (qualityof-life; patient perception) and affordability (cost-effectiveness, including country coverage policies) of solutions based on adjustments of their medical-and-surgical treatment. These solutions implementable in routine may improve their prognosis, according to recent literature data. The project will be based on a large pragmatic randomized phase III trial, sponsored by ARCAGY-GINECO group, and activated in 6 countries (ENGOT network; ~100 recruiting centers), with the objective of demonstrating an OS benefit with the chemotherapy densification (weekly carboplatine-paclitaxel dosedense regimen) compared to the continuation of the standard 3-weekly regimen. A total of 685 patients treated with the standard neo-adjuvant chemotherapy will be pre-screened to randomize 240 patients. Dissemination and communication will be carried-on to ensure the quality of the project, and inform the stakeholders, patients, public, health authorities/payers of the project outcomes, mean to change the practices.

Website: www.salvovar.eu

STREXIT2

Retroperitoneal sarcomas are rare diseases refractory to treatment with dismal prognosis. Surgery is the only standard approach to primary disease. We are proposing an innovative pragmatic approach supplementing a standard phase III clinical trial with an observational cohort. It is proposed to amend the ongoing phase III EORTC clinical trial STRASS2 investigating the added value of neoadjuvant chemotherapy before surgery for high-risk retroperitoneal sarcoma and to add an observational arm STREXIT2 that will capture real world data from patients not participating to STRASS2. We will compare the clinical outcomes between STRASS2 and STREXIT2 and explore the possible combination of STRASS2 and matched STREXIT2 patients to strengthen the results of the randomized clinical trial data and increase the power of subgroup analyses. If conclusive, the proposed research will help to understand the clinical added value and costs-effectiveness of neoadjuvant chemotherapy before surgery for high-risk retroperitoneal sarcoma. We will perform health economics analysis assessing the economic value of different treatment scenarios based on STRASS2 and STREXIT2. If successful, the outcomes of the project will define a new evidence-based standard of care for high-risk retroperitoneal sarcomas. The proposed research could lead to improved patient survival and quality of life but also improving health system sustainability. This is a multidisciplinary and

multistakeholder consortium involving clinical oncologists, surgeons, health economists and patient representatives. The study design was successfully discussed with patients.

The consortium is composed by five partners: the European Organisation for Research and Treatment of Cancer (project coordinator and legal sponsor of the clinical trial), the Syreon Research Institute (Health Economics and communication), Fondazione IRCCS Istituto Nazionale dei Tumori (clinical lead), the Netherlands Cancer Institute (clinical coleader), and Sarcoma Patient Advocacy Global Network (patient organisation). In addition, some 38 clinical sites from 11 countries will join the study.

Website: https://strexit-horizon.eu/

3. Collaborating structure

This DTC provides a unique opportunity to discuss common challenges and find common solutions. The collaborative environment allows for a proactive approach to identifying and resolving problems that may arise during research planning and implementation. Through open dialogue and sharing of experiences, DTC members will work together to strengthen the integrity of each project involved and improve the overall quality of research.

In crafting the collaborative framework within the DTC, the Coordinators agreed to structure the activities into distinct Working Groups (WGs). WG1 will focus on creating an environment that fosters an effective collaboration and ensuring the correct joint data management of the information shared within the Cluster members and relative Consortia. WG2 will create a team dedicated to the translation of our single projects' insights into actionable knowledge to relevant stakeholders. Finally, WG3, WG4 and WG5 are established to represent the real pillars that will raise the collaborative effort within the Cluster. These WGs refers to the main aspects the Cluster is going to face, specifically requested by the European Commission: research and innovation, citizens' engagement and addressing inequalities.

Each WG will be led by a project and the relative Consortium, represented by its Coordinating Organisation, which will the first responsible of the WG development and monitoring. The leadership of each WG should change every year, to allow to all projects involved to guide the specific tasks and discussions in rotation.

