EORTC
European Organisation for Research and Treatment of Cancer

# Improving investigator initiated clinical trials (IIT)

Denis Lacombe, MD, MSc
EORTC CEO

The future of cancer therapy

# EORTC Mission

**AIM**: To increase cancer patients' survival and quality of life

Do this through:

- **Generating robust medical evidence**: design, coordinate and conduct **multidisciplinary**, **clinical and translational** trials, leading to therapeutic progress and new standard of treatment in care

- **Setting Standards**: being a **reference** for methodological research and an **authority** in establishing the standards of treatment in care

# EORTC by numbers (2022)

## World-class Network

**2712** patients screened
**2417** patients enrolled in the CTs
- **244** institutions
- **> 600** Principle Investigators
- **29** countries

**22** intergroup collaborations
**17** active groups & taskforces
**70** peer reviewed papers

**Total EORTC Network**
**> 3400** Members
**917** Institutions

## Centre of expertise

**260+** employees

**> 210,000** patients in database

**± 22,000** patients in follow-up

**6** EORTC HQ peer reviewed papers

## Unique output

**26** studies open on 1/01/2023
- **11** opened studies in 2022

**94** Studies closed/LTFU
- **14** closed in 2022

**7** Studies in protocol development
**11** Studies in regulatory activation

Working on ≈ **138 studies**

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# IIT: what are we talking about?

THE LANCET
Oncology

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FAST TRACK — ARTICLES | VOLUME 6, ISSUE 12, P937-944, DECEMBER 01, 2005

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# Health-related quality of life in patients with glioblastoma: a randomised controlled trial

Dr Martin JB Taphoorn, MD • Roger Stupp, MD • Corneel Coens, MSC • David Osoba, MD • Rolf Kortmann, MD
Martin J van den Bent, MD • et al. Show all authors

Published: November 17, 2005 • DOI: https://doi.org/10.1016/S1470-2045(05)70432-0

# Estimation of Distant Metastasis–free Survival in Trials of Adjuvant Therapy for Melanoma

**TO THE EDITOR:** Recently, trials of adjuvant therapy for melanoma in which therapies that target cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed death 1 (PD-1), or BRAF and MEK are assessed have reported positive results in terms of relapse-free survival and distant metastasis–free survival.[1-4] The European Organization for Research and Treatment of Cancer (EORTC) 18071 trial[1] compared ipilimumab with placebo in patients with resected stage III melanoma; the CheckMate 238 trial[2] compared nivolumab with ipilimumab in patients with resected stage IIIB, IIIC, or IV melanoma; and the COMBI-AD trial (Nov. 9, 2017, issue)[3,4] compared dabrafenib plus trametinib with placebo in patients with stage III melanoma with *BRAF* mutations.

The trials defined relapse-free survival as the time from randomization until first recurrence (local, regional, or distant metastasis) or death (or second primary cancer in the COMBI-AD

European Journal of Cancer 119 (2019) 1–10

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.ejcancer.com

ELSEVIER EJC

Original Research

## Adjuvant ipilimumab versus placebo after complete resection of stage III melanoma: long-term follow-up results of the European Organisation for Research and Treatment of Cancer 18071 double-blind phase 3 randomised trial

Alexander M.M. Eggermont [a,*], Vanna Chiarion-Sileni [b], Jean-Jacques Grob [c], Reinhard Dummer [d], Jedd D. Wolchok [e], Henrik Schmidt [f], Omid Hamid [g], Caroline Robert [h], Paolo Antonio Ascierto [i], Jon M. Richards [j], Celeste Lebbe [k], Virginia Ferraresi [l], Michael Smylie [m], Jeffrey S. Weber [n], Michele Maio [o], Fareeda Hosein [p], Veerle de Pril [q], Michal Kicinski [r], Stefan Suciu [r,1], Alessandro Testori [s,1]

N ENGL J MED 380;14 NEJM.ORG APRIL 4, 2019

The New England Journal of Medicine



# Radiotherapy or surgery of the axilla after a pos node in breast cancer (EORTC 10981-22023 AM a randomised, multicentre, open-label, phase 3 non-inferiority trial

Mila Donker, Geertjan van Tienhoven, Marieke E Straver, Philip Meijnen, Cornelis J H van de Velde, Robert E Mansel, Luigi Cataliotti, A Helen Westenberg, Jean H G Klinkenbijl, Lorenzo Orzalesi, Willem H Bouma, Huub C J van der Mijle, Grard A P Nieuwenhuijzen, Sanne C Veltkamp, Leen Slaets, Nicole J Duez, Peter W de Graaf, Thijs van Dalen, Andreas Marinelli, Herman Rijna, Marko Snoj, Nigel J Bundred, Jos W S Merkus, Yazid Belkacemi, Patrick Petignat, Dominic A X Schinagl, Corneel Coens, Carlo G M Messina, Jan Bogaerts, Emiel J T Rutgers

## Summary

**Background** If treatment of the axilla is indicated in patients with breast cancer who have a positive sentinel node axillary lymph node dissection is the present standard. Although axillary lymph node dissection provides excellent regional control, it is associated with harmful side-effects. We aimed to assess whether axillary radiotherapy provides comparable regional control with fewer side-effects.

