Decentralised Clinical Trials, where are we?

A case study: the alpha-T trial

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Situational Analysis & Problem Statement

Drug development for patients with rare cancers pose particular challenges due to their low prevalence

Clinical trials in these rare cancer settings are very challenging:

- Difficulty in recruiting patients due to their rarity
- Unpredictability of the potential patient location (geographically and hospital department specialty)
- Recruitment of these patients can take many years

Given rarity of populations and difficulty of prospective trial enrolment, sponsors need to think differently when developing drugs for rare cancers

Impact on Clinical Trials During COVID19

A few things we learnt

F2F Patient Interactions with Investigators

- Investigators reported that **57% of patient interactions** were conducted **remotely**
- **Most physicians (90%)** said essential factors for virtual health were absent in their practices

Daily Life of Investigators

- In most hospitals and healthcare institutions, there is a **shortage of staff to treat patients** and almost no ability to conduct Clinical Trials (CTs).
- The overall **remote investigator interactions** is expected to increase by up to **78% post-pandemic**

Impact on Clinical Trial Enrollment

- By April 2020, a significant delay in enrollment timelines, only 1**4% of EU and 20% of US** Onc studies **recruited patients to plan**
- In the UK, CTs had to be **stopped, paused or delayed, impacting 126,000 patients**

Impact on Patient Lives

- **Inability to travel** to sites for the visits due to travel restrictions or quarantine
- Distrust of patients of coming in for non-essential visits

Source: Deloitte Consulting A.G

Site and patient centric interventions

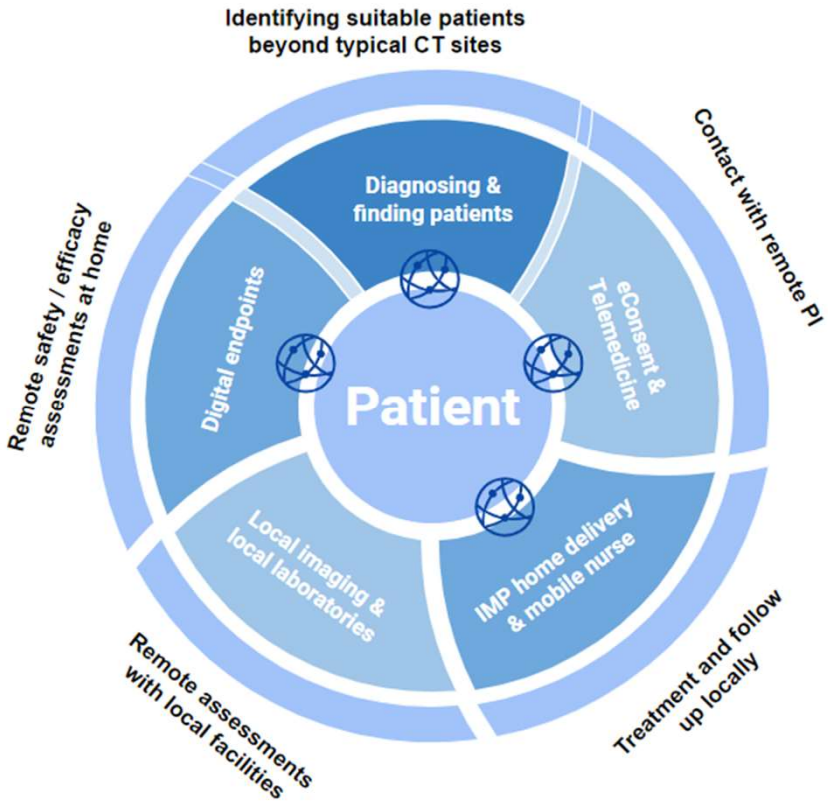
Highly leveraged to manage COVID19 disruption

- Patient outreach and input
- Concierge / SWAT team
- Home nurse visits
- Site-to-patient or pharmacy-to-patient drug supply
- Proactive patient pre-identification
- Site staff augmentation
- Mobile blood draw truck
- Supply augmentation from inactive sites / commercial supply
- Patient support, e.g., transport
- Shift sites to pharmacy / minute clinic
- Online assessments/ rating
- Comparator and combination therapy continuity
- Site visit window extension
- Site-less trials
- Telemedicine consultation
- Direct supply distribution (e.g., via medical field)
- eConsent and eSignature
- eCOA and ePRO
- Direct-to-patient diagnostics equipment
- Remote monitoring
- Equipment and financial assistance (e.g., PPE, bridge loans)
- Wearables
- Vendor and partner collaboration
- Site rebalancing towards geographies in recovery

Clinical outcome assessment (COA): Measurement used to evaluate patient safety and quality of life; COA measures include: ***Patient-reported outcome (PRO)***

Source: Illustration by McKinsey & Company

Innovative technologies and approaches in clinical trials



Key Features of a Decentralized trial?

