

# EORTC TRACE platform

## Tracking and Treating Rare Cancers, AYA and Rare Entities in the EU (TRACE)

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*CDDF Multi-stakeholder Workshop* - Innovation and Access in Rare Cancers

Presented by D Lacombe – 23 September 2024

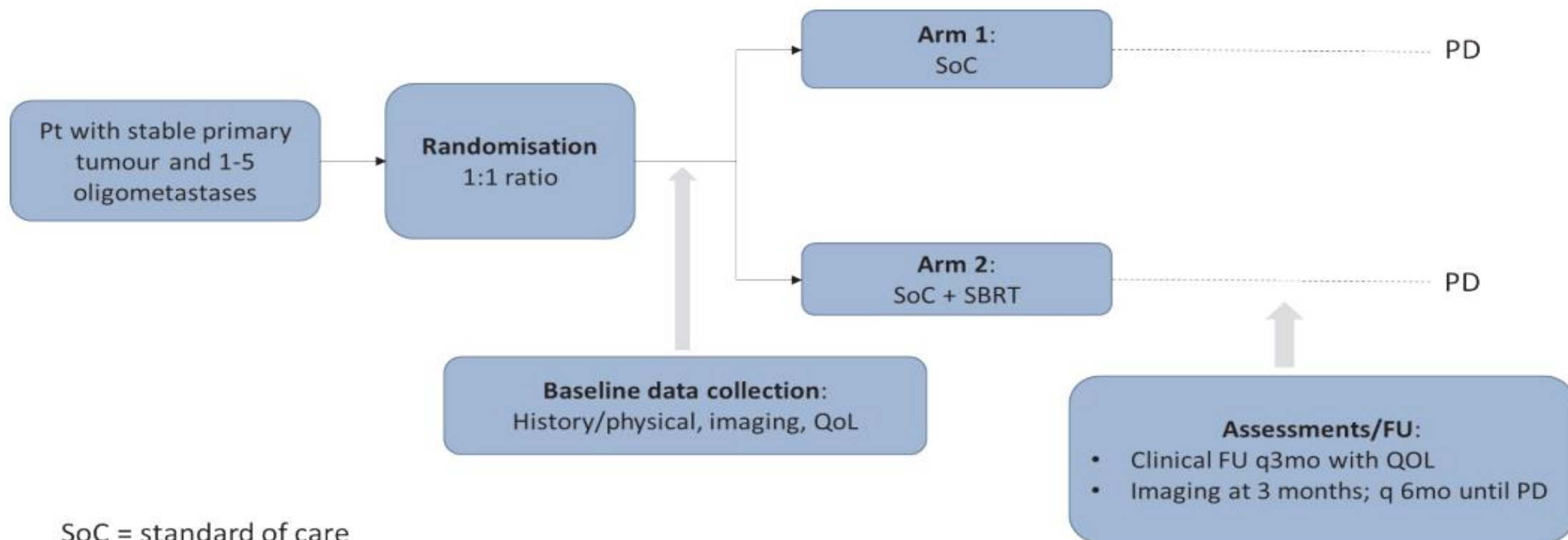
# Where are we coming from?

- We have conducted trial successfully
- We have poorly performed on others
- We have some ambitions to deliver robust evidence to all cancers
- This is probably too complex for a single organisation to sustain solutions that could serve all rare cancers
- We listen to the interests and needs of all stakeholders
- We need to embrace the new data-science opportunities
- We need to reflect how the cross-cutting specificities of rare cancers could benefit from common solutions
- We try to understand the limits of existing methodology for Rare Cancers (RC) and what could be new opportunities

# Some examples in rare cancers

- Radiotherapy: Oligorare
- Molecular diagnostics – Arcagen
- Platform trial lung NET Colinear

# Stereotactic body radiotherapy in addition to std of care treatment in patients with oligometastatic rare cancers (OligoRare)