European Journal of Cancer 109 (2019) 192–195

Available online at www.sciencedirect.com
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EORTC Clinical Trial in Perspective

## A multinational, multi-tumour basket study in very rare cancer types: The European Organization for Research and Treatment of Cancer phase II 90101 'CREATE' trial

European Journal of Cancer 119 (2019) 1–10

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The NEW ENGLAND JOURNAL of MEDICINE

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VOLUME 35 · NUMBER 15 · MAY 20, 2017

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

original reports

# Standard Anthracycline Based Versus Docetaxel-Capecitabine in Early High Clinical and/or Genomic Risk Breast Cancer in the EORTC 10041/BIG 3-04 MINDACT Phase III Trial

Suzette Delaloge, MD, MSc[1,2]; Martine Piccart, PhD[3]; Emiel Rutgers, PD, PHD[4]; Saskia Litière, PhD[5]; Laura J. van 't Veer, PhD[6]; Franchette van den Berkmortel, MD, PhD[7]; Etienne Brain, MD, PhD[8]; Aleksandra Dudek-Peric, PHD[5]; Miguel Gil-Gil, MD[9]; Patricia Gomez, MD[10]; Florentine S. Hilbers, MSc[11]; Zaman Khalil, MD[12]; Susan Knox, MA[13]; Sherko Kuemmel, PhD[14]; Georg Kunz, MD[15]; Anne Lesur, MD[16]; Jean-Yves Pierga, MD[8,17]; Peter Ravdin, MD, PHD[18]; Isabel T. Rubio, MD, PhD[19]; Mahasti Saghatchian, MD[1]; Tineke J. Smilde, MD, PhD[20]; Alastair M. Thompson, MBChB, MD[21]; Giuseppe Viale, MD[22]; Gabriele Zoppoli, MD, PhD[23]; Peter Vuylsteke, MD[24]; Konstantinos Tryfonidis, MD[5]; Coralie Poncet, MSc[5]; Jan Bogaerts, ScD[5]; and Fatima Cardoso, MD[25]; on behalf of MINDACT investigators and the TRANSBIG Consortium

# Ten-Year Progression-Free and Overall Survival in Patients With Unresectable or Metastatic GI Stromal Tumors: Long-Term Analysis of the European Organisation for Research and Treatment of Cancer, Italian Sarcoma Group, and Australasian Gastrointestinal Trials Group Intergroup Phase III Randomized Trial on Imatinib at Two Dose Levels

*Paolo G. Casali, John Zalcberg, Axel Le Cesne, Peter Reichardt, Jean-Yves Blay, Lars H. Lindner, Ian R. Judson, Patrick Schöffski, Serge Leyvraz, Antoine Italiano, Viktor Grünwald, Antonio Lopez Pousa, Dusan Kotasek, Stefan Sleijfer, Jan M. Kerst, Piotr Rutkowski, Elena Fumagalli, Pancras Hogendoorn, Saskia Litière, Sandrine Marreaud, Winette van der Graaf, Alessandro Gronchi, and Jaap Verweij on behalf of the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group, Italian Sarcoma Group, and Australasian Gastrointestinal Trials Group*

ORIGINAL ARTICLE

# Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D., Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*