The DTC has been established in September 2023 (Q4-23) and its ongoing initiatives will be planned and executed in quarters (Q).

3.1. Cluster's Working Groups

WG1 – Collaborative framework and Data Management

WG1 assumes a pivotal role within the DTC, overseeing at first two key common deliverables with their respective monitoring and update — the Common Work Plan and the Data Management Plan (DMP).

Moreover, our collective focus and mission is on the establishment of Standard Operating Procedures (SOPs) for monitoring projects' progress. This collaborative effort is not just about tracking and reporting; it's about fostering an environment where standardized practices ensure transparency and accountability to our Consortia and the European Commission. Our commitment to financial reporting guidelines is a cornerstone, emphasizing the importance of clear and comprehensive reporting practices. Additionally, the exchange of best practices for project management will represent our commitment to mutual growth. It's not just about managing projects; it's about creating an ecosystem where each project contributes to the collective advancement of cancer diagnostics and treatment.

Lead Project:	**PRIME-ROSE**
Key tasks:	• Establish and maintain the DTC Common Work Plan, a collaborative framework for efficient communication and coordination within the DTC (D1). • Formulate and update the Data Management Plan (DMP) for the cluster, ensuring secure and data handling, in accordance with the data management strategy of all the project involved. This DMP will represent a common chapter integrated in each project dedicated DMP (D2). • Develop and implement strategies for engaging external actors and fostering collaborations with key European stakeholders in the field of Project Management and Coordination. • Facilitate the organization of dedicated discussions twice throughout the duration of the collaboration at the European level to address challenges and opportunities in managing complex projects.
Outputs:	• D1 • D2 • White paper on SOPs for the European project management and financial monitoring (including collaborative tools and guidelines)

WG2 – Dissemination and Communication of the Results

Recognizing the profound impact of disseminating results, we commit to developing collaborative strategies that go beyond conventional approaches. Our DTC aims to utilize diverse communication channels and initiatives to reach all relevant stakeholders. Common actions to engage with policymakers at both national and international levels is not a mere formality but a strategic initiative to influence policy decisions related to cancer diagnostics and treatment.

Lead Project:	**SALVOVAR**
Key tasks:	• Develop the common video and brochure within the DTC (D2). • Develop a static web page to be integrated in each project' websites. • Conduct a comprehensive analysis, prioritization, and mapping of stakeholder engagement strategies to enhance interaction and collaboration, in a strength collaboration with the other WGs. • Facilitate the dissemination of results from diverse DTC projects, leveraging various communication channels, including social media platforms and websites.
Outputs:	• D2 • Static online page • DTC stakeholder map, updated yearly

WG3 - Research and Innovation

In the vibrant collaborative environment of the DTC, a core joint foundation of our efforts is the careful implementation of pragmatic clinical trials, in its design and conduction. These studies represent opportunities for individual projects as well as a collective effort that unites us to advance the field of diagnostic interventions for cancer patients across Europe.

The DTC will serve as a forum to share breakthrough techniques and ensure that our experiments go beyond the norm. By pushing the boundaries of research design, we aim to optimize the evaluation of diagnostic interventions and set new standards for effectiveness and applicability.

Beyond individual projects, we will jointly discuss standardized procedures for submitting documents to ethics committees and regulatory authorities. This joint standardization in managing new PCTs ensures compliance, transparency, and ethical integrity throughout the lifecycle of any clinical trial and underscores our commitment to rigorous and responsible research practices.

In this process, data analysis is more than just a technical aspect: it's a shared process to generate meaningful insights. This DTC will serve as a hub for researching cutting-edge approaches to data analysis. By jointly using the latest methods, we will greatly contribute to diagnostic interventions based on scientific evidence.

