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EORTC TRACE platform

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

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

Presented by D Lacombe – 23 September 2024

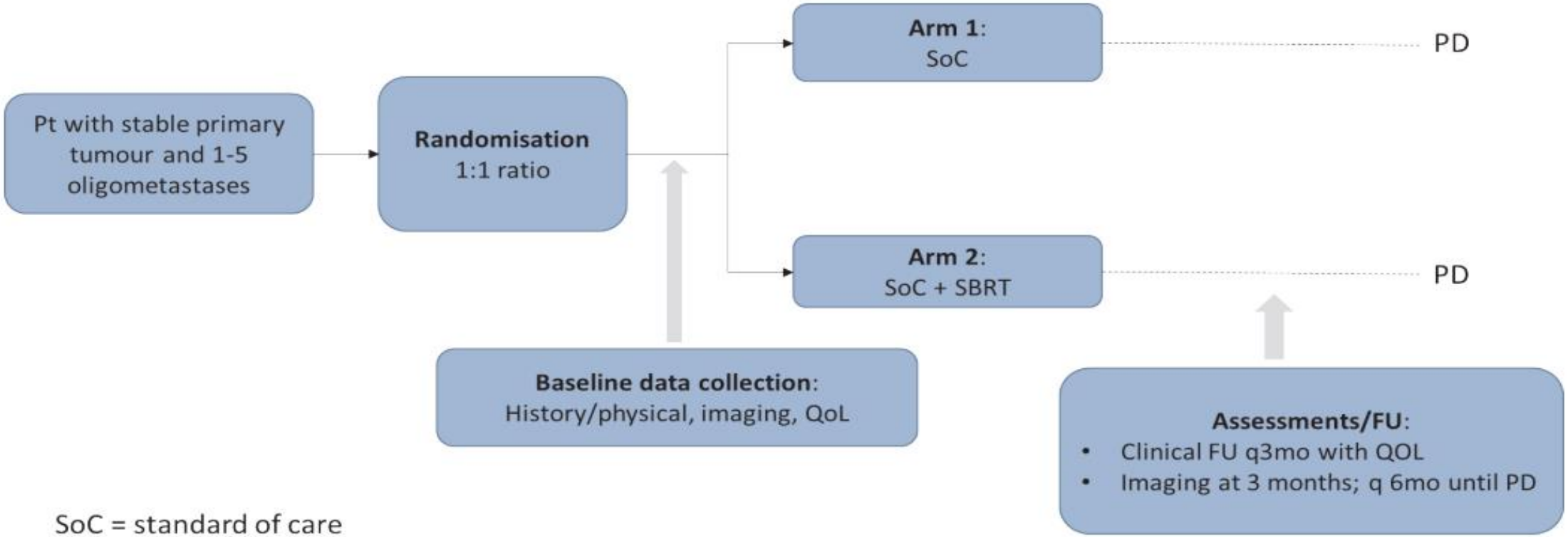
Where are we coming from?

