3º ENCONTRO NACIONAL DE INVESTIGAÇÃO CLÍNICA & INOVAÇÃO BIOMÉDICA

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THE FUTURE OF CLINICAL RESEARCH ACTIVITIES – OPPORTUNITIES FOR EUROPE/PORTUGAL

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- Views expressed are those of the speaker only.
- Speaker has no conflict of interest and is retired.

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Overview

- European healthcare and clinical trial landscape
- Implementation of CTR and CTIS
- ICH Clinical Trial and GCP modernization
- Digitalisation
- ACT EU and multistakeholder platform (MSP)
- Conclusion

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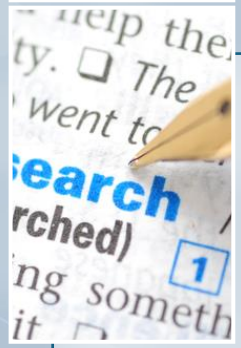
Advantages of Clinical Trials (CTs) in Europe

Access to a **world class Clinical Research Community** with extensive experience in conducting high quality CTs.

An **evolving regulatory environment** that facilitates clinical trial conduct



Policies that promote research into orphan drugs and rare diseases – support for SMEs

Ability to obtain **scientific advice on innovative CT design** and innovative evidence generation

- **Investment** in clinical trials in **EU represents 10s of billions of euros,** a **large p**art of it coming **from outside of EU** – an essential element in **sustaining EU technical expertise, innovation and healthcare**
- Between 20012-2022 approx. **3000** clinical trials of medicines were authorised annually in the EU.
- The EU is home to approx. 1.8 million **practising physicians**, 2.8 million **practising nursing professionals** and 450 000 **practising pharmacists,** 2.6 million **hospital beds** available for use and approximately 3.7 million **long-term care beds .**

Clinical Trials Sponsored by Academia/public health bodies are essential

- **Public health and scientific innovation** in development of medicines and therapeutic approaches **rely on basic and translational research by academic/public health** bodies.
- Academia has **different approaches, priorities, structures and resource**, compared to pharma industry.
- **Infrastructure and resource** for academic/public health trials **need to be funded**,
- **Different ways of working need to be accepted**.
- A strong academic / public health clinical trial infrastructure:
  - Brings **benefit for patients far beyond the clinical trials** per se
  - Supports retention and development **of clinical expertise**
  - **Attracts pharma led trials** and related **expertise**, **access to innovative medicines and investment**
  - **Patients** participating **in clinical trials** also generally fare better

Funding of clinical trials

- Clinical trials sponsored by pharma industry are funded by them. They nonetheless rely on:
  - Good investigator sites with experience and resource (staff and equipment)
  - Networks of sites
- Funding for academic trials is often limited to the country of the funder
- Funders need to connect with each other to fund multinational trials
- Investigators/institutions should work multi-nationally to reach out to funders
- CT regulation enables joint sponsorship supporting a consortium approach
- Funders should ensure (and researchers request) that funding include the resource to be sponsor
  - i.e. to lead, mulitinationally, the scientific, regulatory, logistical and reporting activities from inception of final publication of results

EU R&I actions to facilitate clinical trials across the EU

https://commission.europa.eu/research-and-innovation_en

- Support clinical trial networks and coordination
- Maximise public health impact through innovative trial design
- Partnerships with EU member states, agencies, industry
- Strengthening regulatory environment
- Support through research infrastructures

- Examples:
  - **ERA4Health:** investigator initiated trials, comparative effectiveness and repurposing
  - **ECRAID, REMAPCAP:** adaptive clinical trials and platforms
  - **European Clinical Research Infrastructure Network (ECRIN)**
  - Pragmatic clinical trials to optimise treatments for patients under Cancer mission

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CT Regulation and the Clinical Trials Information System (CTIS)

CTIS is the business tool of the Clinical Trials Regulation.

CTR and CTIS **harmonise the submission, assessment and supervision of clinical trials** in the EU/EEA.

Single application for regulatory and ethics committee review, public registration of the trial and later its summary results, **regardless of the number of Member States** involved, **one timeframe**, **single decision per Member state**

Enabling multinational trials

Public health

Facilitates multinational trials to address key health issues, increase transparency & enables patient enrolment

