ALpha-T: a Pre-Pandemic Decentralized Trial in Oncology

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On behalf of the ALpha-T study team

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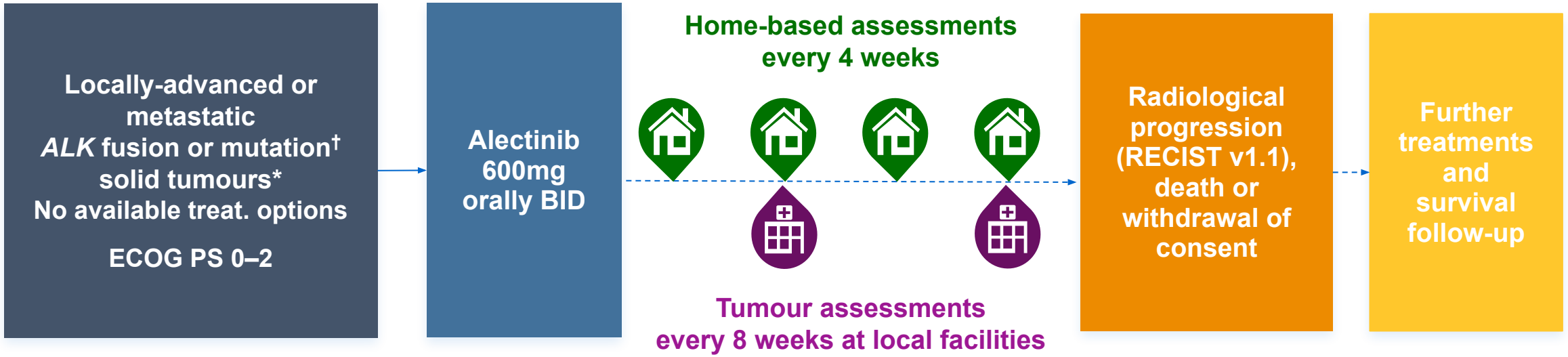
OUTLINE

1. ALpha-T study design
    - Rare disease, precision enrollment and home-based assessments
2. Extensive Collaborations: Patients' Identification and Enrollment
3. ALpha-T Operational Workflow in the US vs EU
4. Patients' safety
5. Data collection and data quality
6. Regulatory landscape
7. Advantages of a decentralised clinical trial

ALpha-T (Alectinib to Patients at Home in Agnostic Tumors)

Ph2 open-label, single-arm trial with decentralized home-based approach



Primary endpoint

Confirmed ORR in *ALK* fusion-positive patients determined by the investigator using RECIST v1.1

Key secondary and exploratory endpoints

ORR by IRF,
PFS, DoR,
CNS –ORR –DoR –PFS,
OS,
Safety

Statistical considerations

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

Kurzrock, et al. Presented at ASCO 2021 (Abs TPS3155)
*Excluding lung cancer; †ALK-positive tumor as per tissue or blood-based FMI NGS; NGS = Next Generation Sequencing; ORR = Objective Response Rate; IRF = Independent Review Facility; PFS = Progression-Free Survival; DoR = Duration of Response; CNS = Central Nervous System; OS = Overall Survival; CI = Confidence Interval

Rare disease, precision enrollment and home-based assessments

- Non-NSCLC tumours with ALK-fusions -> **0.2% prevalence** (Ross et al, The Oncologist. 2017)

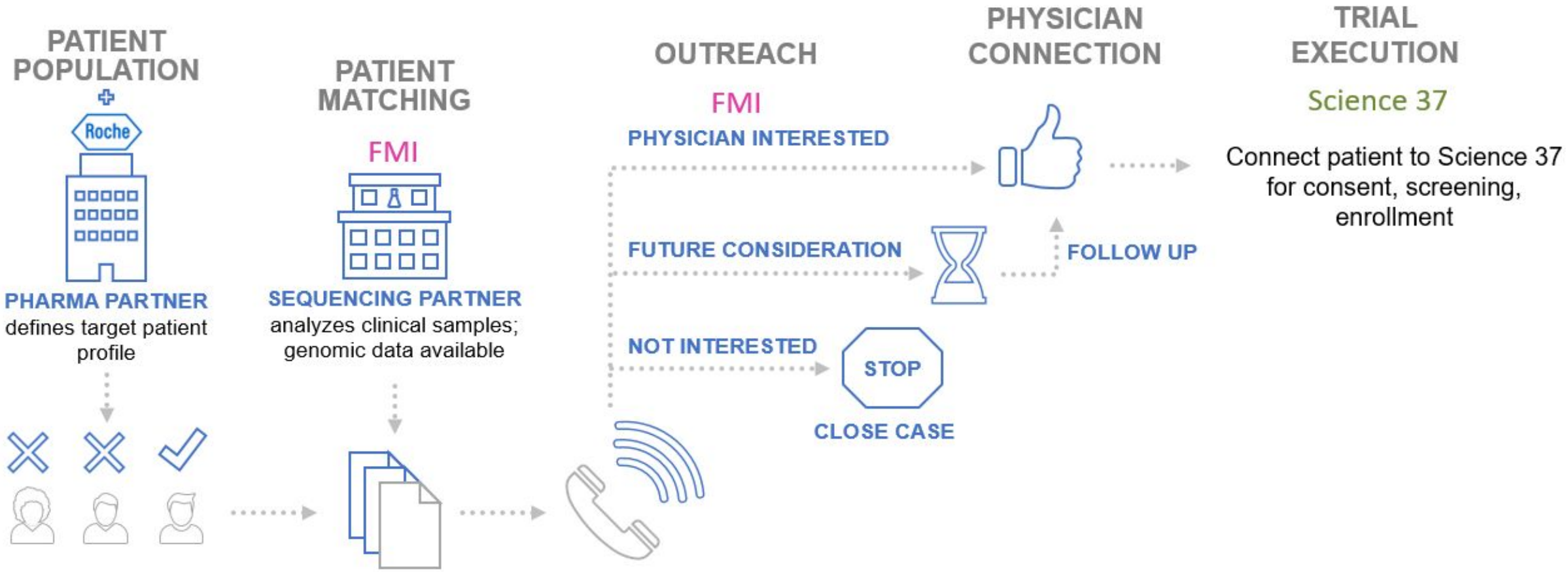
- With traditional recruitment approaches, estimated to require **screening of more than 25,000 patients** in order to enroll **50 potentially eligible patients**