- 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

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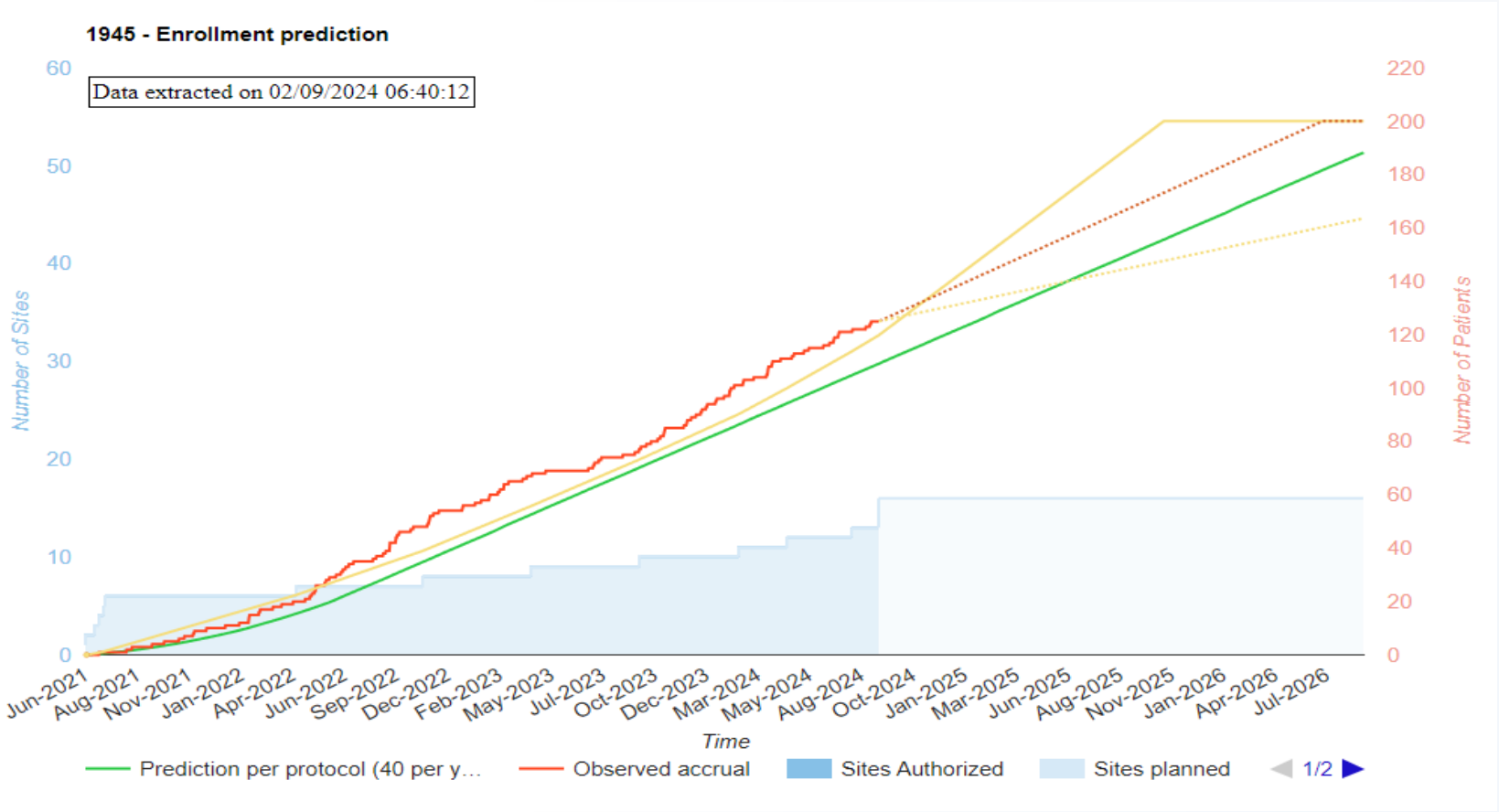
Enrolment status (as of 02/09/2024)



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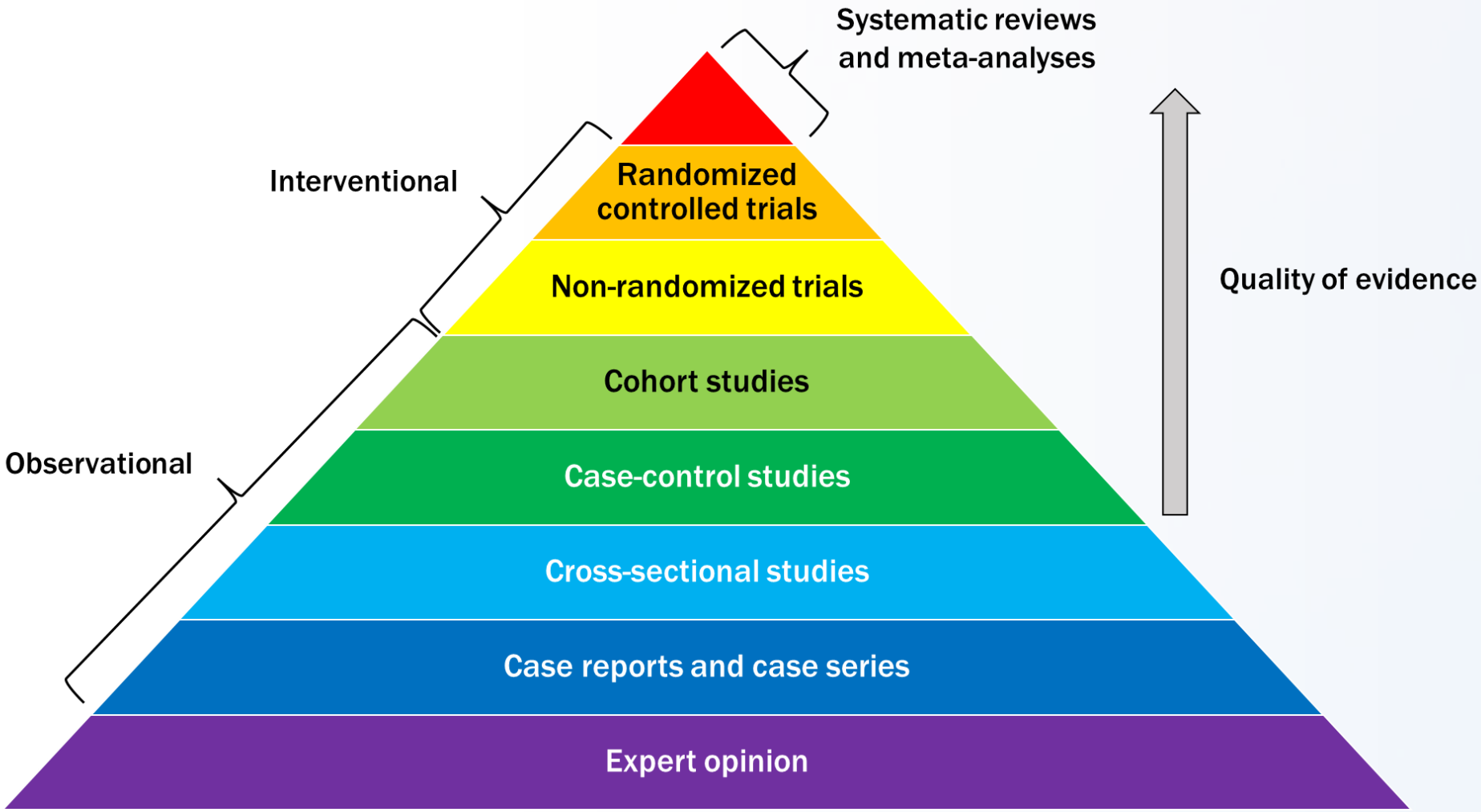
Always aiming to the highest level of evidence