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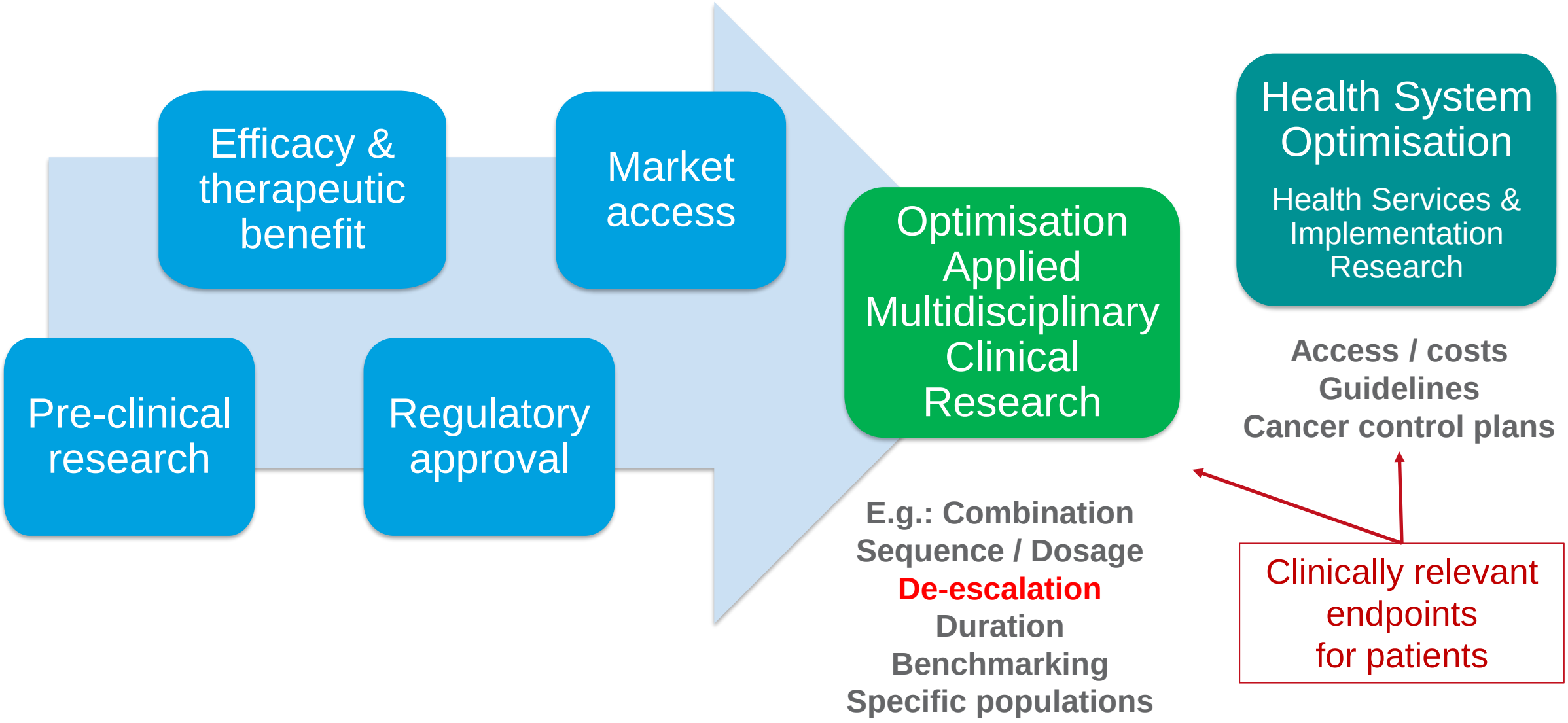
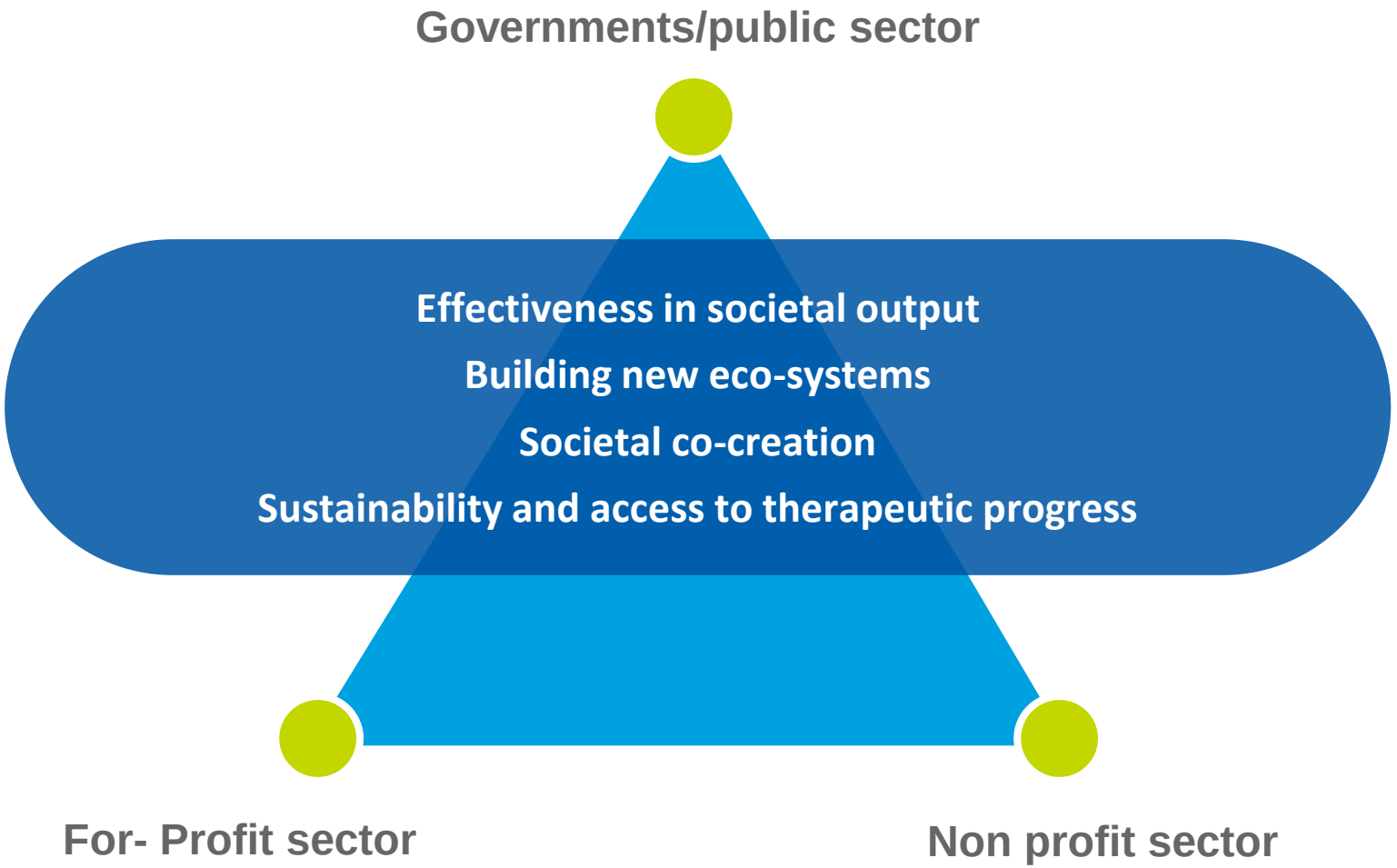
# How do IITs profile in the landscape?