It is a clinical trial that…

- Conducted at or near the patients' homes
- Fits the day to day life of patients
- Allows patients to participate wherever they live (*via* telemedicine) with the investigator
- Allows continued connection to the medical team already known to the patient
- Provides reliable data to support drug labeling claims

… and potentially brings

- ✔ Greater drug/trial access for patients
- ✔ More diverse & representative patient population
- ✔ Identification/inclusion of more patients from rare populations
- ✔ Better patient experience resulting in retention
- ✔ Enhanced feasibility

ALPHA-T Study Design – Phase II, Open-Label

(Alectinib to Patients at Home in Agnostic Tumors)

- Locally-advanced or metastatic
- ALK-fusion* solid tumors
- (excl. NSCLC and CUP)
- No available treat. options
- ECOG 0-2

N=50

→ Alectinib 600 mg BID (oral capsule)

→ Radiological Progression RECIST 1.1

→ Further treatments at Inv. choice and survival follow-up

Primary endpoint (per investigator)

- Confirmed ORR according to RECIST 1.1

Statistical Considerations:

- Target ORR 46%
- With N=50, lower 95% CI is 32% which is considered clinically meaningful in this population

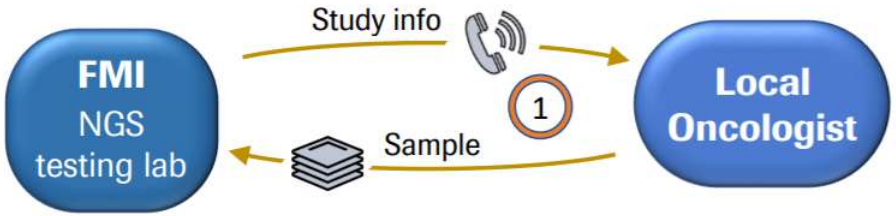
Secondary endpoints

- ORR (by IRF)
- PFS
- DOR
- CNS - ORR, -DOR, -PFS
- OS
- Safety

*ALK-positive tumor as per tissue or blood-based FMI NGS

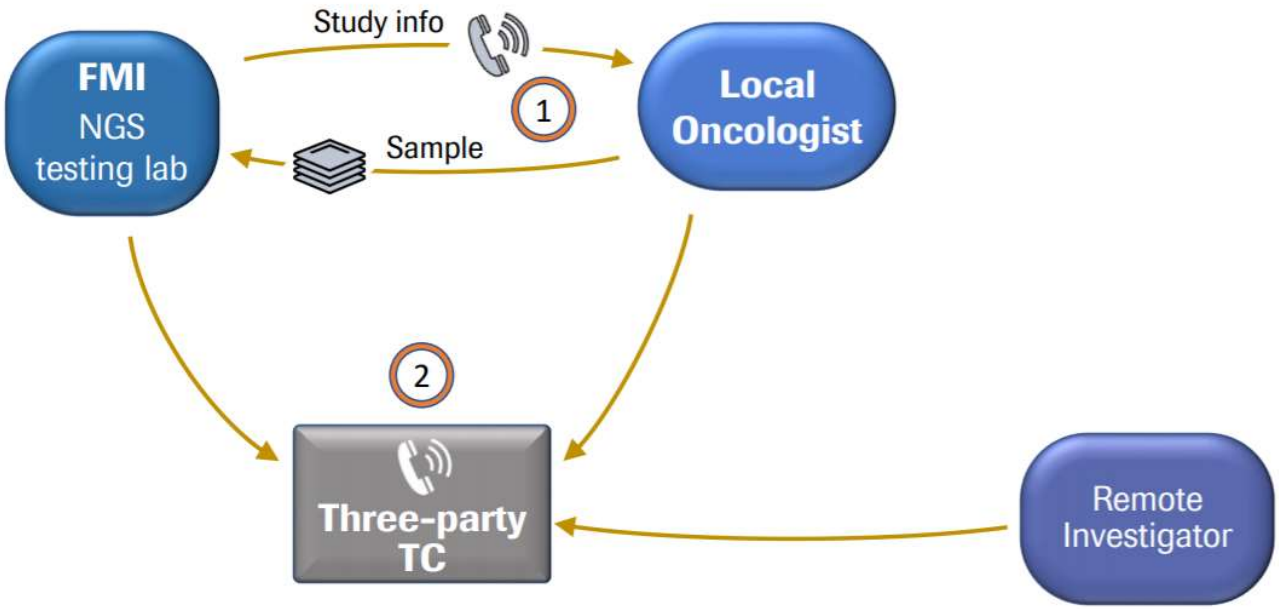
NCT04644315 https://clinicaltrials.gov/ct2/show/NCT04644315?term=alpha-t&draw=2&rank=1