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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?

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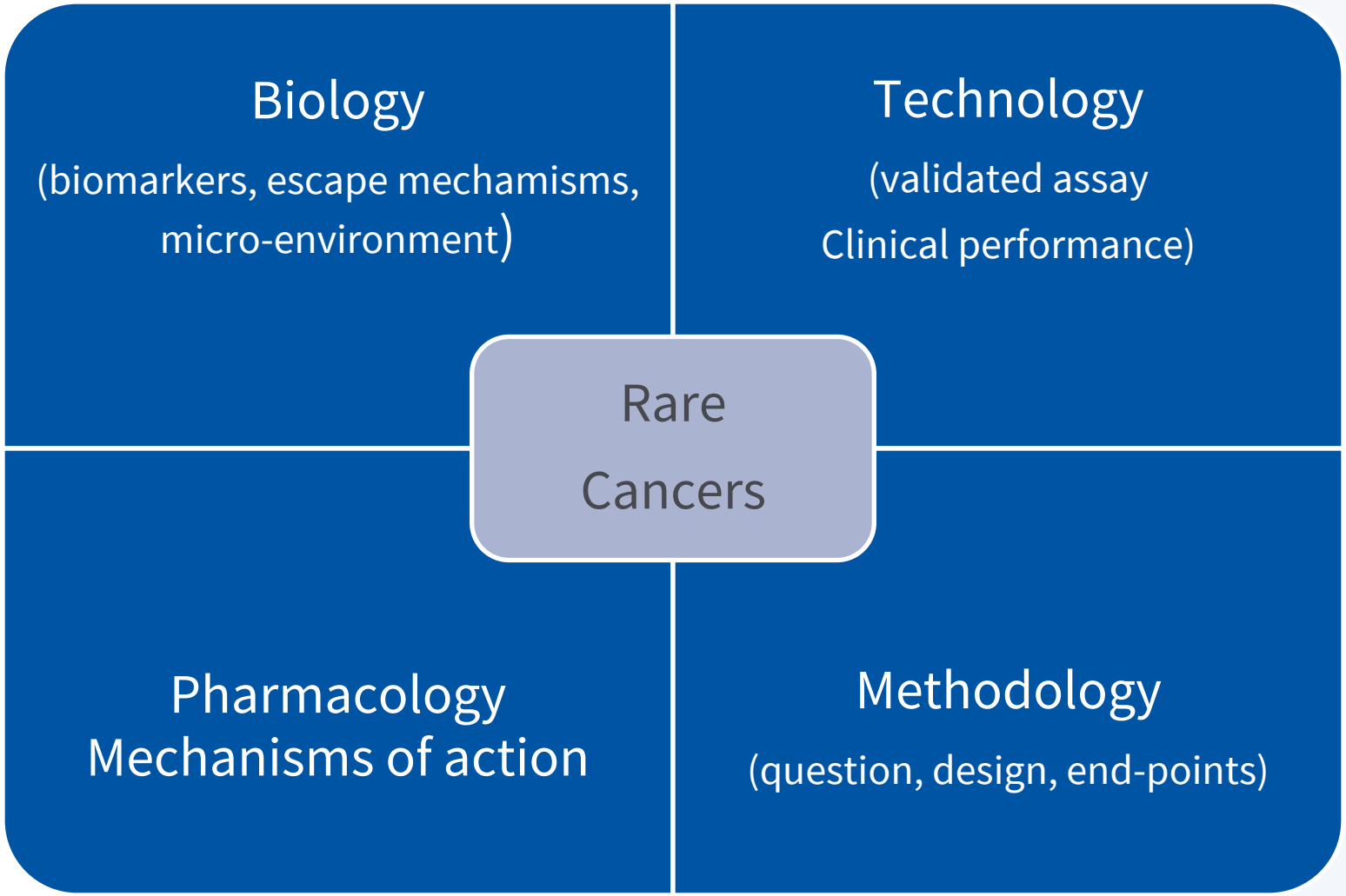
Selected common challenges need common solutions