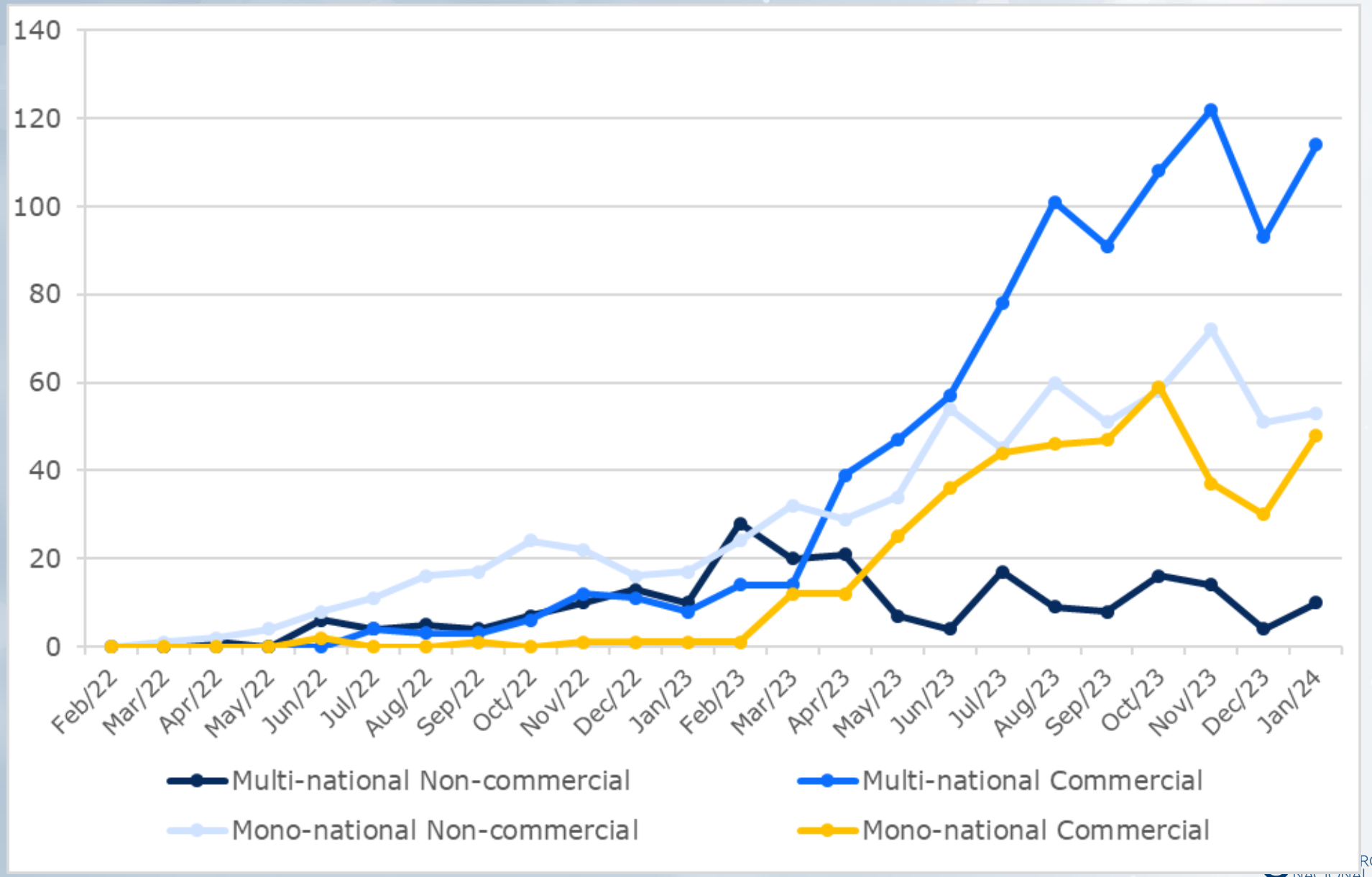
Research and innovation

Enables collaboration and access to clinical research data.

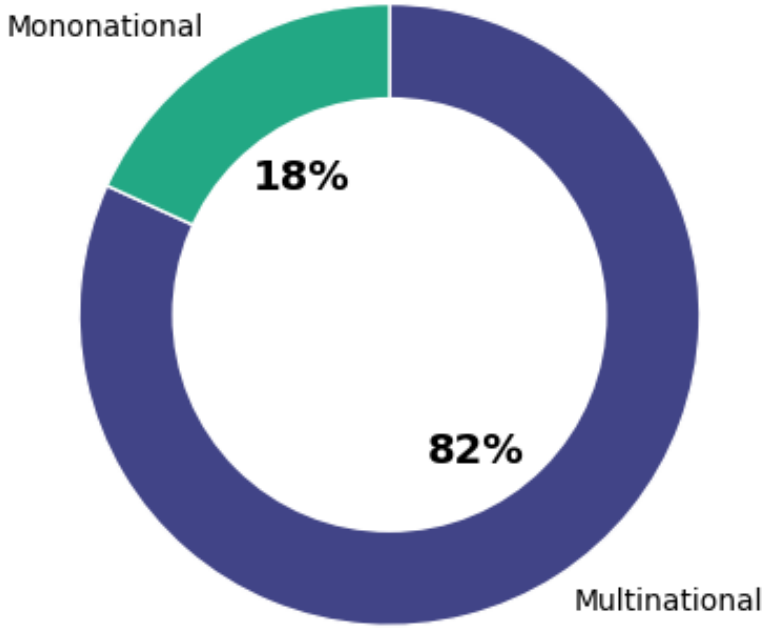
Global hub for clinical trials

Ensures the EU/EEA remains an attractive clinical research hub globally.

Authorised CTs in CTIS: sponsor type, mono/multinational



Distribution of mono- and multinational trials in Portugal under CTR



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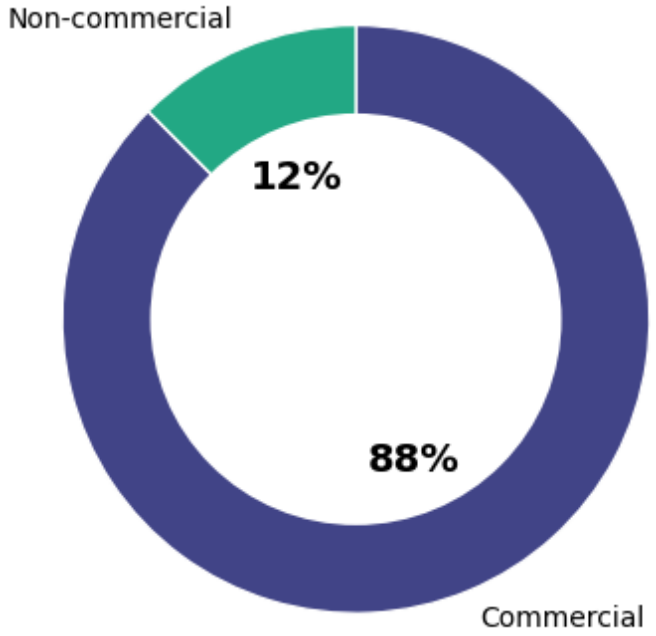
Distribution of sponsor types in authorised trials in Portugal under CTR