# The work starts when a technology reaches the market.



# The eco-system….a societal balance?



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# A European Imbalance

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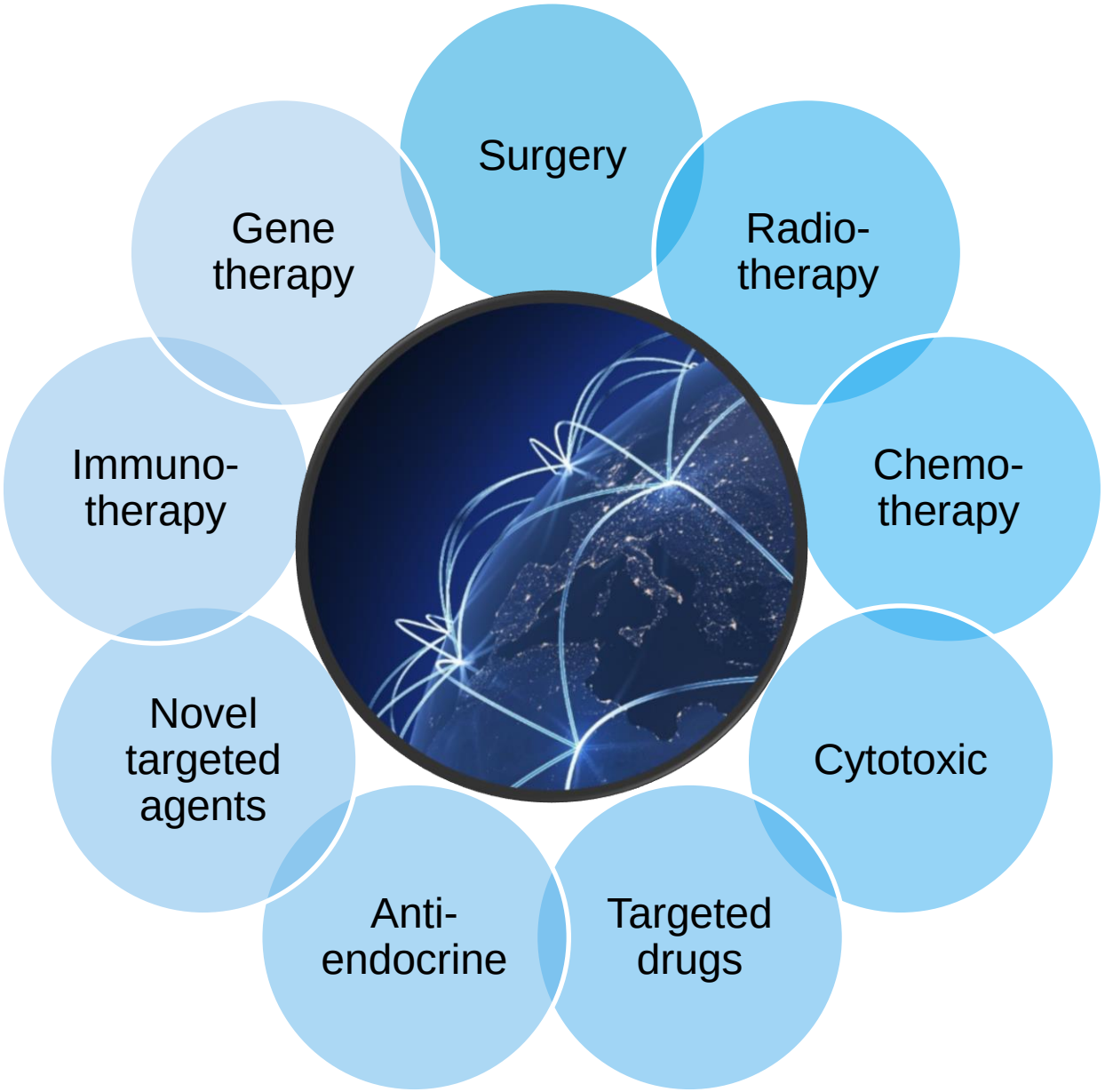
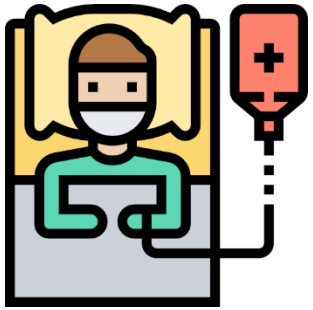
# IITs address multidisciplinary strategies