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From biology and biomarkers to study designs

What have we learned so far

(with frequent cancer or not so frequent tumors)?

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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 Low membrane distribution of the receptors	Low intra- tumoral heterogeneity High Membrane distribution of the receptors

Complex interactions between different pathways may be highly variable across histologies

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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?

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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?

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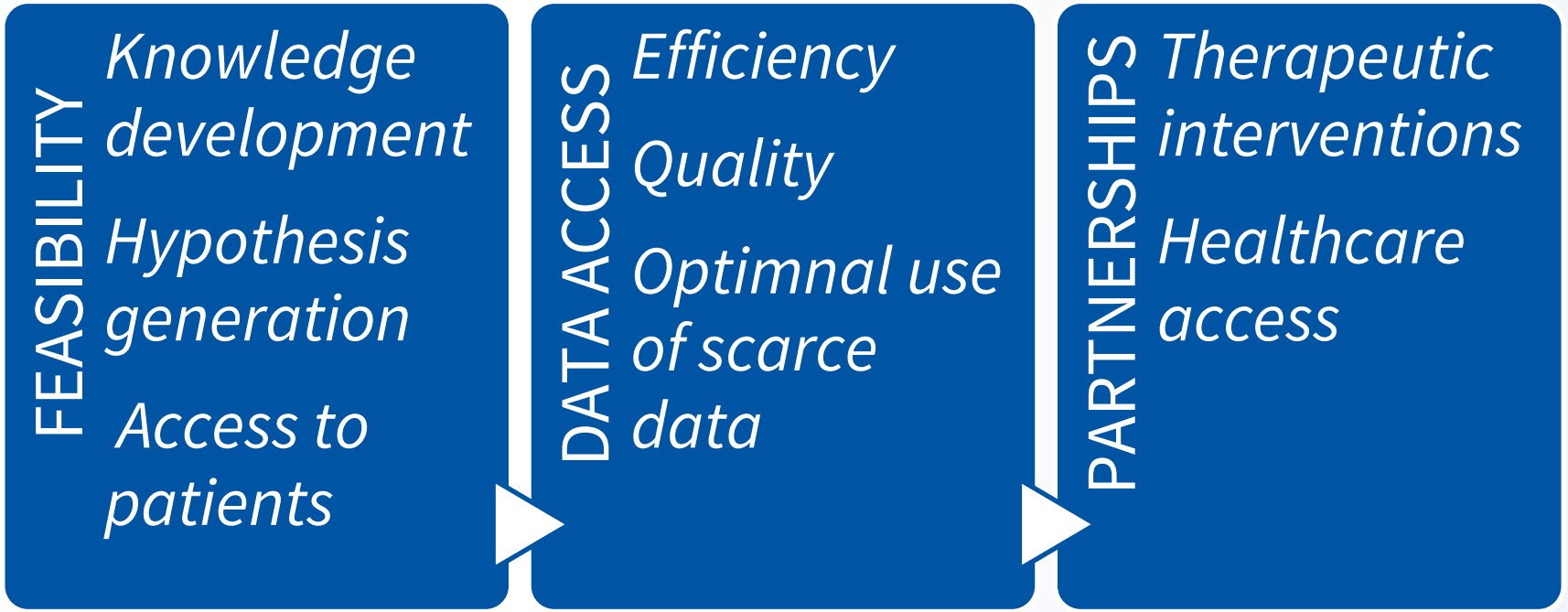
Operational challenges to address