SoC = standard of care

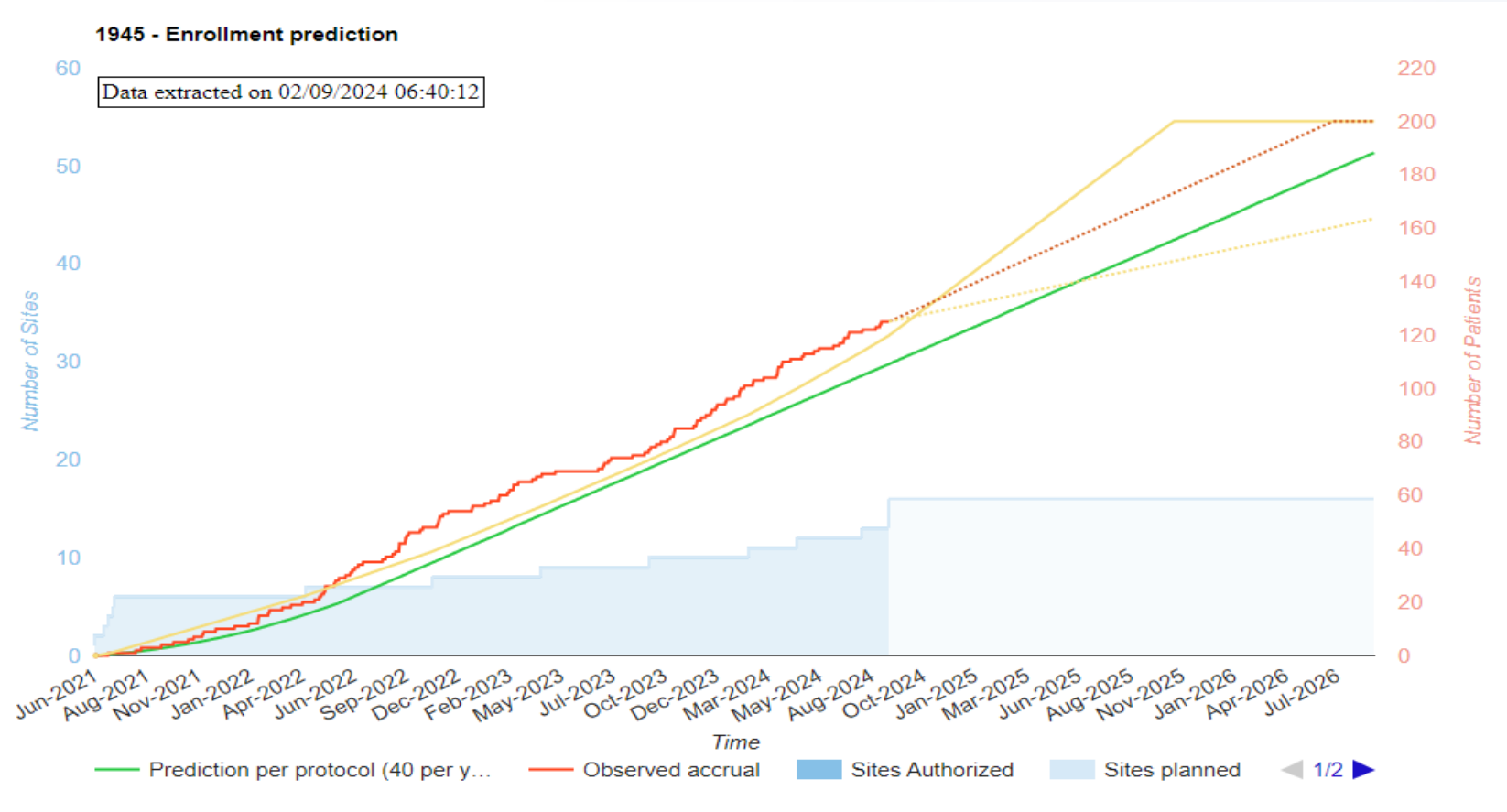
SBRT = stereotactic body radiotherapy

QoL = quality of life

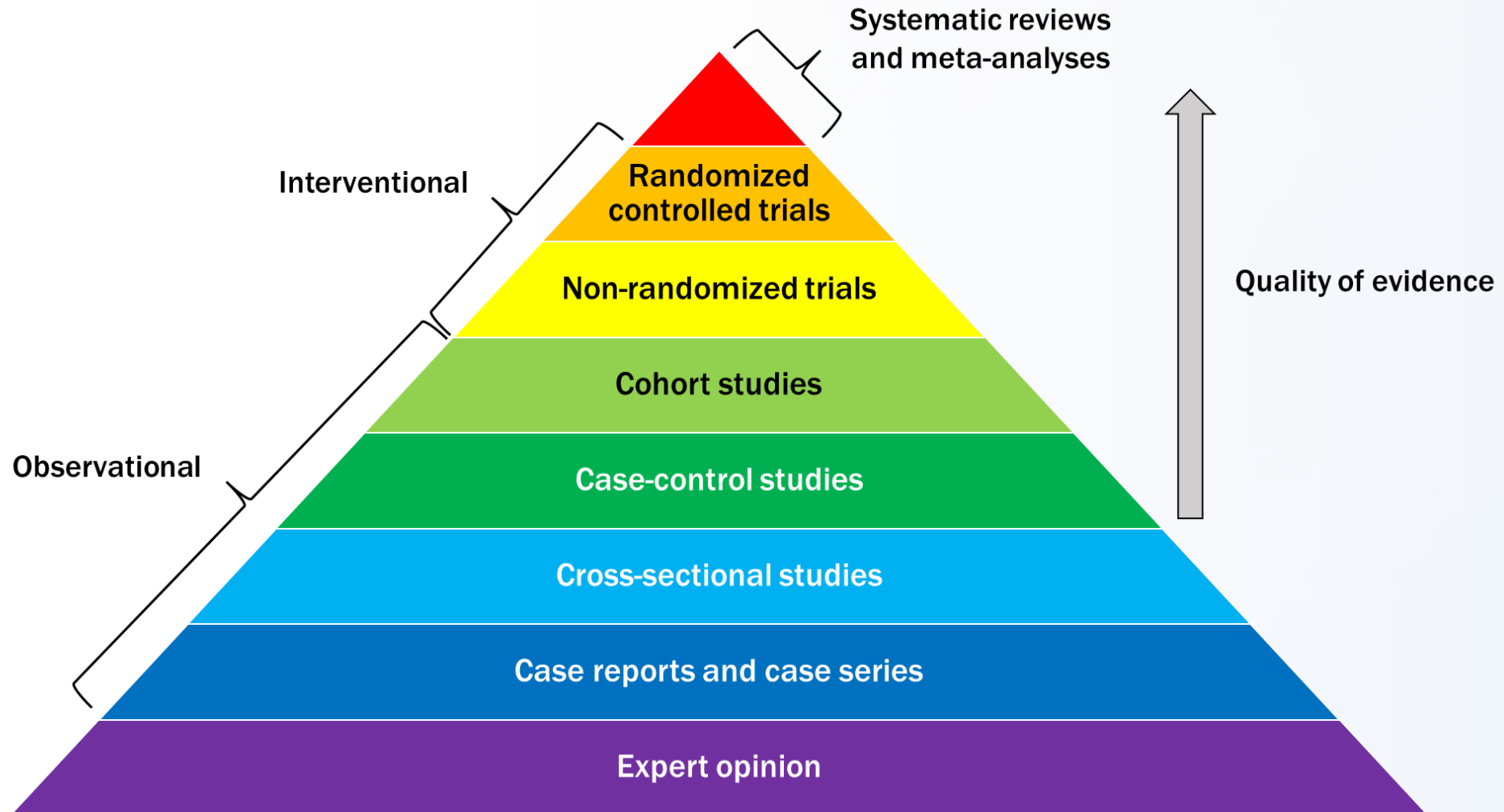
FU = follow-up

PD = progressive disease

# Enrolment status (as of 02/09/2024)



# Always aiming to the highest level of evidence



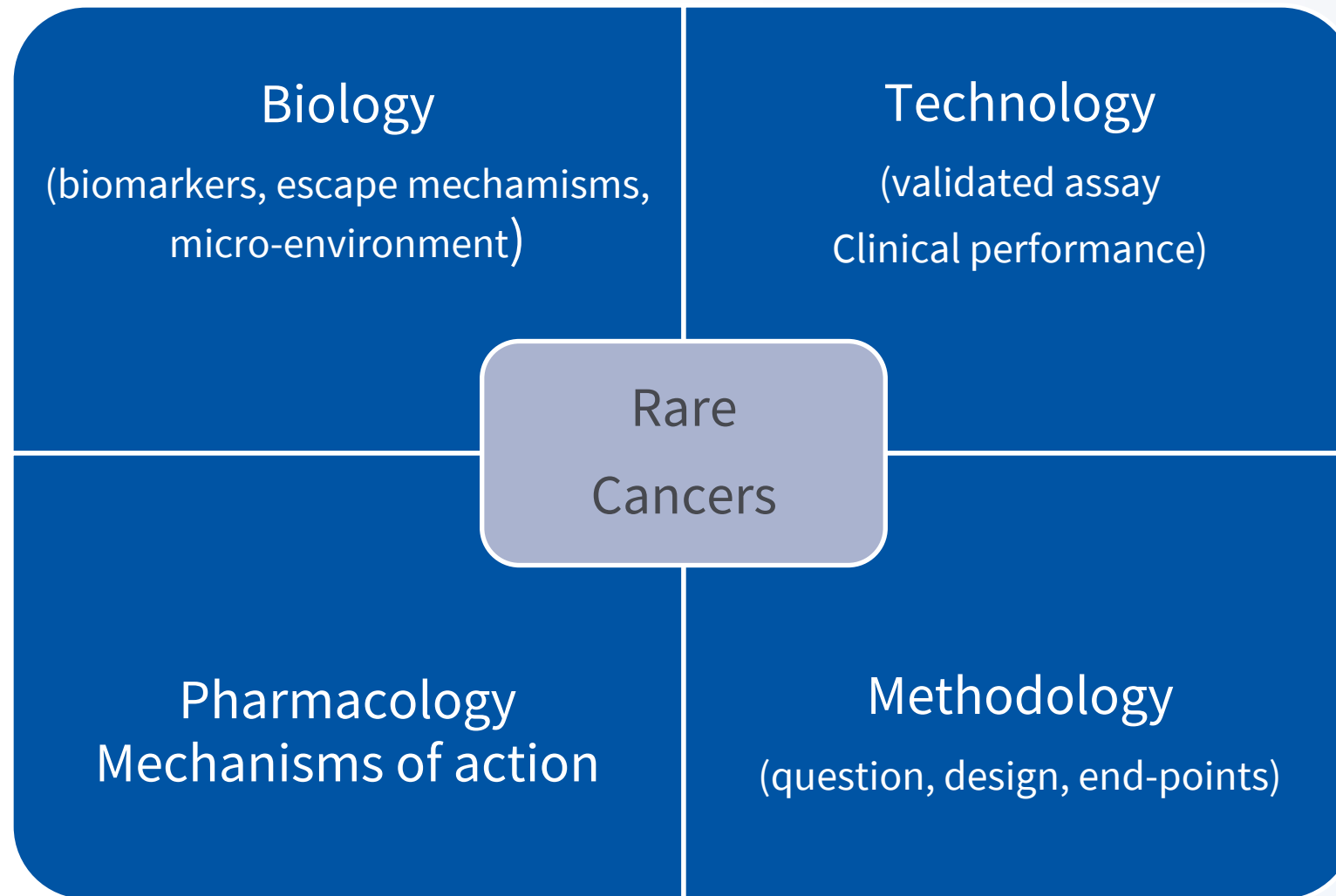
# Consider seriously weaknesses for interpretation of the datasets

- Use of historical controls/ Absence of randomisation
- Limits of RWD: Quality of retrospective datasets
- Variability of the pre-treatment and background treatments
- Variability of recruitment across cohorts in basket trials
- Surrogate end-points
- Subjective assessments
- Variability of response evaluation (interval, technique, RECIST or not)
- Enrichment strategies: may lead to miss capture of other heterogeneity factors such as demographics, micro-environment and question the value of the surrogacy for decision

# **When rarity and randomisation are not compatible**

Are histology agnostic trials a solution?

# Selected common challenges need common solutions



# From biology and biomarkers to study designs

What have we learned so far

(with frequent cancer or not so frequent tumors)?

# Biology can be very specific

|                | Melanoma                     | CRC                                                          |
|----------------|------------------------------|--------------------------------------------------------------|
| BRAF Mutations | No feedback activity of EGFR | Feedback activity of EGFR responsible for primary resistance |

|                  | Gastric cancer                                                                 | Breast Cancer                                                                   |
|------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| HER2 Alterations | High intra-tumoral heterogeneity<br>Low membrane distribution of the receptors | Low intra- tumoral heterogeneity<br>High Membrane distribution of the receptors |

Complex interactions between different pathways may be highly variable across histologies

# Some of the questions

- Development plan: impact on access and acceptability by HTA/payers: what are the missing datasets?
- Optimal integration/ validation of companion diagnostic/ genomic testing in care: clinical utility/performance across tumor types
- *Are histology independent trials designed ONLY to learn? To conclude? At the regulatory level? At the healthcare/clinical level?*
- Should “confirmatory datasets “be required: RCT? RWD?
- (perception of ) loss of equipoise
- Should the process be re-engineered and what is the methodological approach to be developed?