# The Future is Combinatorial

Multidimensional data



Access

Authorisation

Optimal access

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# Selected challenges of IITs

- Challenging and complex by designs
- Recruitment can be an issue: large trials, rare cancers, long follow up
- No regulatory role / poor visibility on the global landscape
- Poor understanding by policy maker, various regulatory bodies
- Poorly supported by the commercial sector
- Other finding sources are scarce and complex to reach (charities, foundations etc…)
- Fragmentation of the funding, specially for international trials
- IITs represent a spectrum of trials (single center to large international trials)

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# The concept of treatment Optimisation

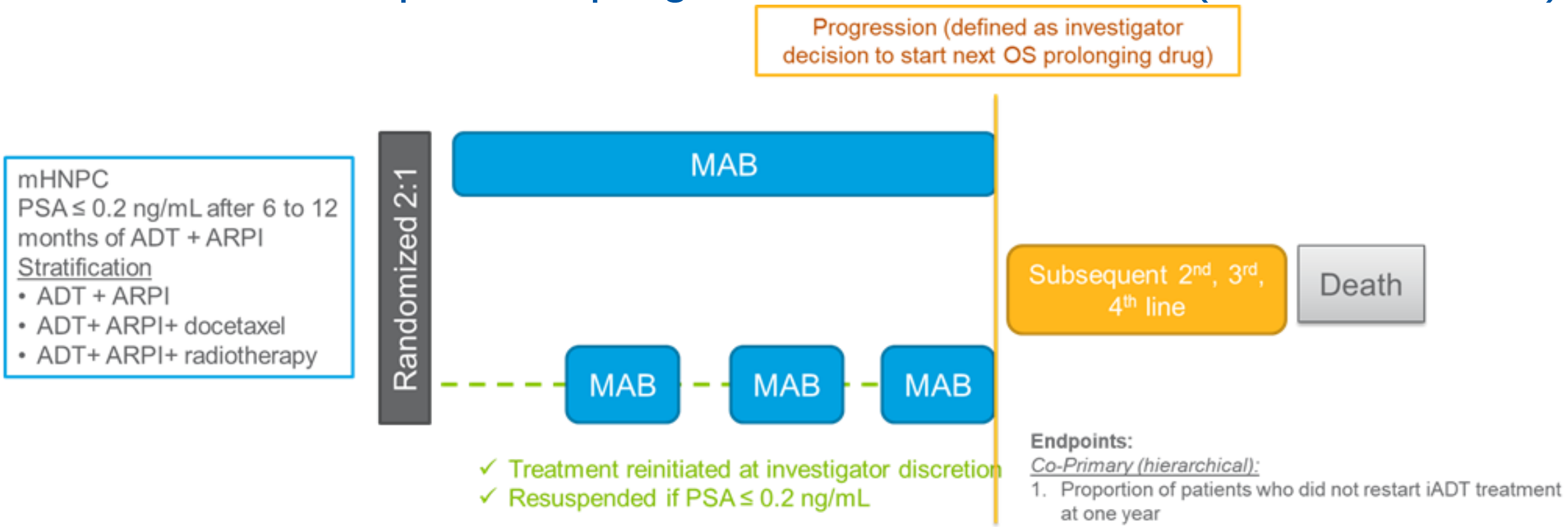
**Combination**
**Sequence / Dosage**
**De-escalation**
**Duration**
**Benchmarking**
**Specific populations**

# Impact of registration of 4 new hormones in newly diagnosed metastatic prostate cancer

| Agent | Study | n | HR (95%CI) | p |
|---|---|---|---|---|
| Abiraterone /P | LATITUDE | 1199 | 0.62 (0.51 - 0.76) | <0.001 |
| | STAMPEDE ITT | 1917 | 0.63 (0.52 - 0.76) | <0.001 |
| | STAMPEDE M1 | 1002 | 0.61 (0.49 - 0.75) | <0.001 |
| | PEACE 1 ITT | 1172 | 0.82 (0.69-0.98) | 0.030 |
| | PEACE 1 Docetaxel | 710 | 0.75 (0.59-0.95) | 0.017 |
| Apalutamide | Titan | 1052 | 0.65 (0.53 - 0.79) | <0.001 |
| Enzalutamide | ENZAMET | 1125 | 0.67 (0.52 - 0.86) | 0.002 |
| | ARCHES | 1150 | 0.66 (0.53-0.81) | <0.0001 |
| Radiotherapy | STAMPEDE RT | 2061 | 0.92 (0.80 – 1.06) | 0.266 |

- 7 trials
- 7 used continuous administration, 0 intermittent regimen.
- 20-30% long-term Grade 3-4 TEAE
- Cost increased 15k to 150k per patients
- No study so far looking a de-escalation, intermittent setting.