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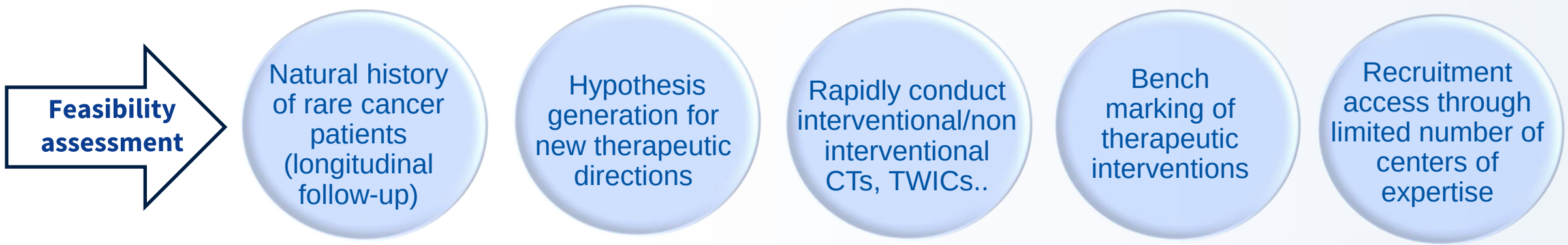
What do we optimally need for rare cancers?
FEASIBILITY



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What do we optimally need for rare cancers?
DATA ACCESS

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What do we optimally need for rare cancers?
PARTNERSHIPS

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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**.

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Arcagen – Study workflow

Eligibity criteria: Patients diagnosed with a recurrent or metastatic rare cancer
Recruitment via the EORTC SPECTA platform