Operational approach:
Patient identification and inclusion into the study



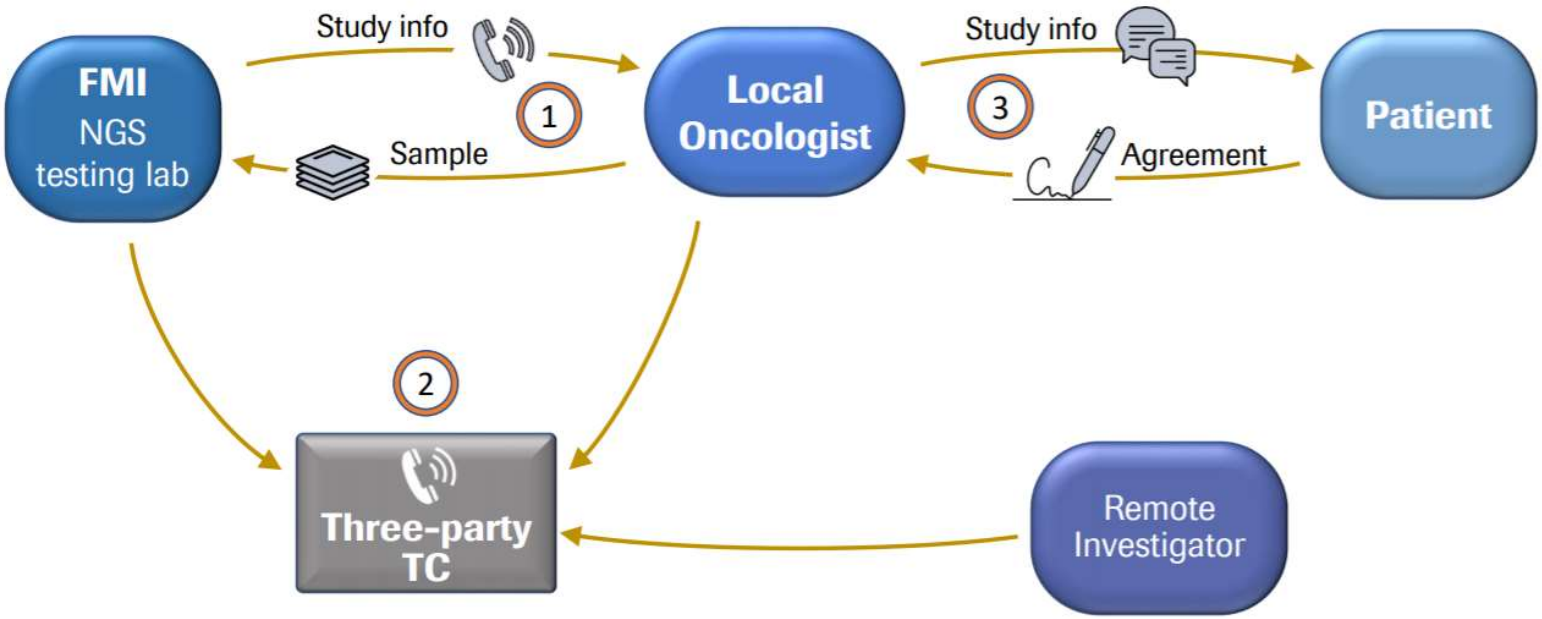
1 Following testing of sample, FMI informs ordering physician of study and establishes connection to remote Investigator

Operational approach:
Patient identification and inclusion into the study



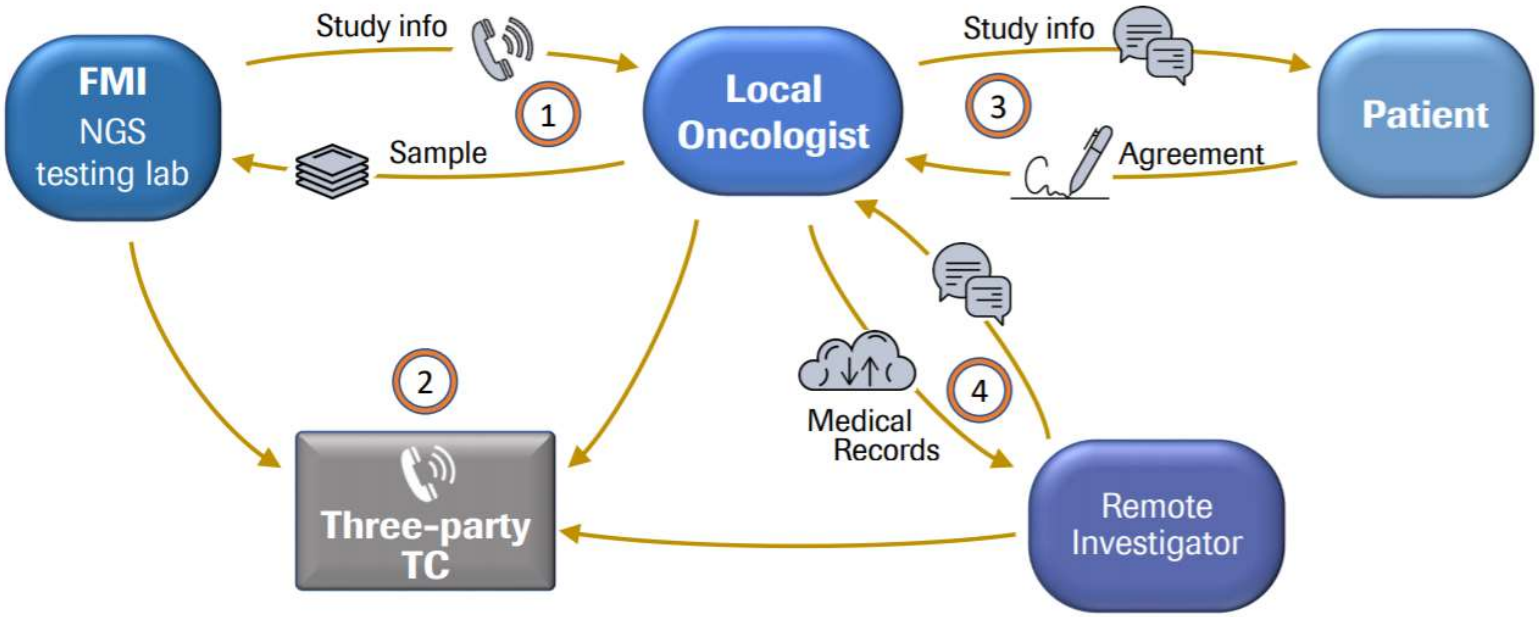
2 "Three-party" TC between FMI, remote Investigator and the Local Oncologist