# Methodological considerations

- Hypothesis: presence of the alteration determines the response to treatment. Can the the null hypothesis be true for all indications?
  - If similar activity cannot be guaranteed across histologies, any type I error (false positive) across diseases will induce bias and increase the possibility of misidentification of activity
  - Unbalanced recruitment across histologies further increase the uncertainty

Think biology: for histology independent trials, consider cohort by cohort approach

- Bayesian vs frequentist: not a debate, the question is rather how much we accept “borrowing” for efficacy? for safety?

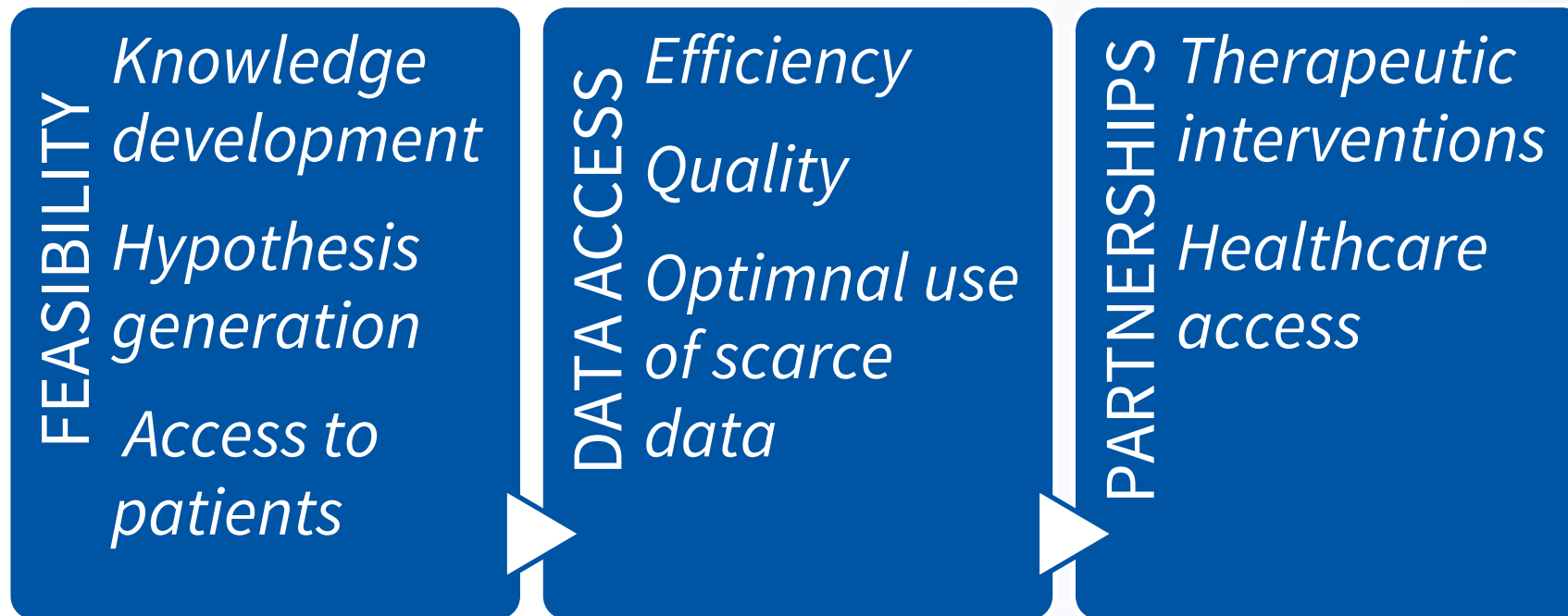
All depending on the ultimate goal for which the study is designed

# From the one size-fits-all in a given histology to precision oncology, would we be moving to a one size-fits-all across histologies?

- How consistent should we be?
- How can all stakeholders reasonably align?
- Should we look at biological pathway development in place of drug development?

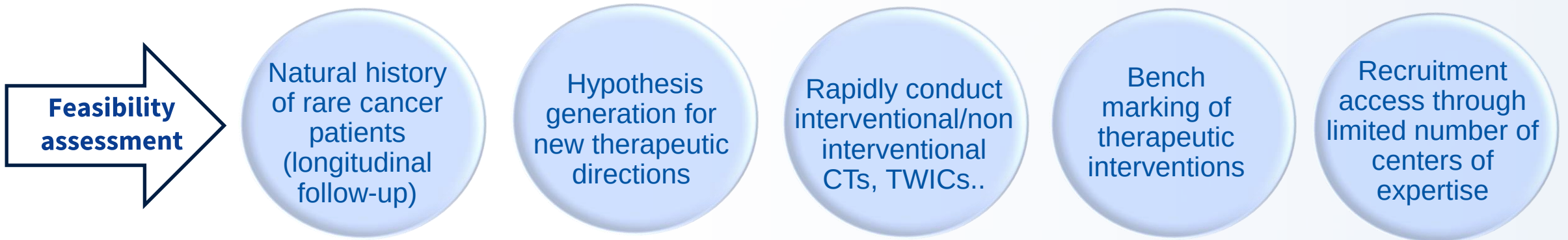
**Could we also consider taking other directions for access to rare cancers?**

# Operational challenges to address



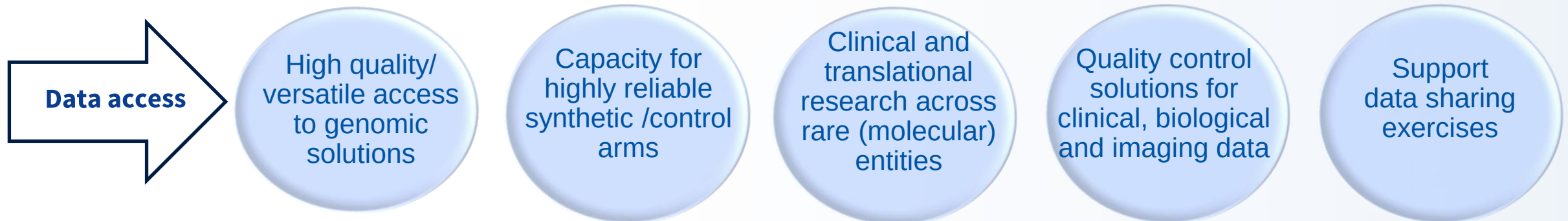
# What do we optimally need for rare cancers?