Lead Project:	**CARE1**
Key tasks:	• Organize internal cluster roundtables to address the agenda of annual meetings, identifying potential stakeholders (in collaboration with WG2) that can be involved, and sharing new critical issues and developments on the topic of conducting pragmatic innovative clinical trials in Europe. • Organize stakeholder verification sessions during the DTC Annual Meetings to ensure alignment with research goals. • Integrate research guidelines and best practices into the cluster's ongoing activities. • Contribute to the report at the end of each annual meeting. • Develop and publish a white paper regarding the Clinical Trial Methodologies: In-depth exploration of innovative pragmatic clinical trial methodologies in cancer research, highlighting best practices, challenges, and recommendations for design and implementation.
Outputs:	• Best practices in preparing and conducting PCTs (dedicated chapter in D4-D8) • White paper on “Clinical Trial Methodologies”

WP4 - Citizen engagement

Citizen engagement in research is defined as the effective and systematic involvement of members of the public or persons from affected community groups such as patients, caregivers, advocates, and representatives in research processes[3]. Organizations worldwide have suggested that citizen engagement in research may confer benefits to the conduct and uptake of scientific research through improving the relevance of study findings, encouraging the representation of diverse groups in research studies, minimizing waste by facilitating stewardship over resources, promoting mutual learning and understanding, and allowing broad dissemination of research findings beyond traditional academic audiences[4]. Most importantly, citizen engagement has demonstrated utility in building public trust in science and research.

In clinical trials, patient experience is recognized as a key dimension in the assessment of quality of care, due to the centrality of the patient’s perception of the care process and its outcome[5]. By actively involving patients in the design, conduct and translation of clinical trials, research and healthcare can be better tailored to meet the patients’ needs. Patient involvement has the potential to enhance the quality and relevance of research, support patient empowerment and contribute to the democratisation of research processes[6].

[3] Shahid A, Rosgen BK, Krewulak KD, Lorenzetti DL, Foster N, Sept BG, Leigh JP, Stelfox HT, Fiest KM. Incorporating and evaluating citizen engagement in health research: a scoping review protocol. Syst Rev. 2021 Sep 28;10(1):260. doi: 10.1186/s13643-021-01812-4. PMID: 34583771; PMCID: PMC8480041.

[4] Canadian Institutes of Health Research. CIHR’s framework for citizen engagement. Ottawa, ON; 2012

[5] . Oben, P. (2020). Understanding the Patient Experience : A Conceptual Framework. Journal of patient experience, 7(6), 906-910. https://doi.org/10.1177/2374373520951672

[6] Price A, Clarke M, Staniszewska S, Chu L, Tembo D, Kirkpatrick M, Nelken Y. Patient and Public Involvement in research: A journey to co-production. Patient Educ Couns. 2022 Apr;105(4):1041-1047. doi: 10.1016/j.pec.2021.07.021. Epub 2021 Jul 19. PMID: 34334264.

The DTC seeks to enhance and promote citizen engagement in PCTs by actively sharing key opinion leader's expertise's and best practices and the involvement of patients and society in the design, planning, executing and evaluation of the proposed projects.

Lead Project:	**PragmaTIL**
Key tasks:	• *Definition & Identification*. Each participating project will identify the patient and citizen involvement actions performed by their consortium. Different experiences and approaches will be shared during each annual meeting. Prospective joint and individual actions regarding citizen engagement can be identified during its dedicated session in each annual meeting. • *Strategic Planning*. During the first annual meeting, a dedicated session on Citizen Engagement will be placed to define the Strategy that will be followed throughout the duration of the Cluster. Internal follow-up meetings will be organized during the year and the strategic plan for the DTC will be updated in each Annual meeting. It is expected that all consortiums will take part in the different discussions and strategic plan definition. • *Best Practices and Recommendations.* After each annual meeting, best practices will be collected, and a report will be integrated in the deliverables D4-D8 and published separately regarding recommendations and best practices on how to potentiate patient involvement and citizen engagement in European projects. A final report will be prepared at the end of this Cluster collaboration (D9).
Outputs:	• Best practices in citizen engagement (dedicated chapter in D4-D8) • D9

WG5 - Addressing inequalities

Despite a trend towards decreased risk for dying from cancer globally[7], substantial differences in mortality rates across countries are evident[8]. Inequalities in cancer have been observed in several aspects of cancer care including primary and secondary prevention, early detection, diagnosis, treatment, and follow-up[9,10]. Interestingly, substantial differences in the accessibility and availability of biomolecular technologies and antineoplastic medicines have recently been highlighted[11,12]. Inequalities can be linked to uneven distribution of resources but also to social disparities associated with ageism, sexual orientation and gender identity, ethnicity, income, and educational level[13].