Operational approach:
Patient identification and inclusion into the study



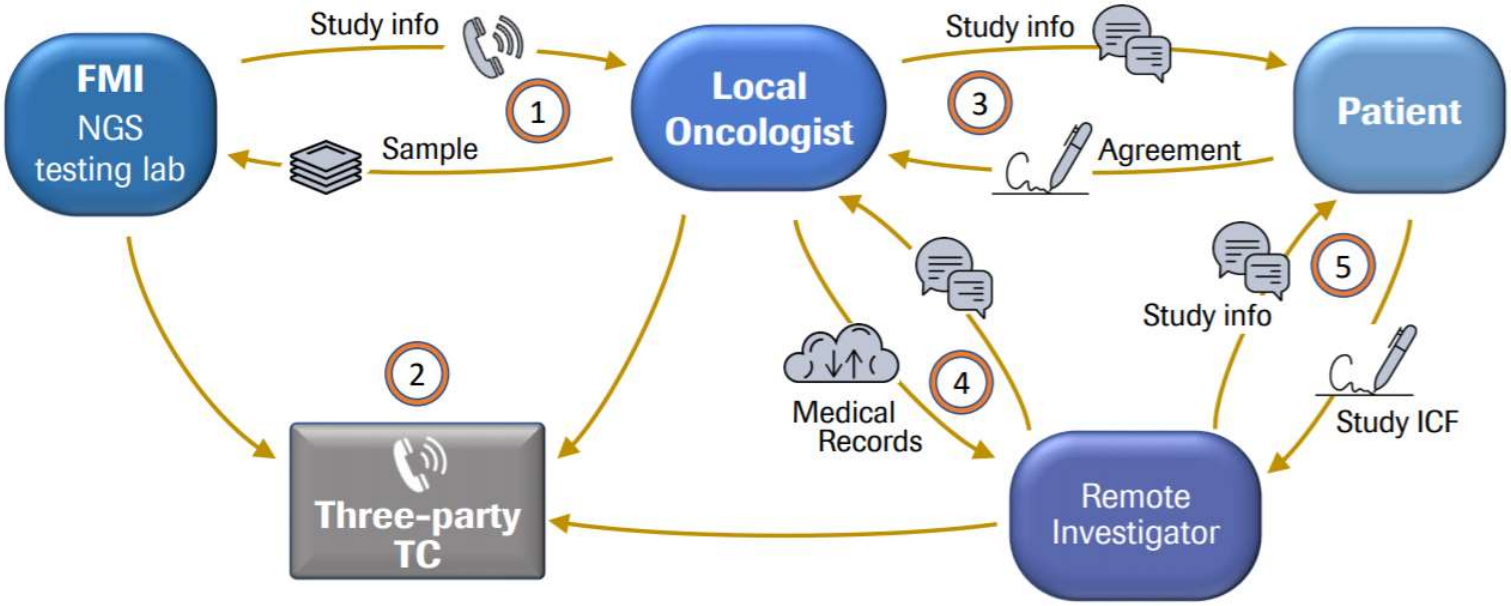
3 Local Oncologist informs the patient of the possibility to participate in the study and obtains agreement to move forward

Operational approach:
Patient identification and inclusion into the study



4 Remote Investigator contacts the patient to initiate enrolment procedures and the Local Oncologist releases the patient's medical records