Patients registered
N=1236

Screen failure
N=246

Patients enrolled
N=990

NGS failure
N=73

TAT= 14 days

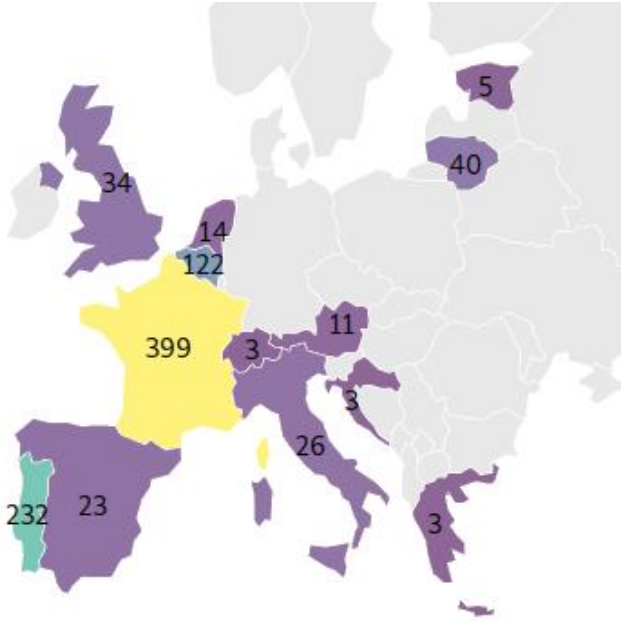
TAT= 12.5 days

Analysis on FFPE
N=674

FOUNDATION MEDICINE

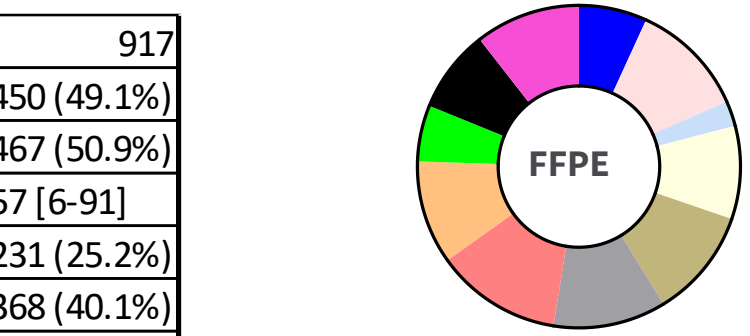
Analysis on ctDNA
N=243

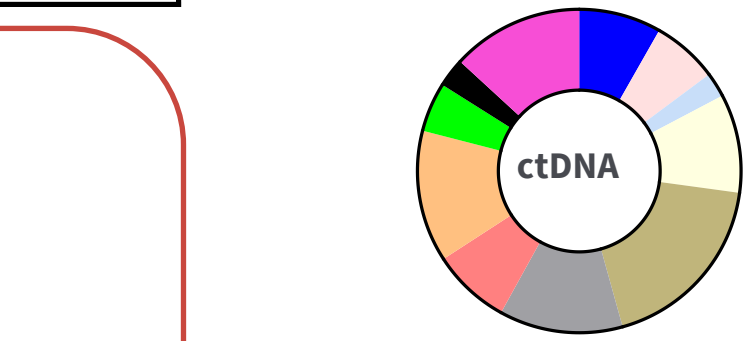
FMI molecular report



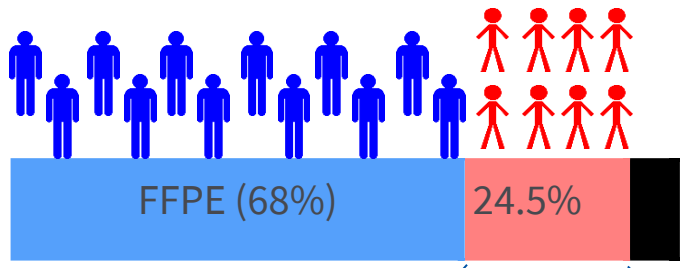
Arcagen – Baseline clinical characteristics (with a max samples / cancer type)

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%)





Reasons for sample failure on FFPE



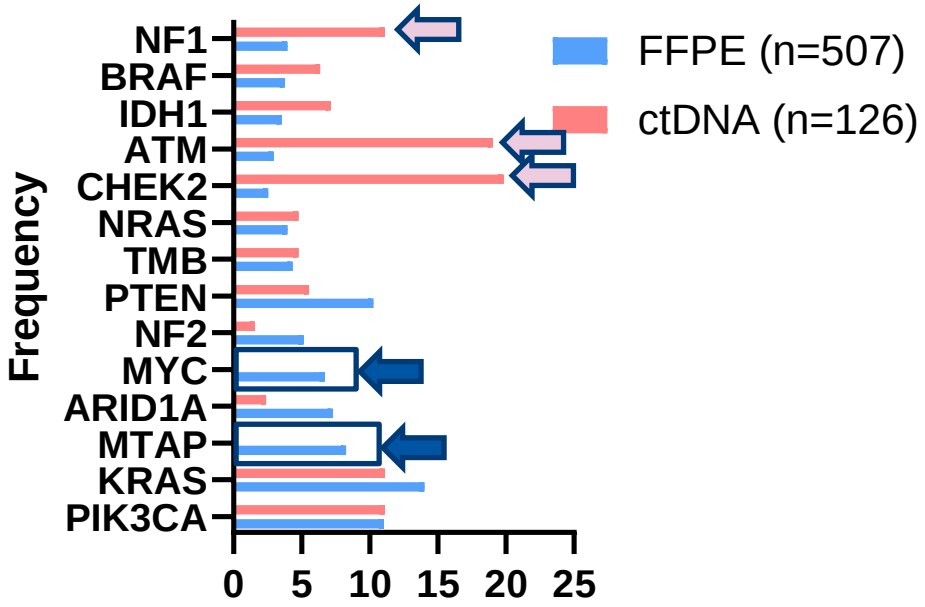
Insufficient FFPE quality (20%)
Insufficient FFPE quantity (25%)
FFPE too old (21%)

Sequencing failure (33%)