## FEASIBILITY



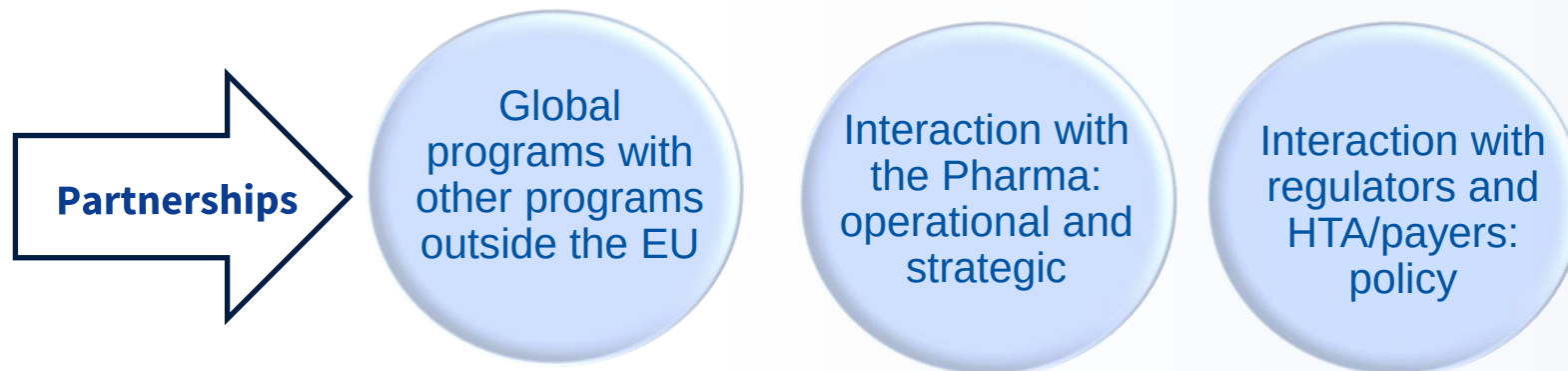
# What do we optimally need for rare cancers?

## DATA ACCESS



# What do we optimally need for rare cancers?

## PARTNERSHIPS



# A registry supporting an observational study

## SPECTA ( all tumors)

- **160 investigators** authorized to recruit
- **20 countries** represented
- Around **4000 patients registered**
- **2940 patients eligible** for a downstream project
- More than **2100 molecular reports** generated
- **10 cohorts opened** to recruitment
- **10 cohorts under analysis** after reaching targeted recruitment

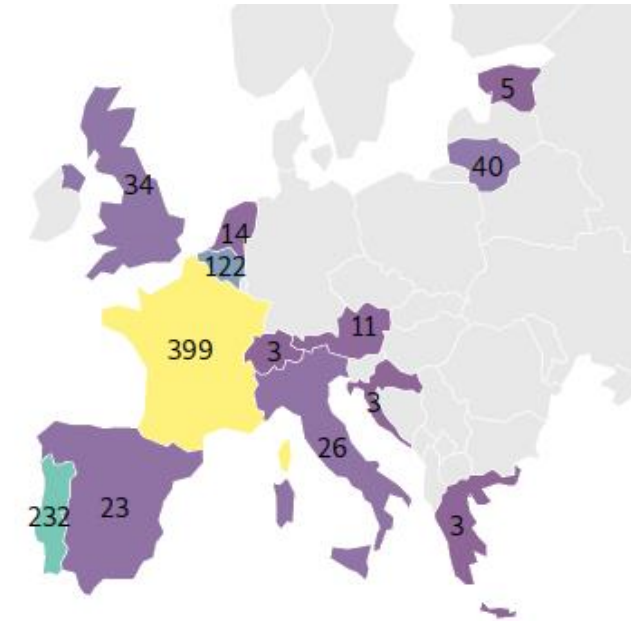
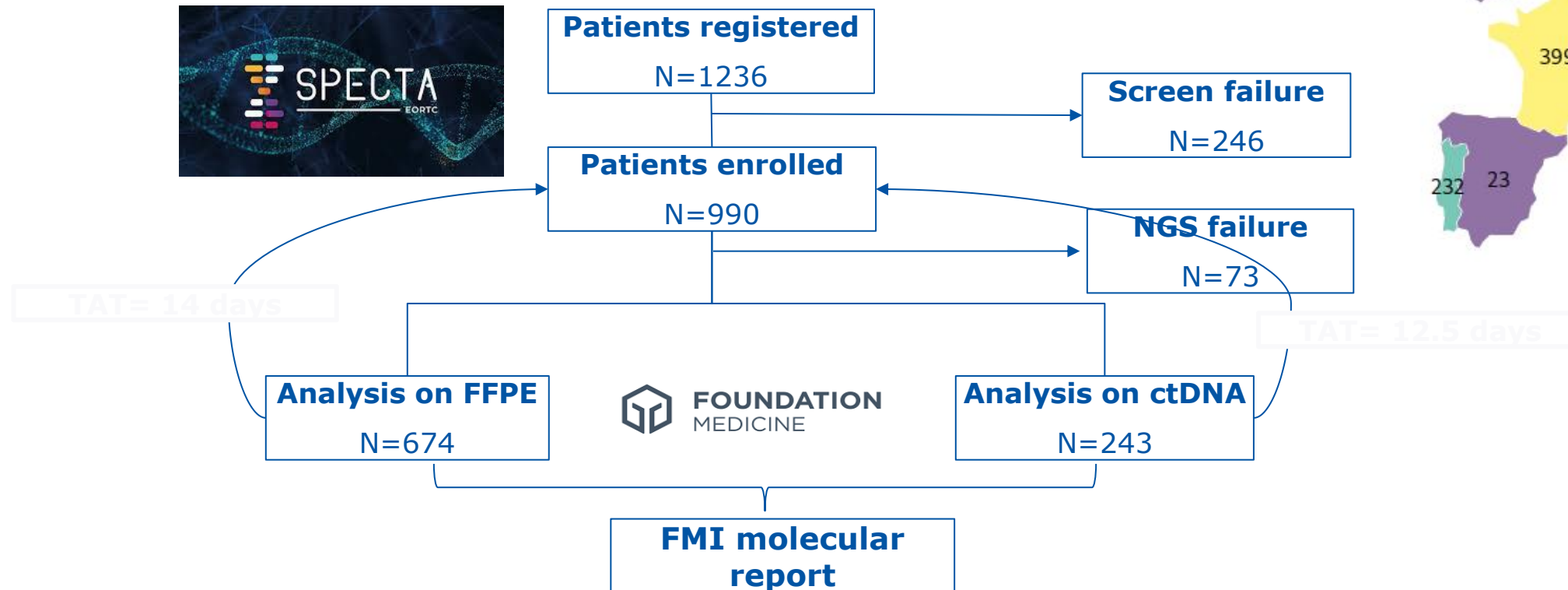
## ARCAGEN (Rare Cancers)