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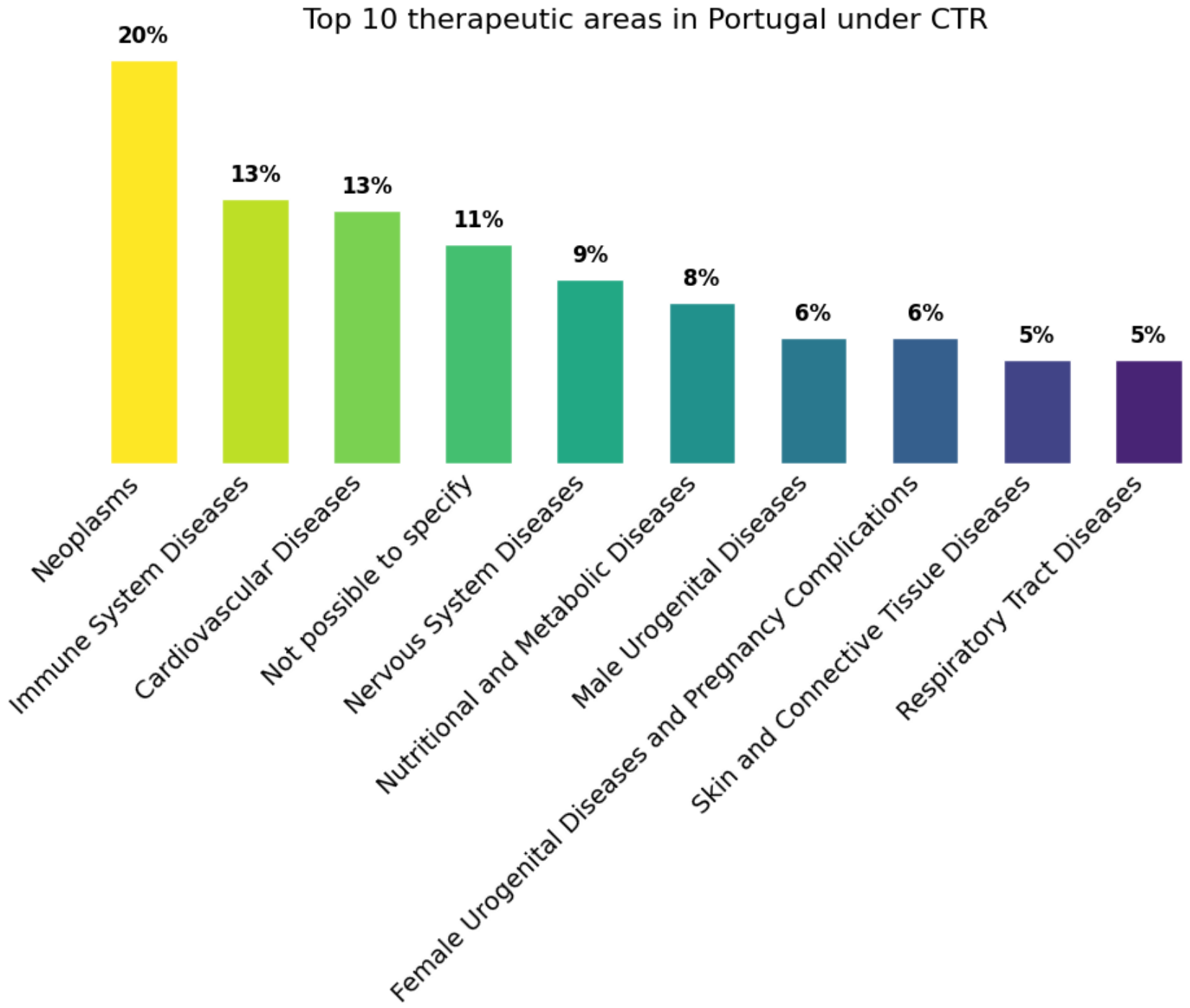