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

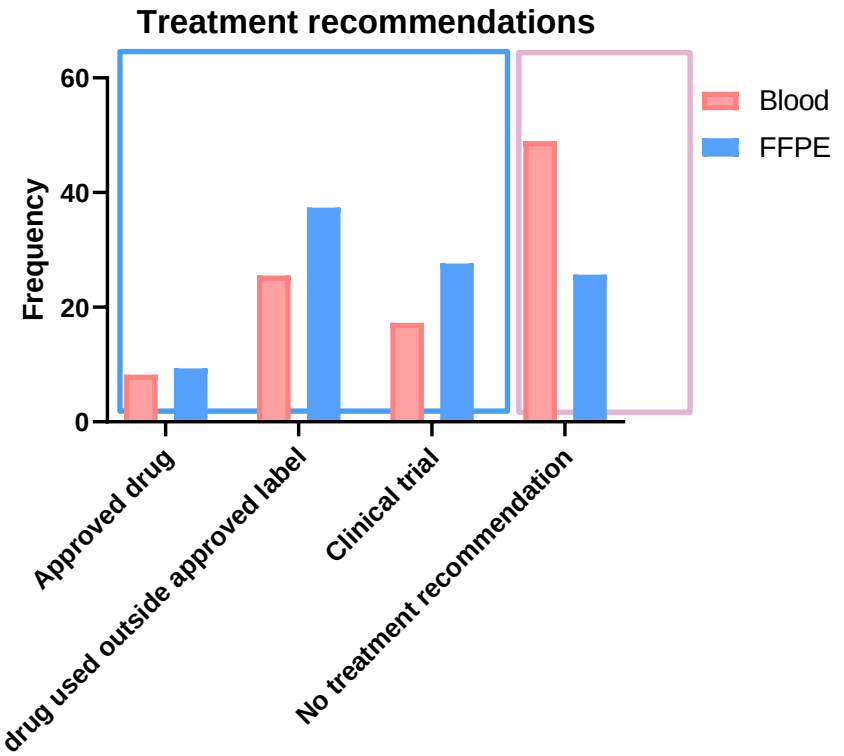
Arcagen – Treatment recommendation

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?

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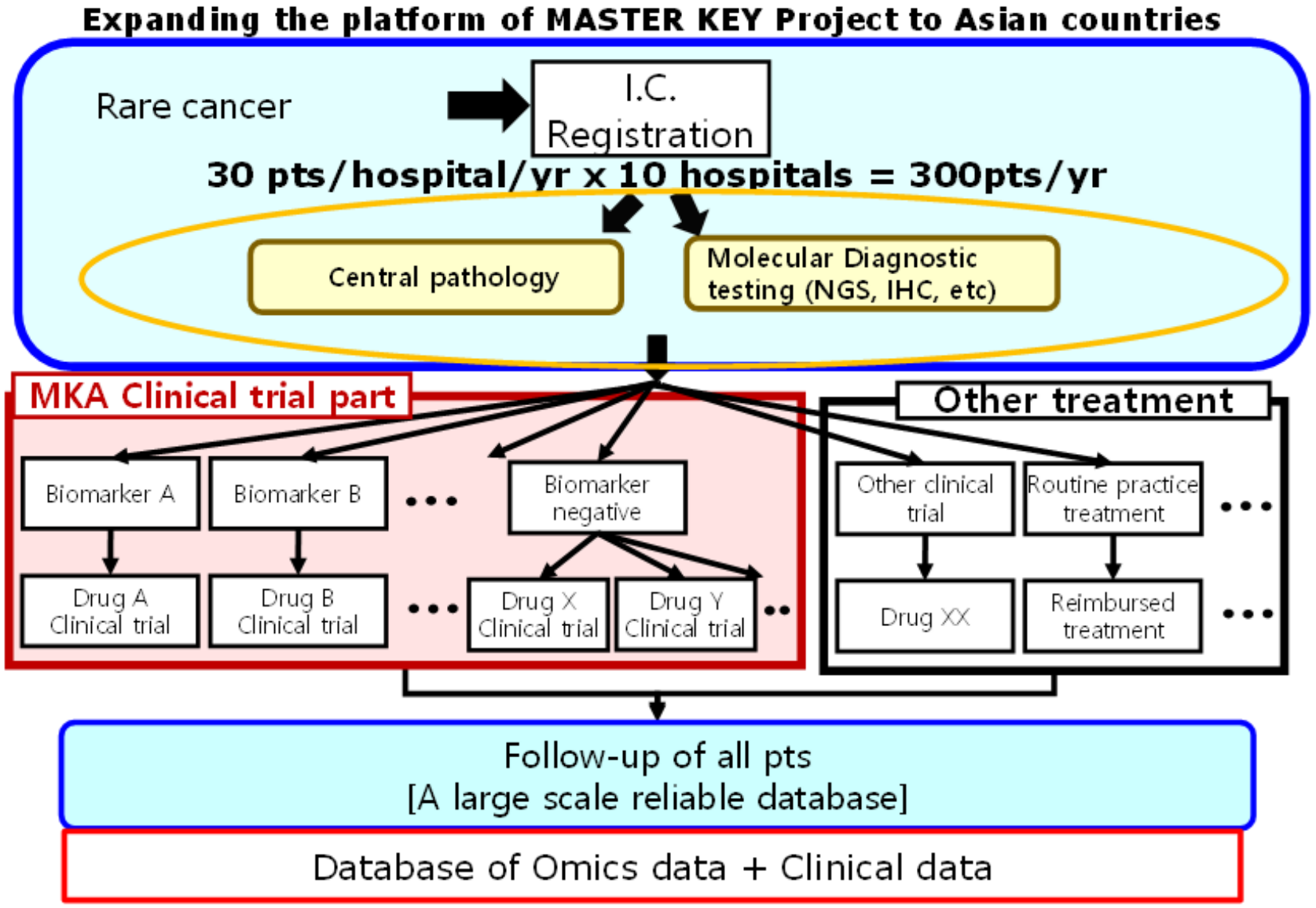
MASTER KEY ASIA: A platform trial for rare cancers