# Intermittent androgen deprivation therapy in the era of androgen receptor pathway inhibitors in prostate cancer ; a phase 3 pragmatic randomised trial (De-ESCALATE)




mHNPC: metastatic hormone naïve prostate cancer patients
ARPI: androgen receptor pathway inhibitor
MAB: Maximum androgen blockade

**Endpoints:**

*Co-Primary (hierarchical):*

1. Proportion of patients who did not restart iADT treatment at one year
2. Overall survival

*Secondary*

1. QoL (EQ-5D-5L)
2. Time spent on treatment
3. Time to next systemic prostate cancer therapy
4. Toxicity with CTCAE v5

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# What can we do for IITs?

# Key questions we are addressing to policy makers

- How to recognise and structure the independent agenda in this continuum?
- How to address the gap supra-national versus national competences?
- If treatment optimisation is to be structured in the process: when, how and who?
- How do we re-engineer the sequence of relevant questions from drug development into access?
- How do we prioritise questions and select the most appropriate methodology?
- How do we finance a multidisciplinary independent agenda at the European level?

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# Manifesto

**for a new approach for better medicine in Europe**
**Establishing Treatment Optimization**
**as part of personalized medicine development**

**(version 29 May 2020)**

## Forewords

Personalized medicine refers to a medical model that tailors the therapy to the patient's molecular profile and other individual information. The principles apply to medicines as well as other treatment modalities, including surgery and radiotherapy. The concept though has specifically emerged due to the increased number of drugs targeting specific molecular vulnerabilities or aberrations in a specific disease. The commercial promotion of genome-wide analyses has led to an increasing expectation among patients.

On the other hand, there are numerous drugs authorized on the market, with limited knowledge on how to use them for dose, sequence, combination and duration of treatment. Sub-optimal administration of costly treatments may generate unnecessary toxicity for the patients and negatively affects national healthcare budgets. Thus, there is a need for investigating the optimal way to use medicines (applied research or "Treatment Optimization")[1].

In Europe, most of the clinical research dedicated to therapeutic innovations aims primarily at regulatory approval. Once a drug enters the common market, each member state determines its real-world use based on its own criteria: pricing, reimbursement and clinical indications.

Such a regulatory approval-centred clinical research landscape may neglect patient-relevant issues in real-world setting, such as comparative effectiveness of distinct treatment options or long-term safety monitoring.

There is a call for reforming the current system to a truly 'patient-centred' paradigm with systematically coordinated Treatment Optimisation in conjunction with drug development.[2] The purpose of this manifesto is to gain stakeholders support for making Treatment Optimization a standard step in medicine development in Europe.

This manifesto was prepared by the European Organisation for Research and Treatment of Cancer (EORTC).

European Parliament

# Treatment optimisation in drug development

STOA | Panel for the Future of Science and Technology

**AUTHORS**

This study has been written by Dr Denis Lacombe of the European Organisation for Research and Treatment of Cancer (EORTC), Robbe Saesen of the Catholic University of Leuven (KU Leuven) and EORTC, Stéphane Lejeune of EORTC, and Prof. Dr Isabelle Huys of KU Leuven, at the request of the Panel for the Future of Science and Technology (STOA) and managed by the Scientific Foresight Unit (STOA) within the Directorate-General for Parliamentary Research Services (EPRS) of the Secretariat of the European Parliament.

**ADMINISTRATOR RESPONSIBLE**

Gianluca Quaglio, Scientific Foresight Unit (STOA)

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STUDY

Panel for the Future of Science and Technology

EPRS | European Parliamentary Research Service

Scientific Foresight Unit (STOA)

PE 641.511 – March 2020

EN

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European Cancer Meeting 2022 › Sessions ›
Masterclass "Access to Multidisciplinary Cancer Treatment: Is the continuum from development into healthcare becoming a reality?"

# Masterclass "Access to Multidisciplinary Cancer Treatment: Is the continuum from development into healthcare becoming a reality?"

Access to innovative therapies is hampered by limited clinically relevant information on high expenditure technologies not alwa
actual health benefit.

Treatment optimisation performed by the non-commercial sector addresses patient-oriented questions in the health care syst
such as but not limited to combination, optimal dose, duration and schedule, biomarker determination and ultimate beneficia
usually not available at the time of registration. All such de-escalation approaches are long needed as patients may be over
expensive treatments where accessible when lack of information prevents access elsewhere, leading to inequalities across

These multi-faceted challenges fall in the gap between supranational approval and long overdue for change national health
Structuring the role of independent clinical research for treatment optimisation in Europe can contribute to ensure this critically
continuum.

- Denis Lacombe, Chief Executive Officer, The European Organisation for Research and Treatment of Cancer (EORTC)

2021
PORTUGAL.EU

**Porto Declaration on Cancer Research**

**Porto, 3 May 2021**

**2. Infrastructures for clinical and prevention trials:**

'Proof-of-concept' studies may serve as a starting point for further clinical and prevention research, with a practice-changing aim, including the assessment of its utility in healthcare or prevention, patients'/individuals 'at risk, cure/survival and health-related quality of life. Well-developed clinical trial structures, and advanced diagnostic methods such as state-of-the-art molecular pathology, omics technologies, and pharmacology to stratify patients as well as innovative imaging are crucial. CCCs can play a role in this together with clinical research networks. The European Organisation for Research and Treatment of Cancer (EORTC) can facilitate this.