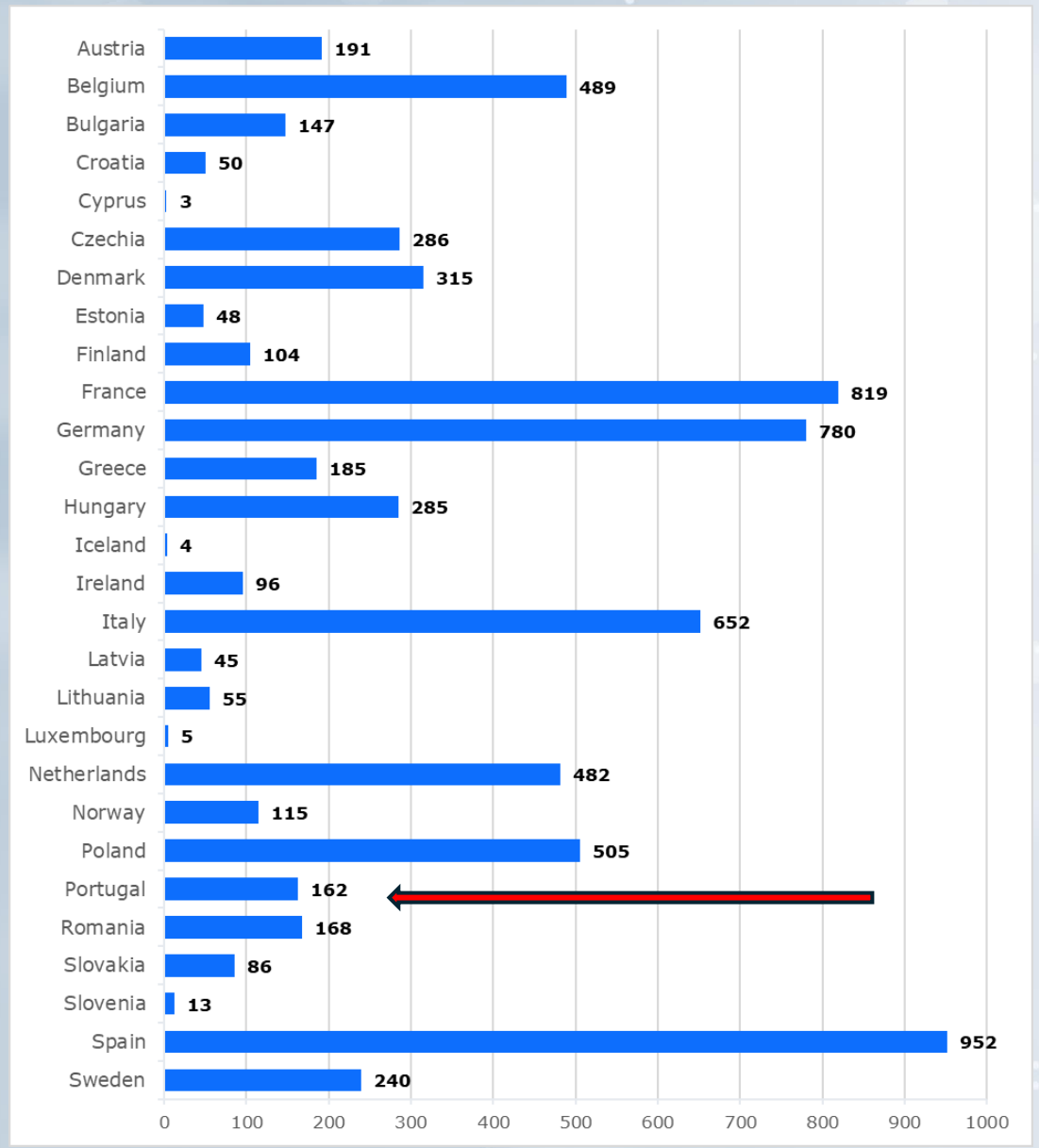
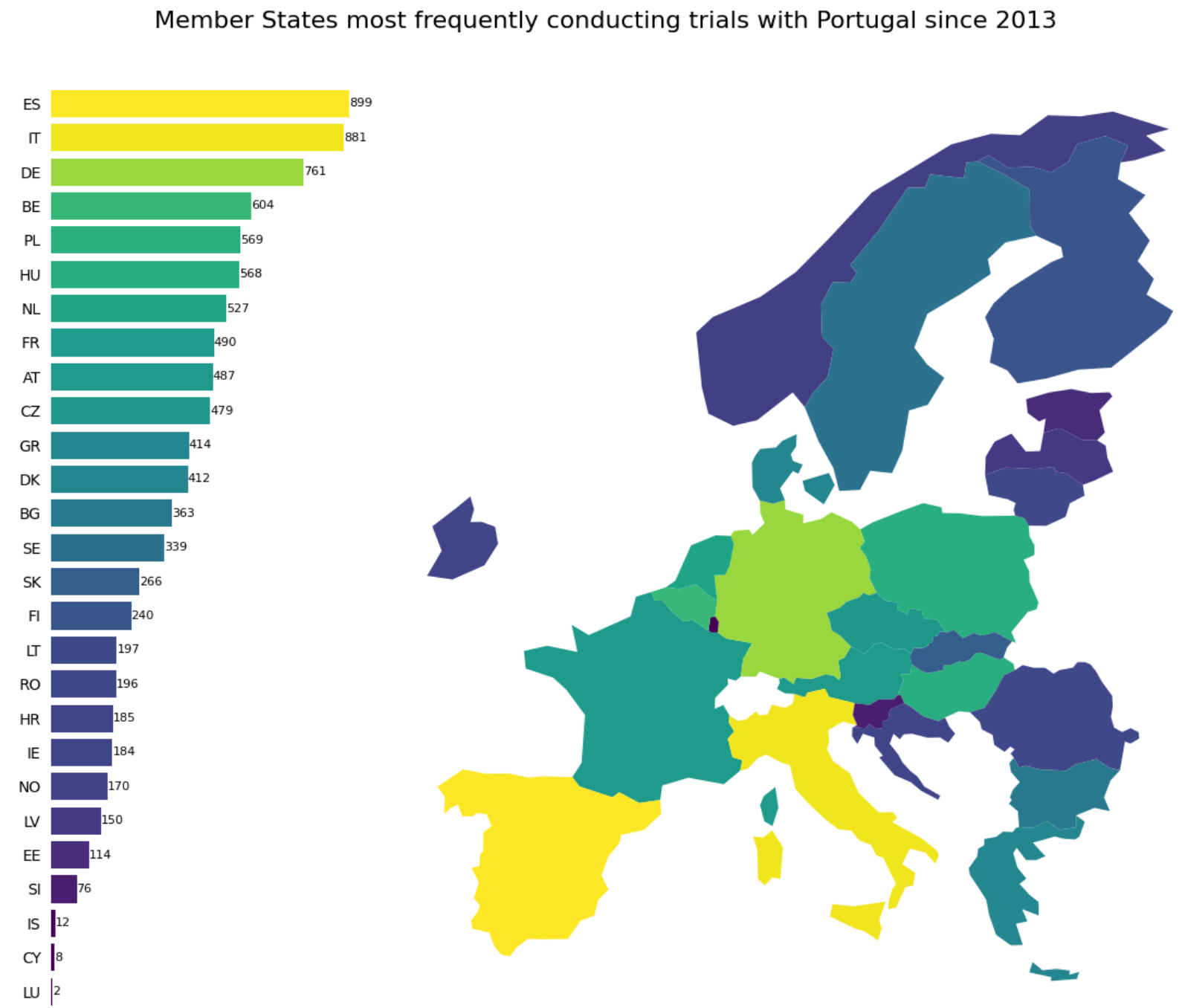