- **991 patients** in 3.5 y
- **10 different tumour types**, **14 countries**
- **918 molecular profile** (92.60% success rate), median turn-around time of 13.25 days
- **606 patients** with clinically relevant molecular alterations
- **456 patients** (46%) received a trt recommendation
- **63 (6.8%) patients** for an already approved treatment
- **232** (25.3%) for an **off-label use** of an approved treatment in another indication with similar molecular alteration
- **161** (17.5%) for a **clinical trial**.

# Arcagen – Study workflow

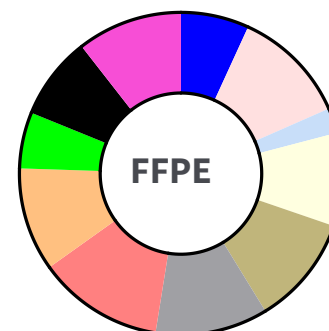
**Eligibility criteria:** Patients diagnosed with a recurrent or metastatic rare cancer

**Recruitment** via the EORTC SPECTA platform

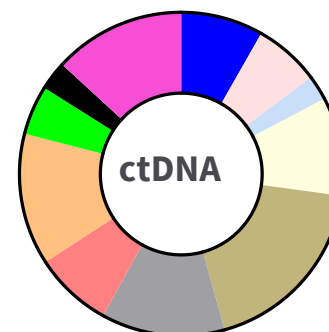


# Arcagen – Baseline clinical characteristics (with a max samples / cancer type)

|                                          |        |             |
|------------------------------------------|--------|-------------|
| Number of patients                       |        | 917         |
| Sex n (%)                                | Male   | 450 (49.1%) |
|                                          | Female | 467 (50.9%) |
| Age at Dx, median [min, max], years      |        | 57 [6-91]   |
| R0 surgery (at least 1) n (%)            |        | 231 (25.2%) |
| RT n (%)                                 |        | 368 (40.1%) |
| Chemotherapy (at least 1 line) n (%)     |        | 714 (77.9%) |
| Targeted therapy (at least 1 line) n (%) |        | 166 (18.1%) |
| Immunotherapy (at least 1 line) n (%)    |        | 109 (11.9%) |

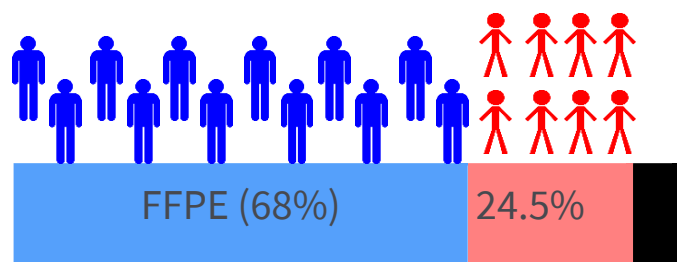


- 12.61% Rare head and neck
- 11.57% Rare gynecological
- 11.28% Adrenal and rare thyroid
- 10.98% Rare gastro-intestinal
- 10.53% CUP
- 10.39% Rare thoracic
- 9.35% NET
- 8.31% CNS
- 6.82% Sarcoma
- 5.64% Merckel cell and uveal melanoma
- 2.52% Rare genito-urinary



- 18.52% Rare gastro-intestinal
- 13.17% CUP
- 13.17% Rare thoracic
- 12.35% Adrenal and rare thyroid
- 9.88% NET
- 8.23% Sarcoma
- 7.82% Rare head and neck
- 6.58% Rare gynecological
- 4.94% Merckel cell and uveal melanoma
- 2.88% CNS
- 2.47% Rare genito-urinary