Recognizing and benchmarking inequalities in cancer is the first step for a better understanding of this global issue and could serve as the basis for strategies to reduce inequalities. To highlight the importance of tackling inequalities, the EU's Cancer Beating Plan has included inequalities as one of the focus topics and led to the

[7] Hashim D, Boffetta P, La Vecchia C, Rota M, Bertuccio P, Malvezzi M, Negri E. The global decrease in cancer mortality: trends and disparities. Ann Oncol. 2016;27:926-33.
[8] Vaccarella S, Georges D, Bray F, Ginsburg O, Charvat H, Martikainen P, Brønnum-Hansen H, Deboosere P, Bopp M, Leinsalu M, Artnik B, Lorenzoni V, De Vries E, Marmot M, Vineis P, Mackenbach J, Nusselder W. Socioeconomic inequalities in cancer mortality between and within countries in Europe: a population-based study. Lancet Reg Health Eur. 2022;25:100551.
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[10] Berchet C, Dedet G, Klazinga N, Colombo F. Inequalities in cancer prevention and care across Europe. Lancet Oncol. 2023 Jan;24:10-11.
[11] Bayle A, Bonastre J, Chaltiel D, Latino N, Rouleau E, Peters S, Galotti M, Bricalli G, Besse B, Giuliani R. ESMO study on the availability and accessibility of biomolecular technologies in oncology in Europe. Ann Oncol. 2023;34:934-945.
[12] ESMO Study on the Availability, Out-of-Pocket Costs and Accessibility of Antineoplastic Medicines 2.0. Available at: https://oncologypro.esmo.org/meeting-resources/esmo-congress-2022/esmo-anms-2.0-survey-about-access-to-cancer-medicines (Accessed: 10th Dec 2023).
[13] The Lancet Regional Health-Europe. Reduce cancer inequity and inequality to reduce cancer mortality. Lancet Reg Health Eur. 2023;25:100591.

setup of the European Cancer Inequalities Registry aiming at monitoring disparities through reporting on trends in key cancer prevention and care at regional, national and EU level[14].

This DTC offers a unique opportunity to address inequalities in cancer considering the broad spectrum of cancer-related topics that are addressed across the projects thus enabling to capture and address several aspects of inequalities and disparities.

Lead Project:	**IntReALL 2020**
Key tasks:	• Each participating project will identify inequalities and disparities associated with the project's specific setting. During the first annual meeting, a dedicated session on Inequalities will be held to define the future work on this topic throughout the duration of the Cluster. • Through internal follow-up meetings, strategies addressing inequalities that are applied at each project as well as potential future strategies will be further elaborated and presented for discussion in each Annual meeting. • After each annual meeting, all aspects related to inequalities and disparities that are captured and discussed within the Cluster will be collected, and a report will be integrated in the deliverables D4-D8. • At the end of the Cluster work, a dedicated deliverable (D10) on addressing inequalities recommendations will be developed.
Outputs:	• Contribute to the report at the end of each annual meeting (dedicated • chapter in D4-D8). • □ Deliverable on addressing inequalities recommendations (D10). • D10