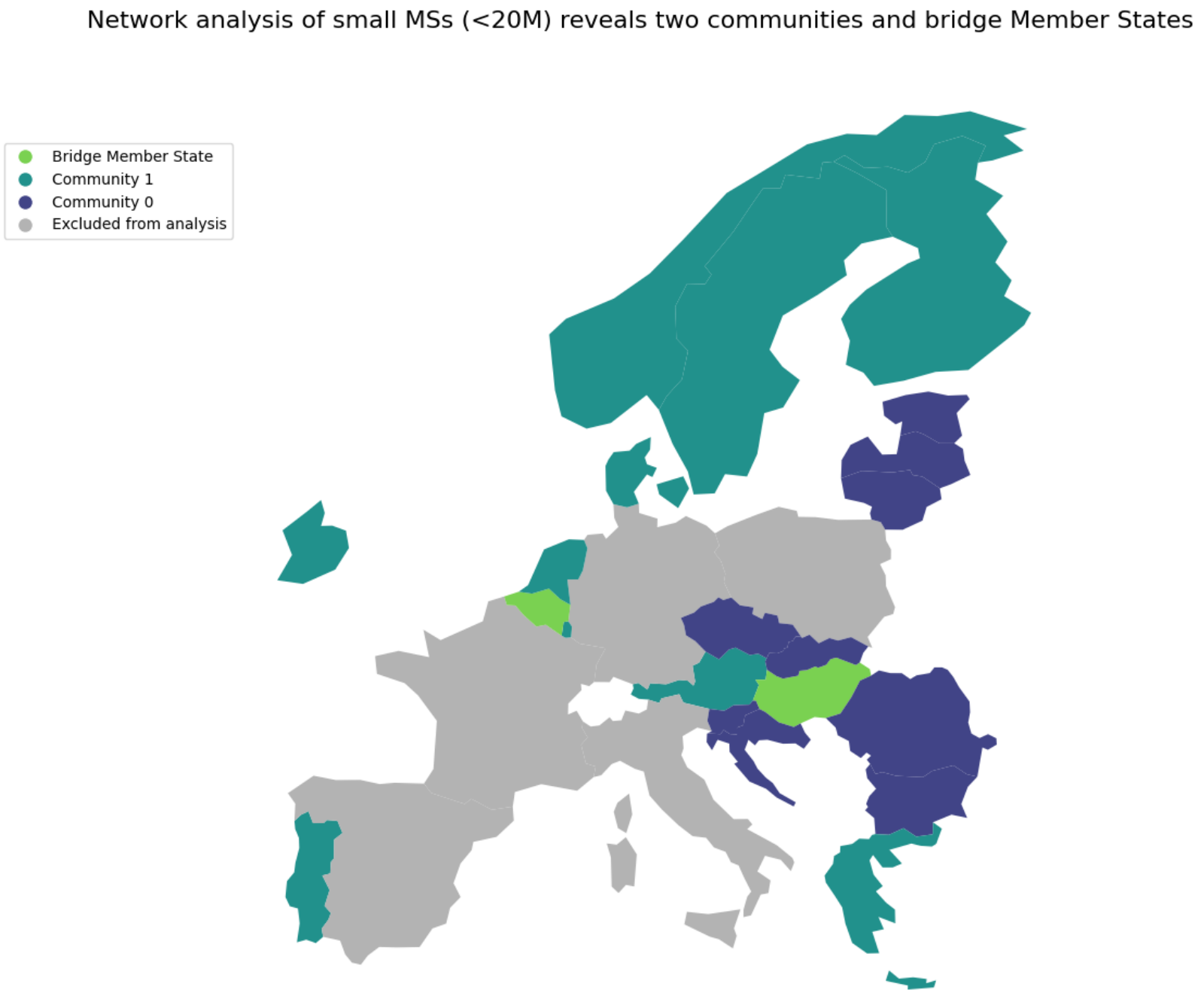
Top 10 Therapeutic areas in Portugal in CTIS (so 2022 to present)