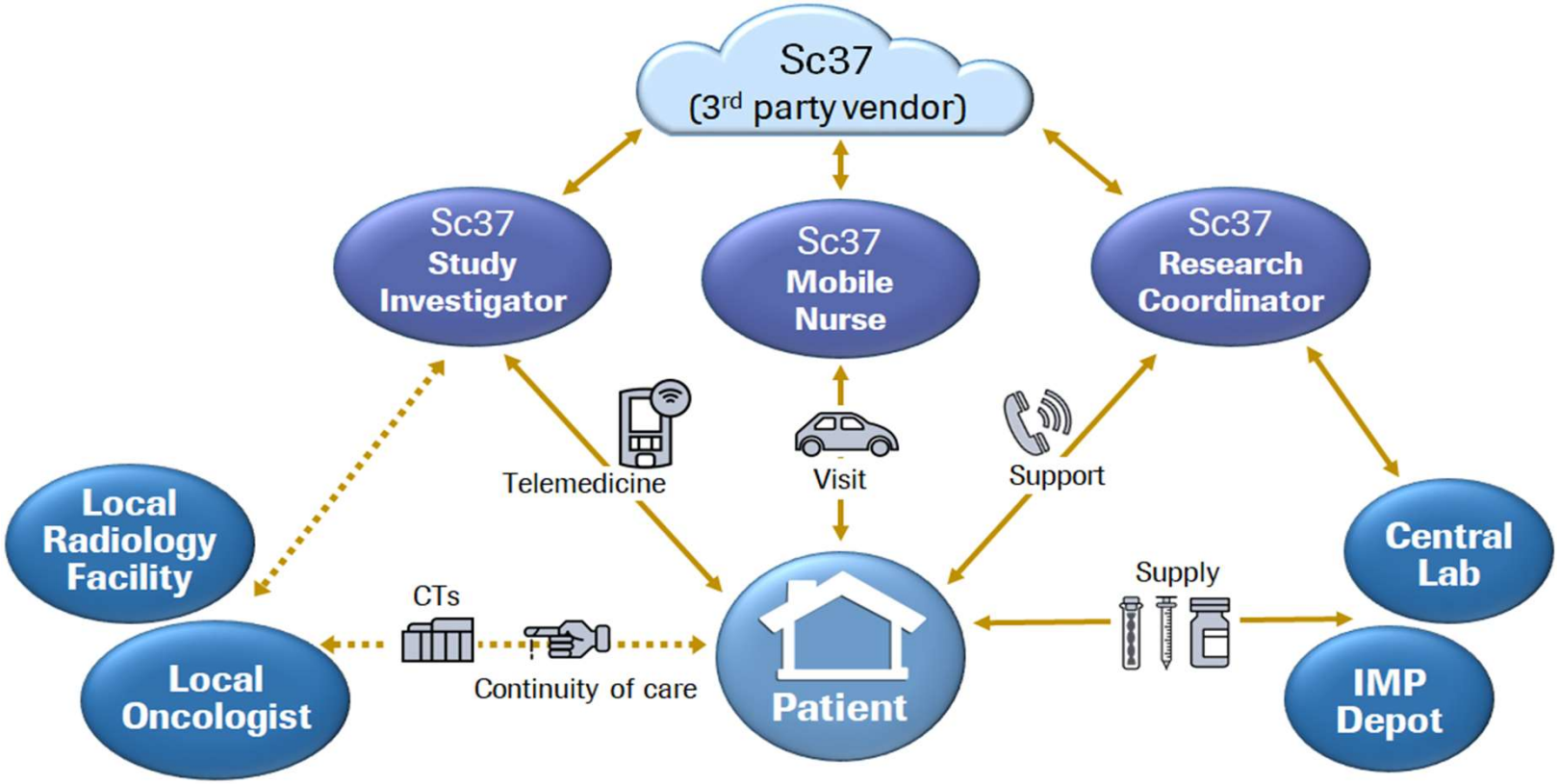
Operational approach:
Patient identification and inclusion into the study



5 If patient is considered potentially eligible, the Study Investigator obtains the ICF from the patient to start screening procedures

ALpha-T patients' visits in practice

ALPHA-T USA model



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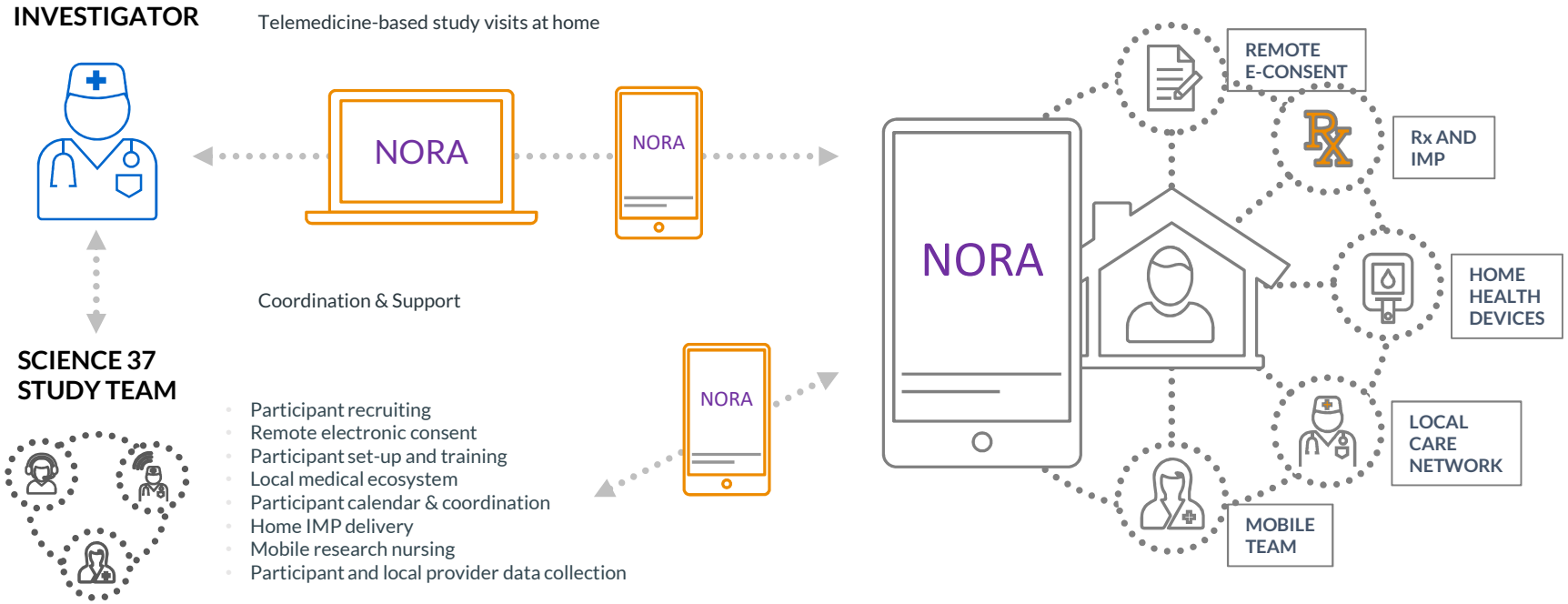
Transforming Operational Logistics