## Reasons for sample failure on FFPE

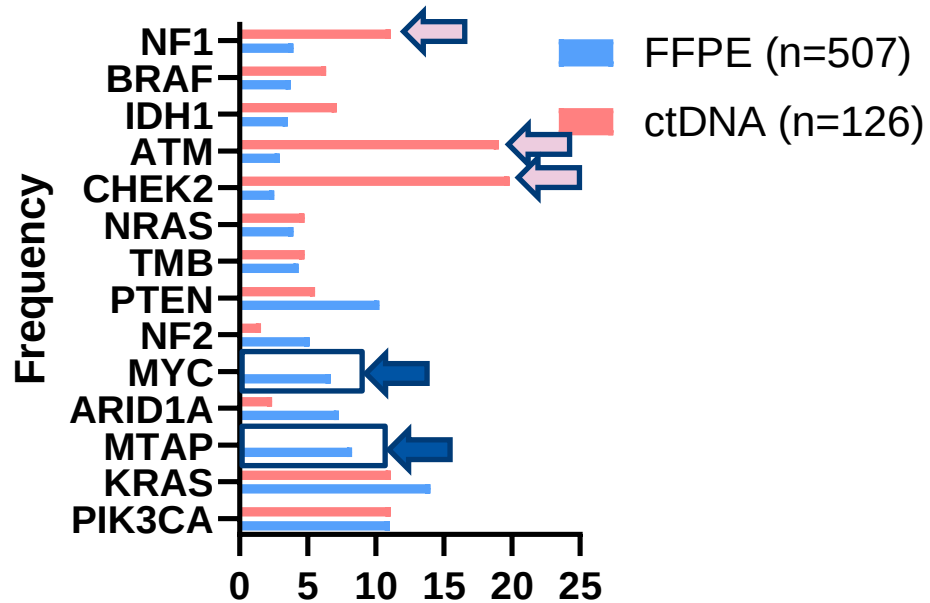


- Insufficient FFPE quality (20%)
- Insufficient FFPE quantity (25%)
- FFPE too old (21%)
- Sequencing failure (33%)

⇒ **Use of liquid biopsy to rescue up to 25% of clinical cases**

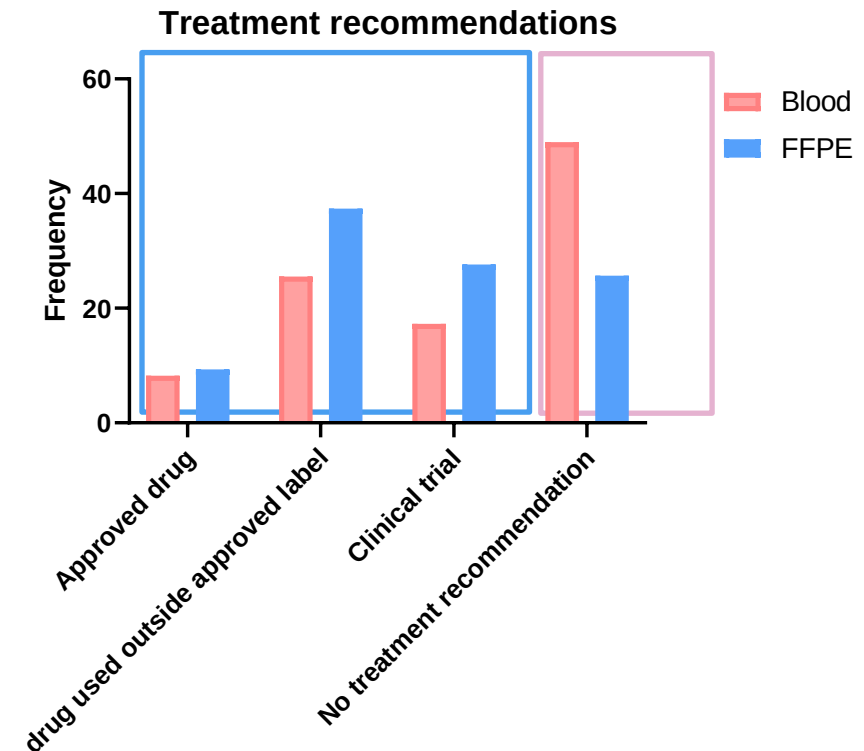
# Arcagen – Treatment recommendation

Top alterations associated with a treatment option  
(according to FMI report)



➡ Loss/amplification: reduced detection in our liquid biopsy analysis

Recommended treatment options (according to FMI report)



**But we need to move on to interventional trials.....**

**Are there solutions existing elsewhere?  
Could we tailor our solutions to improve  
therapeutic progress for rare cancer  
patients?**