Authorised CTs, in CTIS, per Member State Concerned

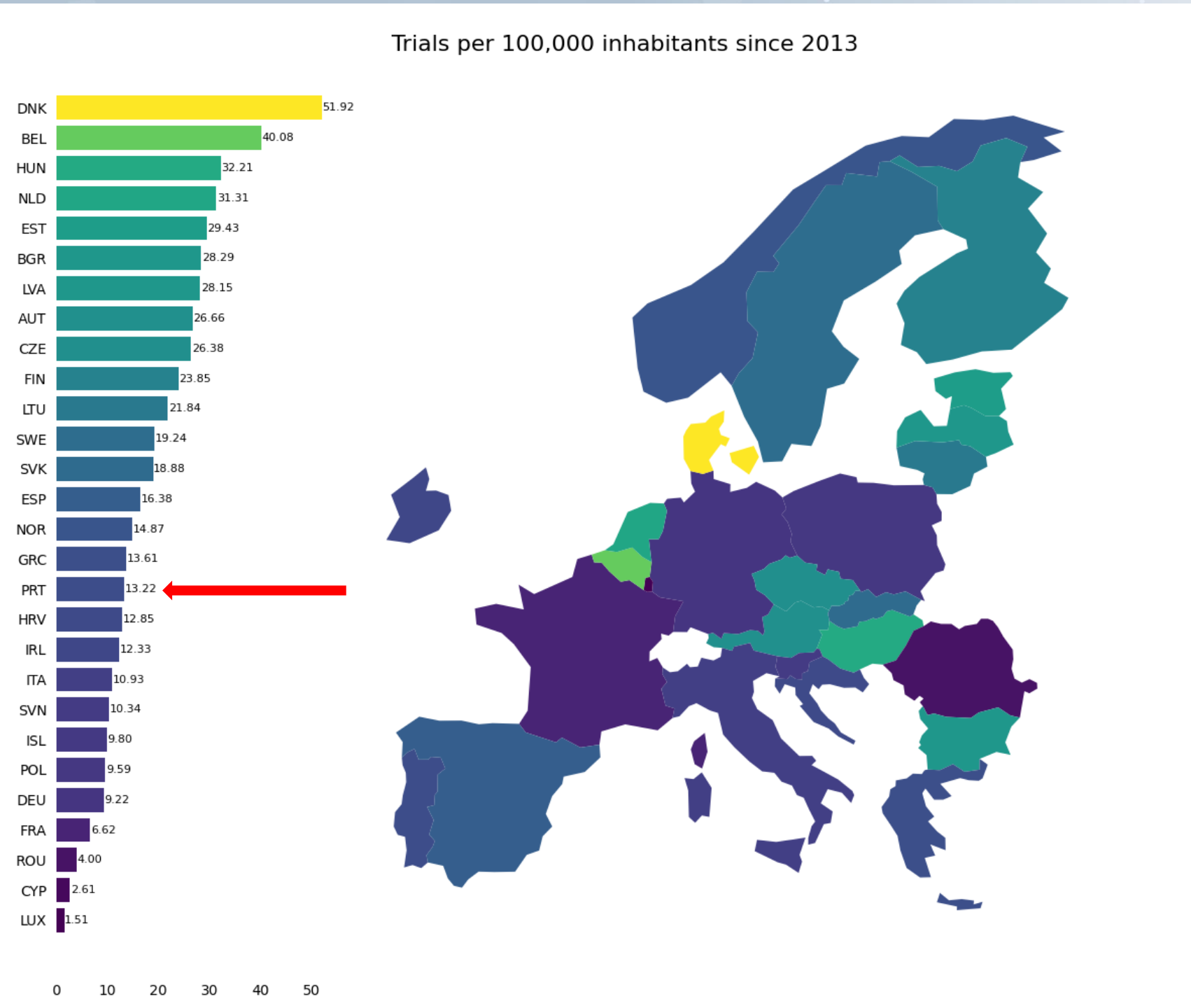




Member States carrying out trials also carried out in Portugal – 2013 to 2024



Network analysis of MS with <20m inhabitants participating in CTs – two communities and bridging MS – 2013 to 2024



No. of trials per 100,000 inhabitants – 2013 to 2024

Supporting participation in multinational trials a major goal of Clinical Trial Regulation

- Reach out and build connections with clinical trial networks in other countries
- Use CT Regulation and CTIS to facilitate multinational trials:
  - **Sponsors and regulators should establish a role of CTIS coordinator** with backup(s),
    - Operate CTIS effectively
    - Enable experts, and assessors to perform their scientific, clinical or regulatory assessment roles
  - **Academic research** centres/sponsors should **build sponsorship** capacity:
    - Build capacity to manage clinical trials, including larger multinational trials
    - Act as partner in a co-sponsorship agreement with groups in other countries
  - **Regulators and Ethics Committees** assessing CT applications should **rely on RMS**:
    - Rely on the Reporting Member State (RMS) assessment when another MS is RMS, and lead it when acting as RMS
    - Focus list of outstanding issues to sponsors on the essential issues to enable timely responses – sponsors only have 12 days to reply

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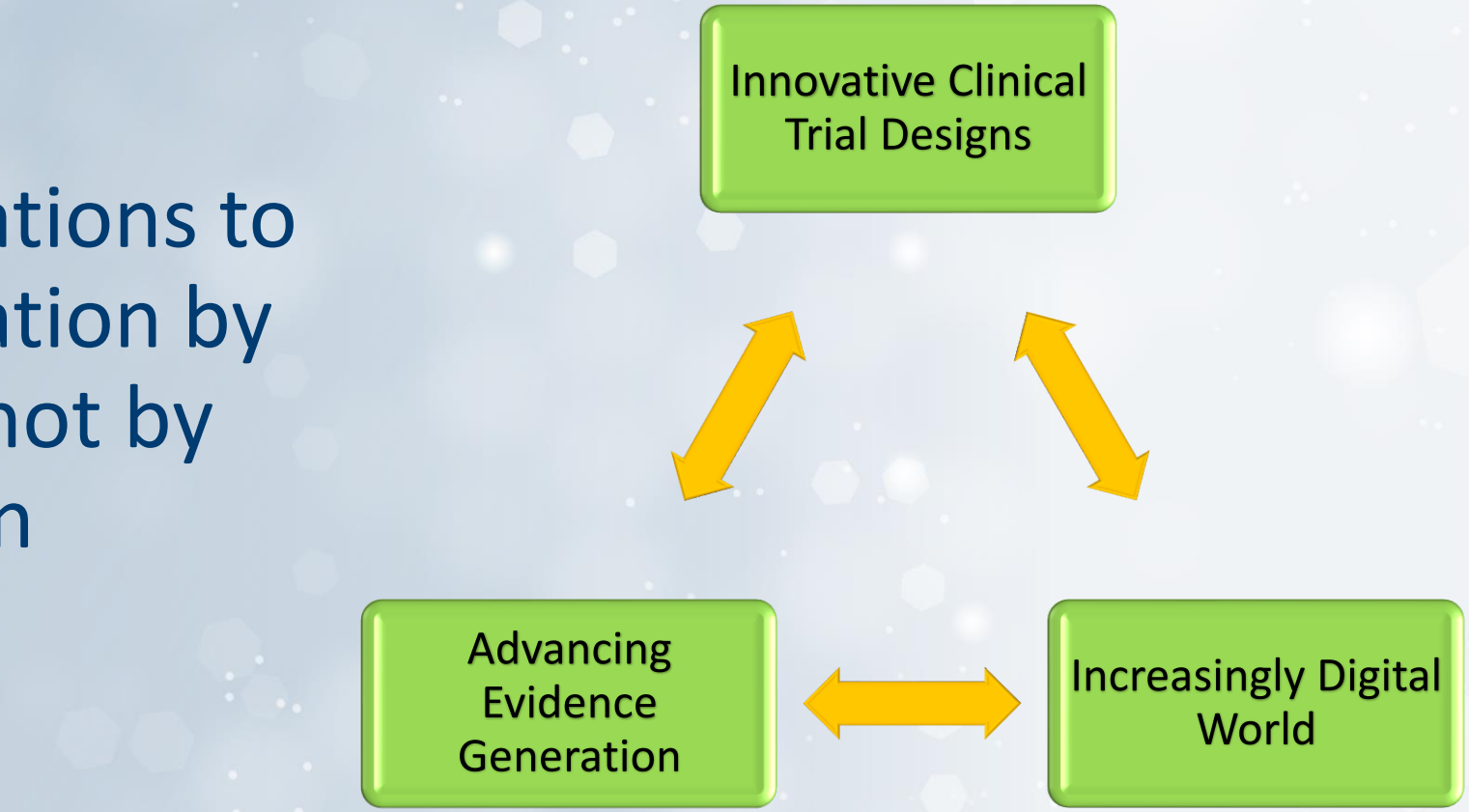
ICH GCP renovation: Redesign our approach to enable innovation in a Rapidly Evolving Ecosystem