3.2. List of common deliverables

D	Name	Due Date (Q)	Lead Project	Description
1	Initial common work plan for scientific collaboration	Q1-24	IMPACT-AML	Initial common work plan for scientific collaboration under the 'Diagnosis and treatment' cluster to meet the requirements of the Cancer Mission cluster
2	Data Management Plan – common chapter	Q1-24	Sagittarius	The aim is of the chapter is to address commonalities in data standards, data validation, data protection and foster data exchange.
3	"Diagnosis and treatment" common video and/or a common cluster brochure	Q2-24	SALVOVAR	"Diagnosis and treatment" cluster brochure to meet the requirements of the Cancer Mission cluster.
4	First annual "Diagnosis and treatment" cluster meeting report	Q3-24	DE-ESCALATE	• Conclusions of common annual meeting of the 'Diagnosis and treatment' cluster • Policy brief formulating recommendations based on the research and innovation strand of the 'Diagnosis and treatment' annual cluster meeting
5	Second annual "Diagnosis and treatment" cluster meeting report	Q3-25	TBD	• Conclusions of common annual meeting of the 'Diagnosis and treatment' cluster • Policy brief formulating recommendations based on the research and innovation strand of

[14] ECIR – European Cancer Inequalities Registry Available at: https://cancer-inequalities.jrc.ec.europa.eu/framework (Accessed: 10th Dec 2023).

				the 'Diagnosis and treatment' annual cluster meeting
6	Third annual "Diagnosis and treatment" cluster meeting report	Q3-26	PragmaTIL	• Conclusions of common annual meeting of the 'Diagnosis and treatment' cluster • Policy brief formulating recommendations based on the research and innovation strand of the 'Diagnosis and treatment' annual cluster meeting
7	Fourth annual "Diagnosis and treatment" cluster meeting report	Q3-27	TBD	• Conclusions of common annual meeting of the 'Diagnosis and treatment' cluster • Policy brief formulating recommendations based on the research and innovation strand of the 'Diagnosis and treatment' annual cluster meeting
8	Fifth annual "Diagnosis and treatment" cluster meeting report	Q3-28	TBD	• Conclusions of common annual meeting of the 'Diagnosis and treatment' cluster • Policy brief formulating recommendations based on the research and innovation strand of the 'Diagnosis and treatment' annual cluster meeting
9	Citizen engagement summary report	Q3-28	LIVERATION	Citizen engagement summary report to meet the requirements of the Cancer Mission cluster of projects on 'Diagnosis and treatment'
10	Addressing inequalities recommendations	Q3-28	IMPORTANT	Addressing inequalities recommendations to meet the requirements of the Cancer Mission cluster of projects on 'Diagnosis and treatment'

The leadership of the upcoming "TBD"-marked deliverables will be set after the first annual meeting.

Deliverable's submission procedure

In ensuring a cohesive and streamlined approach, the projects' coordinators have collaboratively agreed to submit common deliverables following the timing established in the work plan. This collaborative effort involves each coordinator submitting the deliverable using their project-specific template, following thorough consultation and information-sharing within their respective consortia.

4. Collaborative tools and SOPs

Effective internal communication is integral to the success of collaborative efforts within the 'Diagnosis and Treatment' cluster. To facilitate seamless information exchange and collaborative document management, we have established a centralized platform using Microsoft SharePoint (HUS' digital workspace). This platform serves as a dynamic hub for sharing and collectively editing essential operational documents, fostering real-time collaboration among project teams. Through Microsoft SharePoint, Cluster members can access, modify, and track document changes, ensuring transparency and efficiency in our collaborative workflows.

In addition to document management, routine communications within the Cluster are primarily conducted via email. Email serves as a reliable and widely accessible medium for disseminating announcements, updates, and important information across all project stakeholders. This ensures that key information reaches relevant parties promptly, promoting timely decision-making and alignment.

Regarding online meetings, the tools employed may vary based on the organizing entity responsible for each meeting (e.g. Microsoft Teams, Google Meet). While the specific e-meeting platform might differ, the overarching objective is to ensure effective communication, collaboration, and knowledge-sharing among

Cluster members. This flexibility allows us to adapt to the diverse preferences and requirements of the organizations responsible for coordinating cluster meetings, fostering a collaborative environment that maximizes the impact of our collective efforts.