NORA connects the patient with the investigator and Science 37 study team to collect all trial data from home (EU General **Data Protection Regulation** compliant)



Comparison of Classical Clinical Trials vs Fully Decentralized Approach

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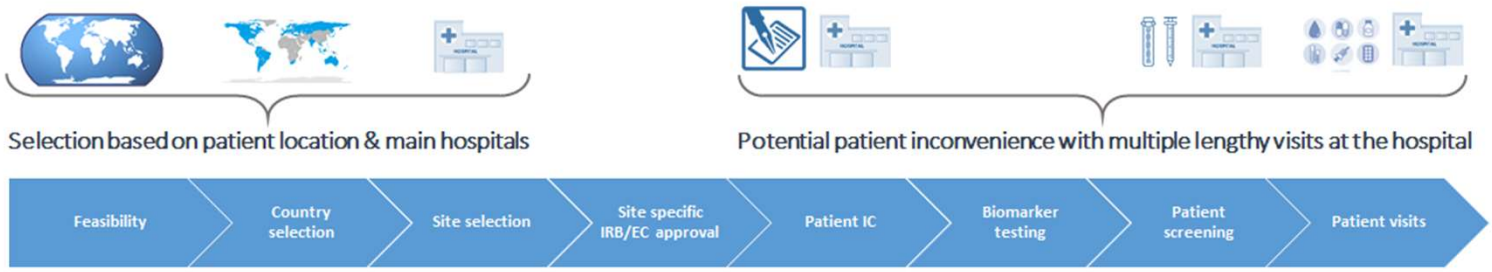
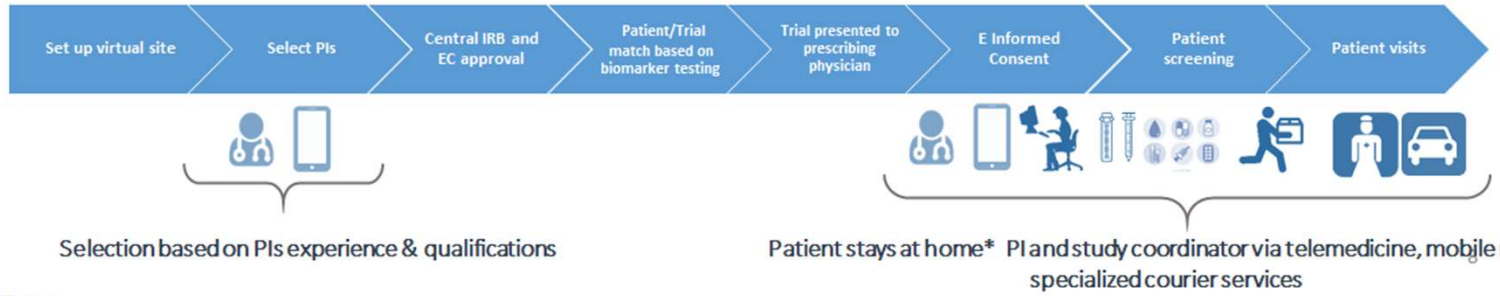
Classical approach to Clinical trials