Set the foundations to enable innovation by design and not by reaction



ICH Clinical Trial Guidance Renovation

General Considerations on Clinical Studies (ICH E8)	finalised October 2021
Good Clinical Practice (ICH E6 R3) – principles and detailed guidance	finalisation Q4 2024

- Purpose of clinical trials is to generate **information of sufficient quality** to **support good decision making**
- **Focus** on achieving **quality by good design**, with a **proportionate**, **risk based approach**, to trial design and conduct.
- **Focus resources** and efforts on **what matters most** for participant protection and the reliability of trial results

ICH E8 2 GENERAL PRINCIPLES

2.1 Protection of Clinical Study Participants

- **"… have their origins in the Declaration of Helsinki…."**

2.2 Scientific Approach in Clinical Study Design, Planning, Conduct, Analysis, and Reporting

- **"Quality - fitness for purpose."**
- **"Purpose … generate reliable information to answer the research questions and..quality ..sufficient to support good decision making. "**
- "**Quality by design** .. quality….**driven proactively** by **designing quality** into ..**protocol and processes**... "

2.3 Patient Input into Drug Development

- **"Consulting with patients**/patient organisations …. ensure .. **patients' perspectives are captured. "**
- **"Involving patients early** in the design .. **increase trust … facilitate recruitment .. promote adherence."**
- **"…. supports the development of drugs …better tailored to patients' needs."**

ICH E8 Section 3.3 Approach to Identifying the Critical to Quality Factors

Identifying attributes whose integrity is fundamental to study quality

3.3.1 Establishing a Culture that Supports Open Dialogue

3.3.2 Focusing on Activities Essential to the Study

3.3.3 Engaging Stakeholders in Study Design

3.3.4 Reviewing Critical to Quality Factors

ICH GCP Renovation

- The **GCP Principles** contain the **essential reference** for trial conduct
- **Enable** and **facilitate** good clinical trials.
- **Focus on** the **intent and goal** of GCP and **allow** for the **many ways** these can be achieved.
- **Proportionate, efficient approaches** – design/resource **focus**sed on **what matters most.**
- **Enables** centralised monitoring, decentralised trials, simpler trials, digital processes, new trial designs and approaches

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Digitalisation

- Use of digital tools is progressing in healthcare as well as in clinical trials.
- Use these opportunities to support innovation and new approaches in clinical trials
- Establishing Trust, Enabling Research:
  - Data provenance, validity (technical and scientific),
    - Open, future proof standards that enable innovation
  - Personal data protection is an enabler of research –
    - Patients have a legal right that their personal data is protected.
    - Patients have a legitimate expectation that they have access to involvement in research and to its benefits, and that their data is well used so research can answer important questions.
    - These rights and expectations need to be properly balanced.
- Facilitate decentralised trials, use of wearables, patient reported outcomes and centralised monitoring
- Healthcare and research can be complex but we should not make them complicated

Enabling decentralised clinical trials

- Decentralised tools and approaches may be used singly or in combinations.
- Individual elements mostly not new, are possible, and used in trials and healthcare for a long time.
- Pandemic - clear use case – but advantages of decentralised trials need to be permanently and widely available.
- A clinical trial should deliver reliable results usable as the basis of decision making
- The science should be addressed first, and then a determination of which element can use decentralised approaches
  - Depends……on the research question, the medicine, the therapeutic indication, need for in person contact for the tests, treatment administration and care of the participant.
  - The choices based on what is clinically appropriate and feasible for the participants' care and scientifically valid to answer the question that is being addressed by the trial.
- Sponsor and investigator have clear legal roles and responsibilities. These can be fulfilled in decentralised trials.
- Role of the investigator needs to be clear … medical care of the trial participant, in the context of the trial…..controlled by the investigator.
- The autonomy of the trial participant needs to be respected.
- ICH GCP revision is working to further enable and support decentralised clinical trials.

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Accelerating Clinical Trials in the EU (ACT EU)

- **a joint initiative of HMA/European Commission/EMA**
- to **transform the EU clinical research environment** in support of medical innovation and better patient outcomes.

Problem statement

- Need for more impactful multi-state trials which drive decision-making
- Need for an overarching strategy to bring stakeholders together
- Multiple actors requiring clear roles and responsibilities
- Need to leverage the EU's strong healthcare and research infrastructure in the EU

ACT EU vision

- EU as an attractive region for clinical research
- Enabling **larger and more impactful CTs**, with seamless coordination among regulators and stakeholders
- Smart CTs through **regulatory, technological and process innovation**
- Empowering, engaging and supporting **stakeholders**

A multi-stakeholder approach for progress in clinical trials

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Clinical trials are a key element of European innovation, therapeutic expertise and healthcare:

- Seize the opportunities that change and innovation are offering
- Enable and support clinical trials including new approaches and multinational trials
- Focus on what is essential, ensure effectiveness and efficiency
- Engage with all stakeholders
- Reinforce public health/academia trials

Change the way we all work – Change Management is the greatest challenge

– adjusting behaviors, attitudes – away from preconceived ideas and interests – and on to a new, better, way of working.

The greatest achievements will be by those who embrace new approaches and seek to make them work – there is no regulatory impediment per se.