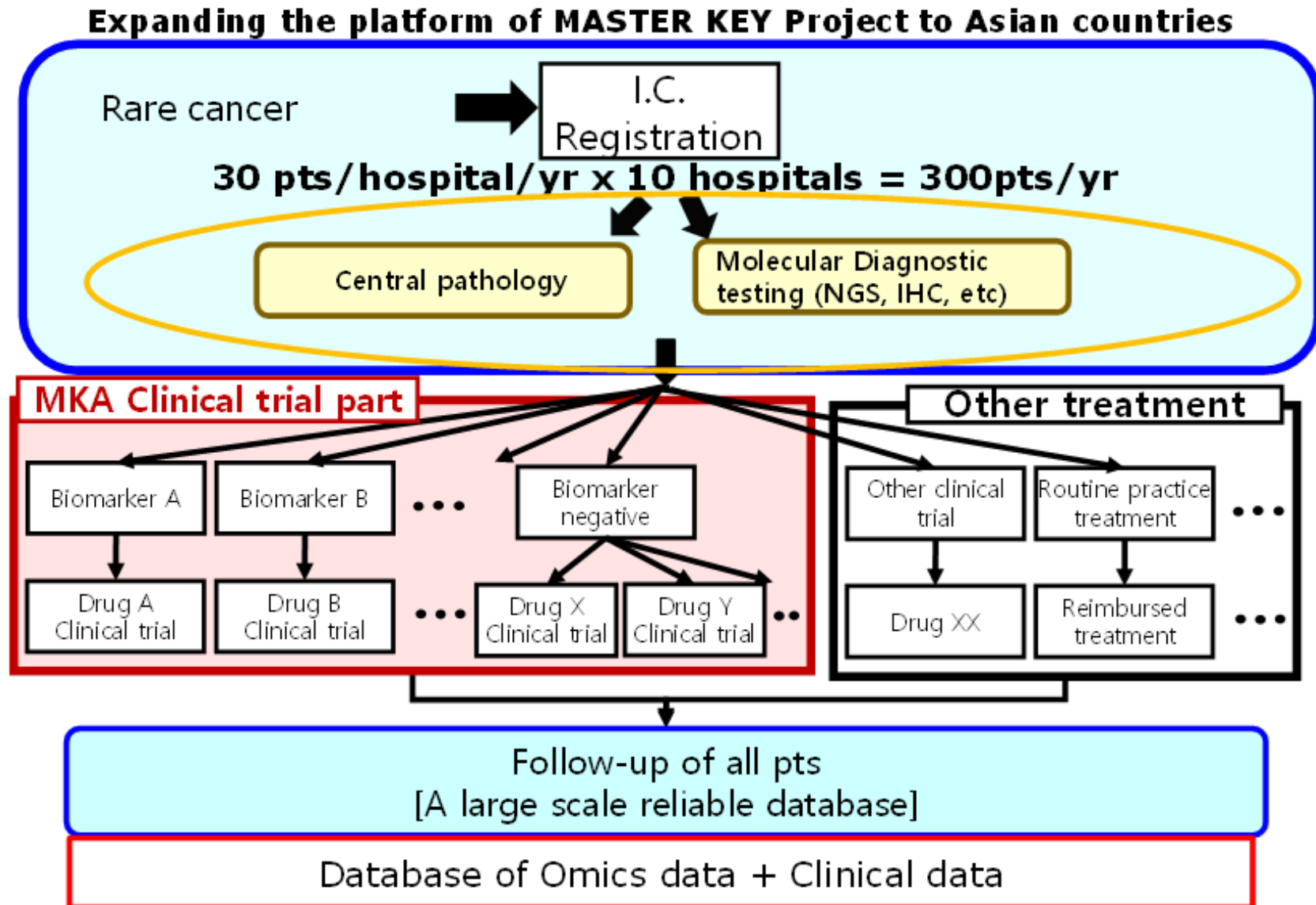
# MASTER KEY ASIA: A platform trial for rare cancers

## Registry part

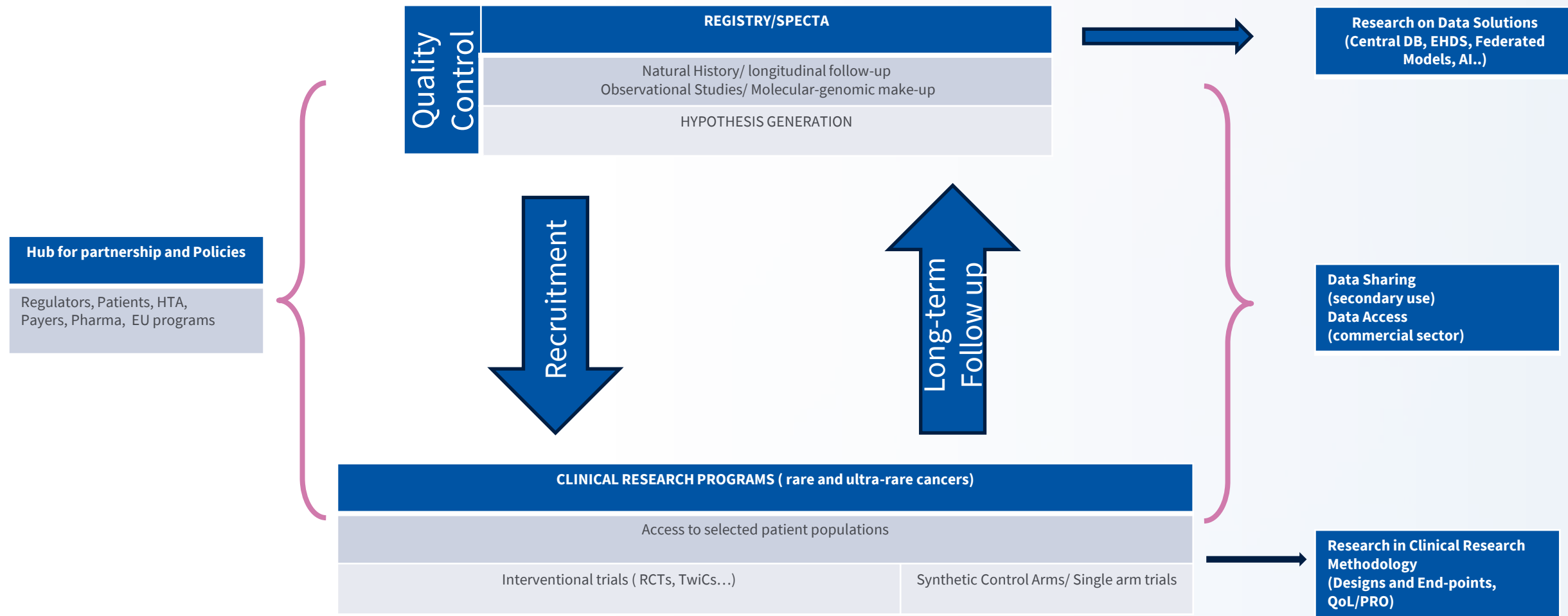
(Ongoing  
Observational  
Study)

## Clinical trial part

(Future  
Interventional  
Studies)



# TRACE design and opportunities



Building a patient oriented Rare Cancer Accelerator.....

# Current assets and next steps

- SPECTA is on going and has the capacity to access to patients but new datascience to be considered
- Research in methodology is moving forward: external control, relevant end-points etc..
- From observational to interventional is a regulatory challenge
- New forms of partnerships should be explored to meet the interests and needs of all stakeholders
- The economic dimension of the project also needs new forms of financial collaborative partnerships