Registry part

(Ongoing Observational Study)

Clinical trial part

(Future Interventional Studies)



NCC

Source: Hitomi Okuma, MD PhD, Department of International Clinical Development, National Cancer Center Hospital, Tokyo Japan

TRACE design and opportunities

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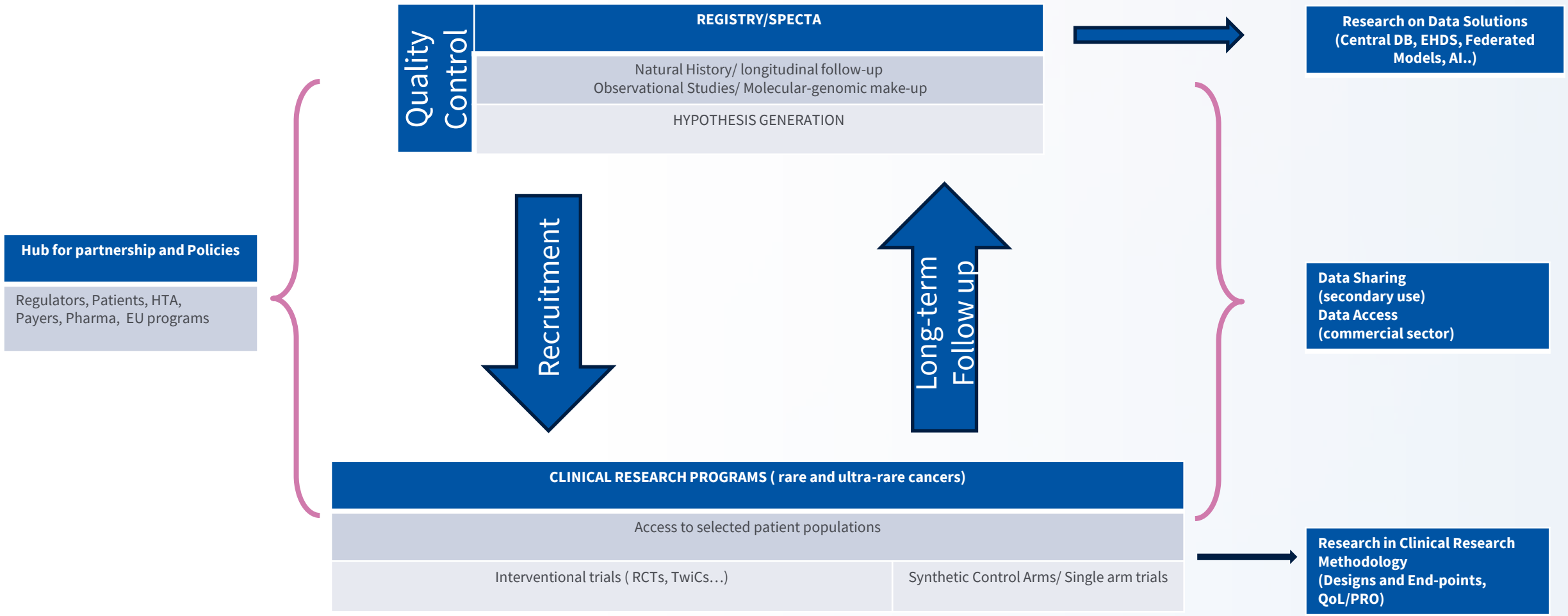

Building a patient oriented Rare Cancer Accelerator……

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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