"Perfection is achieved not when there is nothing more to add but when there is nothing left to take away" *Antoine de Saint-Exupéry*

"Everything should be made as simple as possible but not simpler" *Albert Einstein*

Thank you for your attention

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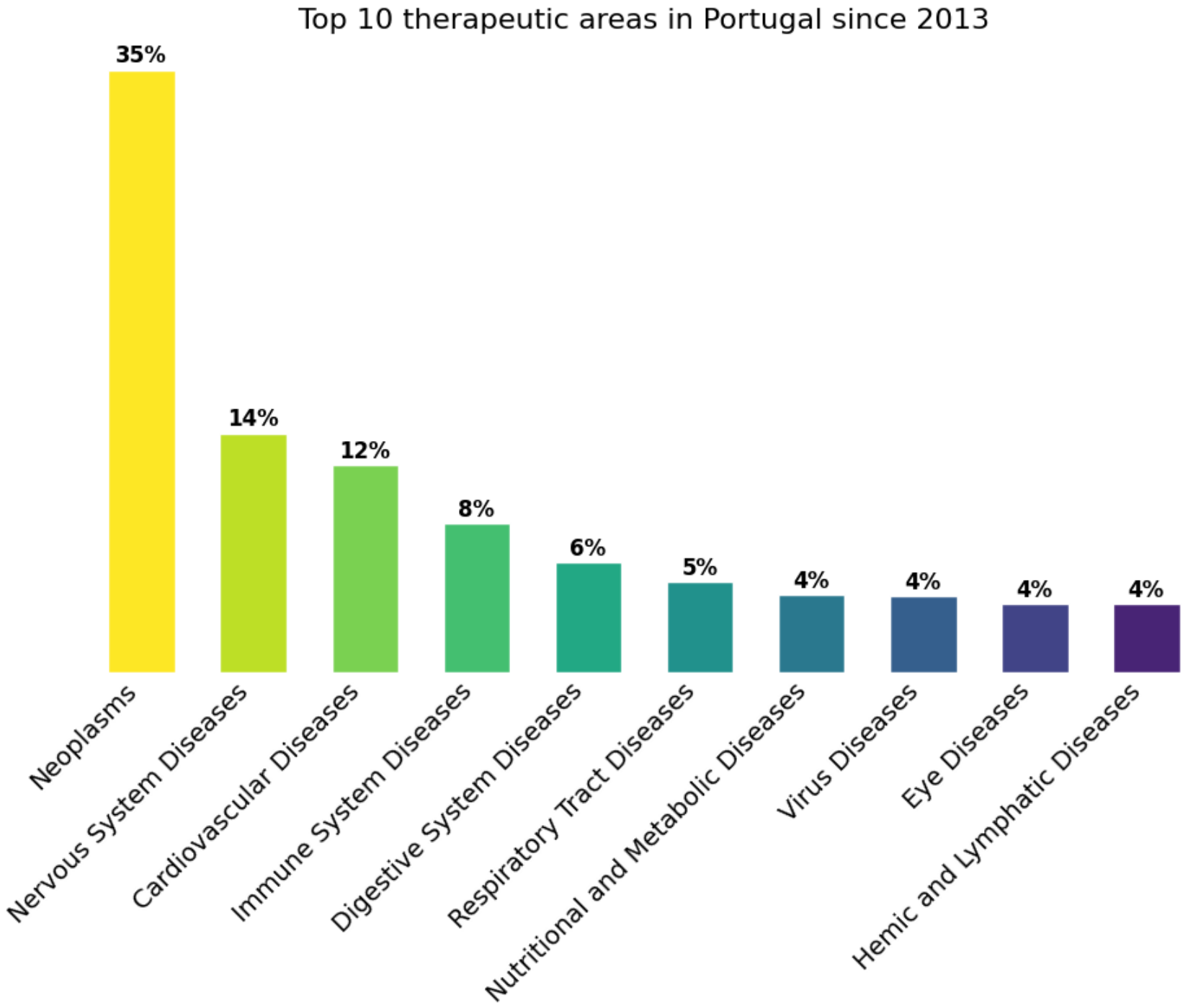

Top 10 Therapeutic areas in trials in Portugal – 2013 to 2024

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ICH E family of guidelines – need to be read together

E8 General Considerations for Clinical Studies

Design and analysis:

E4 Dose-Response Studies
E9 Statistical Principles for Clinical Trials
E10 Choice of Control Group in Clinical Trials
E17 Multi-Regional Clinical Trials
E20 (in draft) Adaptive Clinical Trials

Conduct and reporting:

E3 Clinical Study Reports
E6 Good Clinical Practice

Safety reporting:

E1 Clinical Safety for Drugs used in Long-Term Treatment
E2A - E2F Pharmacovigilance
E14 Clinical Evaluation of QT
E19 Safety Data Collection

Populations:

E5 Ethnic Factors
E7 Clinical Trials in Geriatric Population
E11 - E11A Clinical Trials in Paediatric Population
E12 Clinical Evaluation by Therapeutic Category
E21 (in draft) Inclusion of Pregnant and Breastfeeding Individuals in Clinical Trials
E22 (in draft) /general Considerations for Patient Preference Studies

Genetics/genomics:

E15 Definitions in Pharmacogenetics / Pharmacogenomics
E16 Qualification of Genomic Biomarkers
E18 Genomic Sampling

Over the next 4 years ACT EU aims to

- Ensure **effective operation** of the clinical trials regulation
- **Simplify governance** and **align CT approval** with scientific advice
- Support academic sponsors to conduct **impactful, multinational, clinical trials**
- Encourage use of **novel methodologies**
- Enable **decentralised approaches**
- Training: create an **educational "ecosystem"** (leveraging existing initiatives)
- **Align internationally** (including GCP modernisation)
- **Optimise the use of data** about clinical trials for better research and decision-making
- Build and operate the ACT EU **Multi-Stakeholder Platform** (MSP)
- Enable CTs in **public health emergencies**