Fully Decentralized approach to Clinical trials



* except from CT scans

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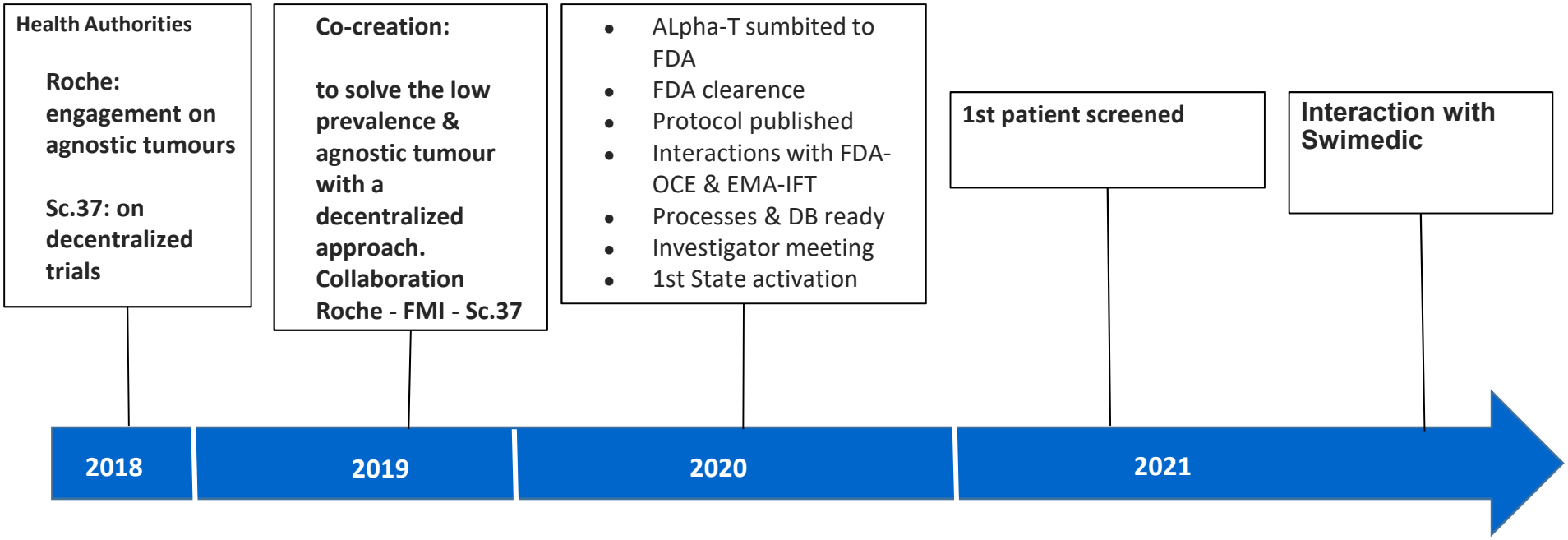
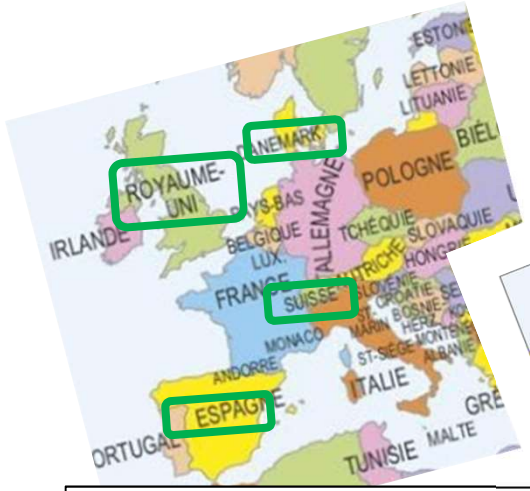
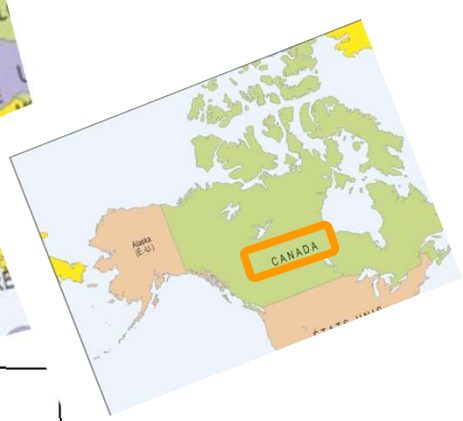
It all started in 2018...



Next Steps





FPI May 2021

Implement **Audit Plan** for this new model concentrating on Science 37

- F-up Call with Swissmedic
- Discussion with sites in Spain (Vall d'Hebron - Dr. Tabernero)
- The UK Crities hospital – Dr Matt Krebs
- HA interactions: Denmark, Spain, UK, Sweden
- **Opening European countries**

Interim Analysis (15th patient reaching week 8; ~Q3-2022)

Primary Analysis (50th patient reaching week 24) ~Q3-2024

2021 | 2022 | … | 2024

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Main challenges we need to collectively address for patients

Wide variability on the possibility to conduct decentralized trials in the different EU countries, with regards to local application of:

- Remote Principal Investigator
- Telemedicine
- Home Nurse
- IMP delivery at home
- Local Imaging Centers

Some countries are more amenable to this concept whereas others face more challenges due to constraints coming from National Laws

Ensure that data integrity and quality is not compromised to support registration