5. Work plan update frequency

The Initial work plan outlined in this deliverable is intended to be a dynamic and responsive framework that recognizes the changing nature of the research development and the need for change. Updates will be required to be completed to ensure that the program remains current and aligned with each project and the overall goals of the DTC. As a rule, annual group meetings will play an important role in reviewing and revising the collaboration plan. These meetings will provide a platform for collaborators, stakeholders, and experts to share insights, discuss successes, and work together to solve emerging problems. Updates to the joint plan will be made at the end of each annual reporting period to ensure that the plan not only reflects changes in the findings of the research but also preserves the knowledge and experience gained throughout the collaboration. This improvement process ensures the continued impact and effectiveness of our collaboration on the Horizon European Healthcare Programme.

6. Conclusions

In conclusion, our work extends beyond the boundaries of individual projects. The Cluster recognizes the importance of reporting research progress and results to key stakeholders and policy makers. By pooling resources and presenting consistent reporting, we aim to amplify the impact of our shared findings and advocate for advances in cancer diagnosis more broadly.

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Annexes

Annex A. Summary of the projects included in the DTC with the main characteristics.

Acronym	Title	ID	Start date	Duration (M)	PO	COO Institution
CARE1	First line randomized study platform to optimize treatment in patients with metastatic renal cell carcinoma	101104801	5/1/2023	60	Aizpurua Nerea	IGR
DE-ESCALATE	INTERMITTENT ANDROGEN DEPRIVATION THERAPY IN THE ERA OF ANDROGEN RECEPTOR PATHWAY INHIBITORS; A PHASE 3 PRAGMATIC RANDOMISED TRIAL	101104574	6/1/2023	60	Da Silva Marianne	EORTC
IMPACT- AML	Master Framework and Pragmatic Clinical Trial for Relapse or Refractory Acute Myeloid Leukemia	101104421	4/1/2023	60	Escobar Romina	IRST
IMPORTANT	IMPlementing geriatric assessment for dose Optimization of CDK 4/6-inhibitors in older bReasT cAncer patieNTs	101104589	5/1/2023	60	Contor Laura	ORU
IntReALL 2020	International Study for Treatment of Childhood Relapsed ALL 2020	101104582	5/1/2023	60	Escobar Romina	CHR
LEGATO	Lomustine with or without reirradiation for first progression of glioblastoma: a pragmatic randomized phase III study	101103655	6/1/2023	60	Kougoulis Jiannis	EORTC
LIVERATION	Unravelling the impact of Radiofrequency in liver surgery: the key to decrease local recurrence?	101104360	6/1/2023	60	Monika WOZINSKA	PSMAR
PragmaTIL	Pragmatic approach to Adoptive Cell Therapy (ACT) using Tumor Infiltrating Lymphocytes (TIL) in selected solid tumors	101104684	4/1/2023	60	Monika WOZINSKA	VHIO
PRIME-ROSE	PRecisIon Cancer MEdicine RepurpOsing SystEm Using Pragmatic Clinical Trials	101104269	7/1/2023	60	Bonanomi Maria Grazia	HUS
Sagittarius	A precision medicine trial leveraging blood-based tumor genomics to optimize treatment in operable stage III and high-risk stage II colon cancer patients - the Sagittarius trial	101104657	7/1/2023	60	Bonanomi Maria Grazia	IFOM

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SALVOVAR	A European multi-disciplinary clinical project meant to improve the management of patients with poor prognostic ovarian cancer after neoadjuvant chemotherapy: restoring hope, salvaging lives	101104469	5/1/2023	60	Da Silva Marianne	CHU
STREXIT2	A pragmatic clinical study of neoadjuvant chemotherapy followed by surgery versus surgery alone for patients with high risk retroperitoneal sarcoma	101103843	6/1/2023	60	Contor Laura	EORTC

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