# The roadmap continues..

- EMA Management Board: access to MS agency and presentation by EORTC June 2023
- Accelerating Clinical Trials in the EU (ACT EU): application to the multistakeholder platform
- EUnetHTA: HTA stakeholder network application
- WHO: Novel Medicines Platform - Consultation with non-State actors + application for Membership
- Pharmaceutical regulation:
- National Competent Authorities for Pricing and Reimbursement

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# The Cancer Medicine Forum

The future of cancer therapy

# Objectives of the Cancer Medicines Forum

**To serve as a direct and official communication channel with the academic community in oncology**

**To identify key research questions and best methodological approach to improve the clinical use of cancer medicines**

**To discuss the uptake of academic work in the wider context of regulatory decision-making in oncology**

Treatment optimisation

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# Structuring Treatment Optimisation

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# The role of Pragmatic Clinical Trials (PCT)

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# What is a PCT?

- Aims to generate results that are *applicable to the healthcare context in which the trial was done*.
- Does not exclude people who would receive/deliver the treatment were the treatment being used in routine practice.
- Is done in settings where care would be generally be delivered.
- Measures only things that are important to decision-makers.
- Is unlikely to be able to tell you *why* something happened, only if it did.

# The value of pragmatic trials

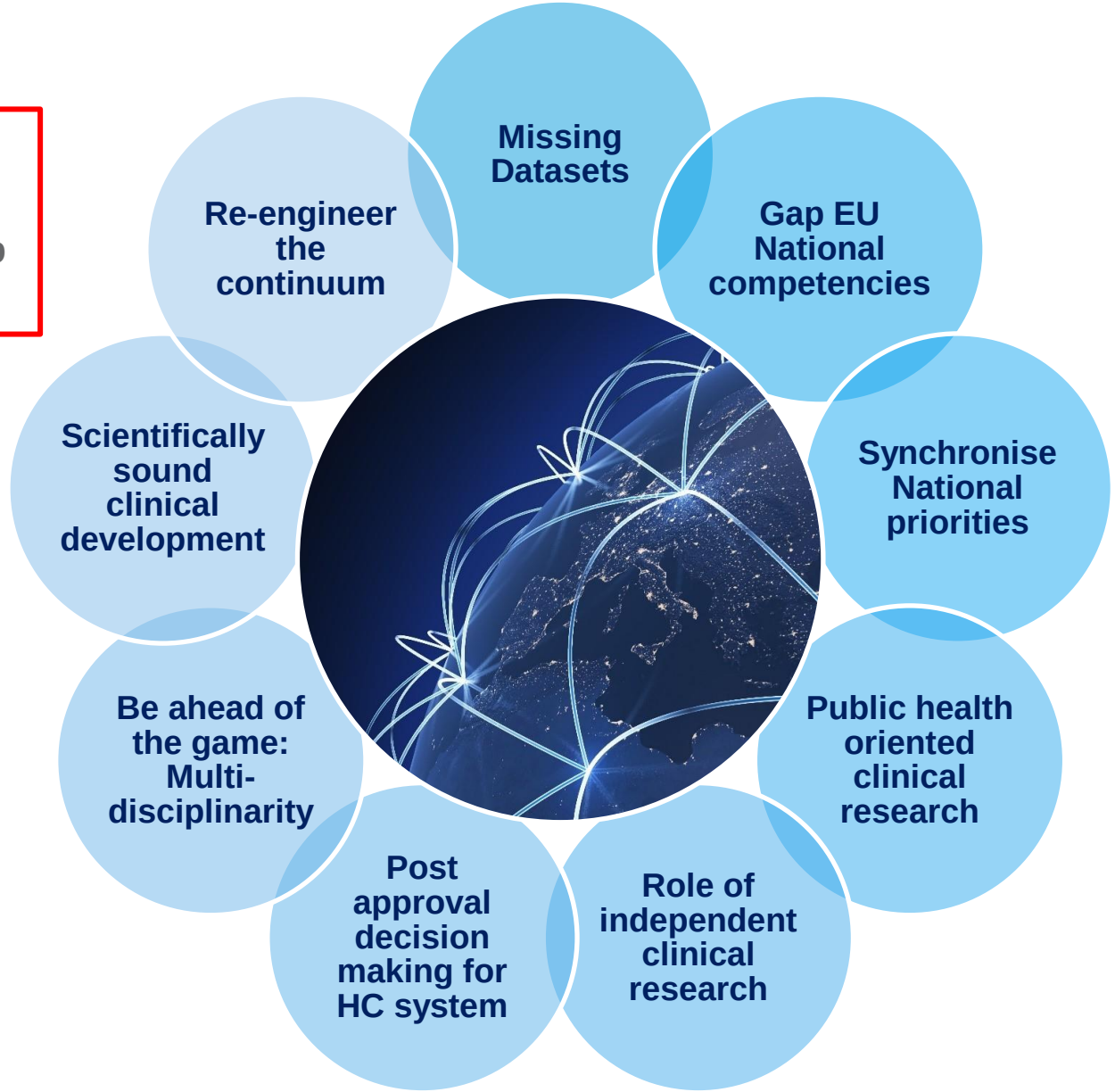
- Pragmatic trials are especially valuable to:
  - **Patients**, by painting a more realistic picture of a treatment's benefits and harms for the average patient
  - **Clinicians**, by guiding clinical decision-making
  - **Payers**, by informing reimbursement-related decision-making