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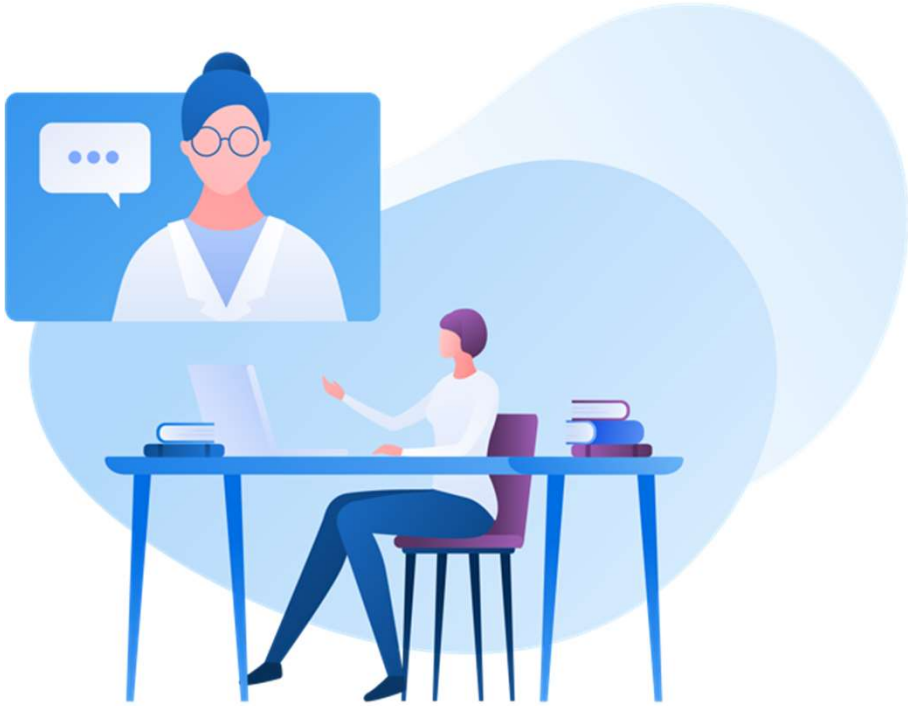
Thank you for your attention

Time for questions and considerations you would like to share



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Back up

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eCRF data integration Science 37 Platform (NORA) -> Roche database (RAVE)

De-risks the Data Integrity elements of the study

- eCRF data is collected in Science 37 Platform which mimics RAVE eCRF's
- Real time eCRF data integration from Science 37 Platform to RAVE
- Process is as per normal study for:
  - DM and Science cleaning and query
  - Coding
  - Now SAE reporting and reconciliation

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FDA Approval of ALPHA-T trial

Protocol submitted May 30th

FDA approval with clearance of IND on Sept 1st

FDA comments for clarification were as follows:

- Provide local oncologists with a Task or Responsibility Log which lists their names and any trial-related tasks they will be required to do, including the time frame in which the tasks should be completed.
- Provide a plan for remote oversight of personnel by the investigator in the final protocol.
- Clarify how a typical remote visit will take place with oversight by the investigator.
- Include the radiology facilities utilized by the trial on a separate list of service providers available to the investigator.
- Describe how local health care providers will be accessible to patients in the event of adverse events, e.g. whether local oncologists will receive regular communication (electronic or otherwise) from the investigator regarding the patients' remote visits and/or any clinical concerns that arise during the course of treatment.
- Provide a communication plan that describes how trial personnel, investigators, and patients will interact.
- Describe how shipment of the medical product is planned. Consider requiring the investigator to control the release of the investigational product to each trial participant.

Challenge / Safety of Patients

Use of local healthcare resources co-located with the patient

- Considering local labs are already accepted in trials if patients are unable to go to site:
  - How can we fully leverage the available network of local labs, and what would be required?
    - Normal ranges
    - Any specific accreditation?
- To give patients more choice, could local physicians provide routine safety support during study conduct?
  - Performing routine safety assessments and tests (including labs)
    - Ensuring data are readily transferred to trial database and available for Investigator to review
    - Investigator remains responsible for patient safety and treatment decisions

Challenge / Quality of data for primary analysis

Ensuring consistency in quality and interpretation of scans performed at different facilities

- Between patients enrolled in the same trial (Some using Central sites, some local radiology facilities (LRF)
- Across different sites used by the same pts (e.g, Baseline Scan performed at Central Site, and follow-up scans performed at LRF)
- Well defined and clear communication of scan criteria (image acquisition parameters and body areas) across all sites involved (Central and LRF)
- Assessment of LRF equipment and knowledge of study-required criteria (e.g. RECIST 1.1)
  - If required, provide training to LRF to ensure competency

Potential Research Questions

Research Question	Comparison Of Trial Site Vs. Remote Assessments
What is the effect of allowing for remote laboratory assessments?	Compare missing data rates, out-of-window rates
	Compare dose modification rates, adverse event/serious adverse event rates
What is the effect of allowing for remote imaging assessments?	Compare missing data rates, out-of-window rates
	Compare scan quality (interpretable vs. uninterpretable)
What is the effect of telemedicine replacing in-person follow-up clinic visits?	Compare missed visits, out-of-window visits
	Compare dose modification rates, AE/SAE rates
What is the effect of allowing remote investigational product administration?	Compare missed doses, dose modifications