- Pragmatic trials combine the methodological strengths of RCTs with the inclusiveness of studies that analyze real-world data
  - Sources of robust and actionable real-world evidence

Simon et al. *N Engl J Med* (2020)
Neyt et al. *J Comp Eff Res* (2016)
Zuidgeest et al. *J Clin Epidemiol* (2017)

# Need for strategic intelligence approaches

**EORTC AICIB SPO**
**Process for IIT should be considered as a national step in strategic re-engineering**



# Reality on the ground:
# Mozaic of legal requirements in clinical research (EU)

**Cross-sector !!!!!**

**Universal Declaration of Human Rights**

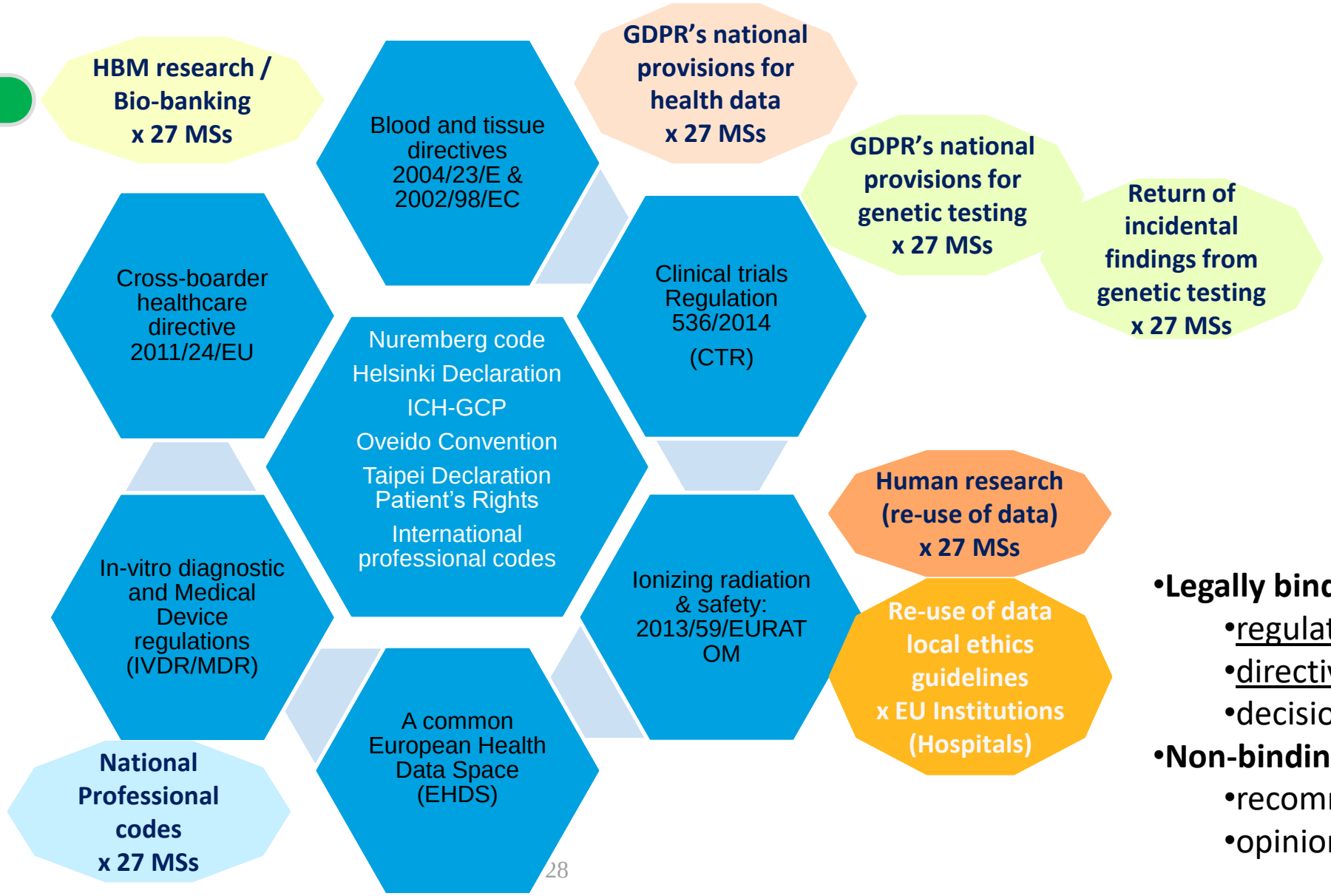
**GDPR**

**ePrivacy Directive**

**Data Governance Act**

**Cloud code of Conduct**

**AI framework**




- **Legally binding acts**
  - regulations
  - directives
  - decisions
- **Non-binding acts**
  - recommendations
  - opinions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The future of cancer therapy