- Drug development for patients with rare cancers pose **recruitment challenges** due to **low prevalence**
  - **very difficult to open clinical trial sites in advance** (no prediction of where potentially eligible patients may be located)
  - **inappropriate to activate site once an eligible patient is identified** (significant delays to the start of treatment)

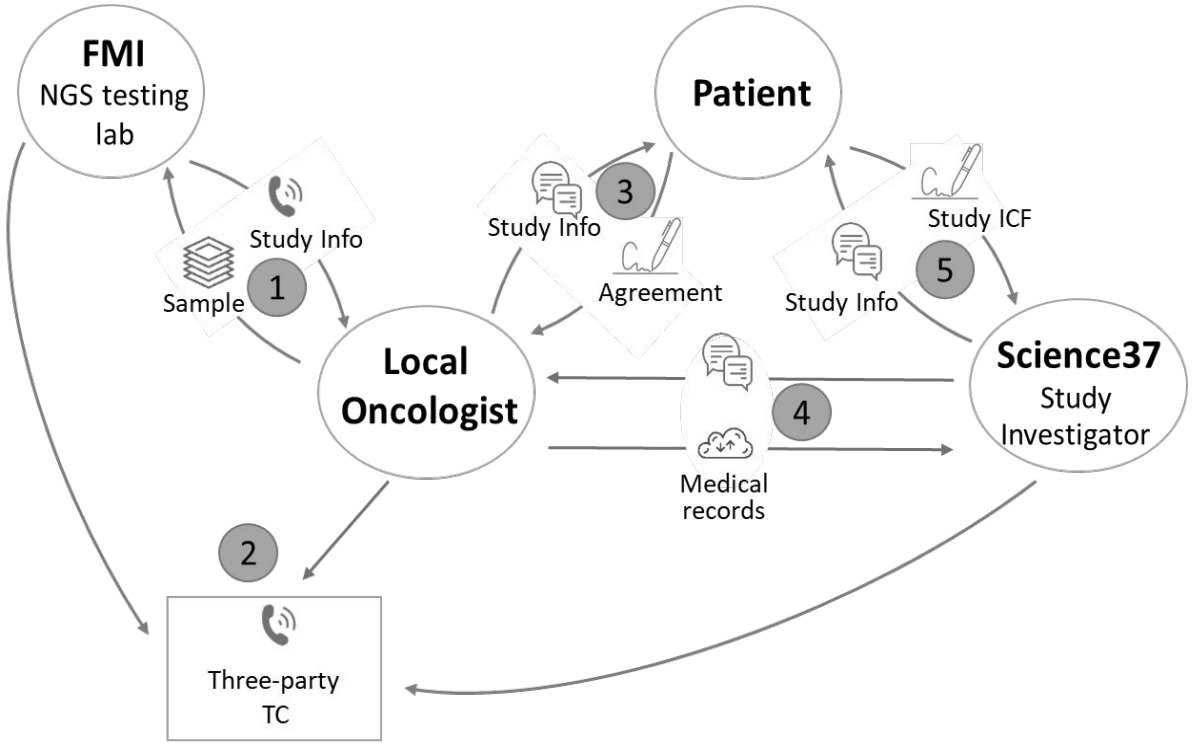
- Centralised Foundation Medicine inc. (FMI)'s **precision enrollment approach**
  - FMI analyzes thousands of samples from patients, potentially eligible for our trial based on biomarker
  - FMI can reach out to physicians who asked for the test, who can then **inform the patient**

- Without traditional sites, patients' consent and visits will be home-based, ALPHA-T is a decentralized trial that brings the "**Trial to the Patient**"

Collaboration: *Patients' identification*



Collaboration: *Patients' enrollment into the study*



1. Following **testing** of sample, **FMI** informs **ordering physician** of the study and establishes **connection to Science 37**

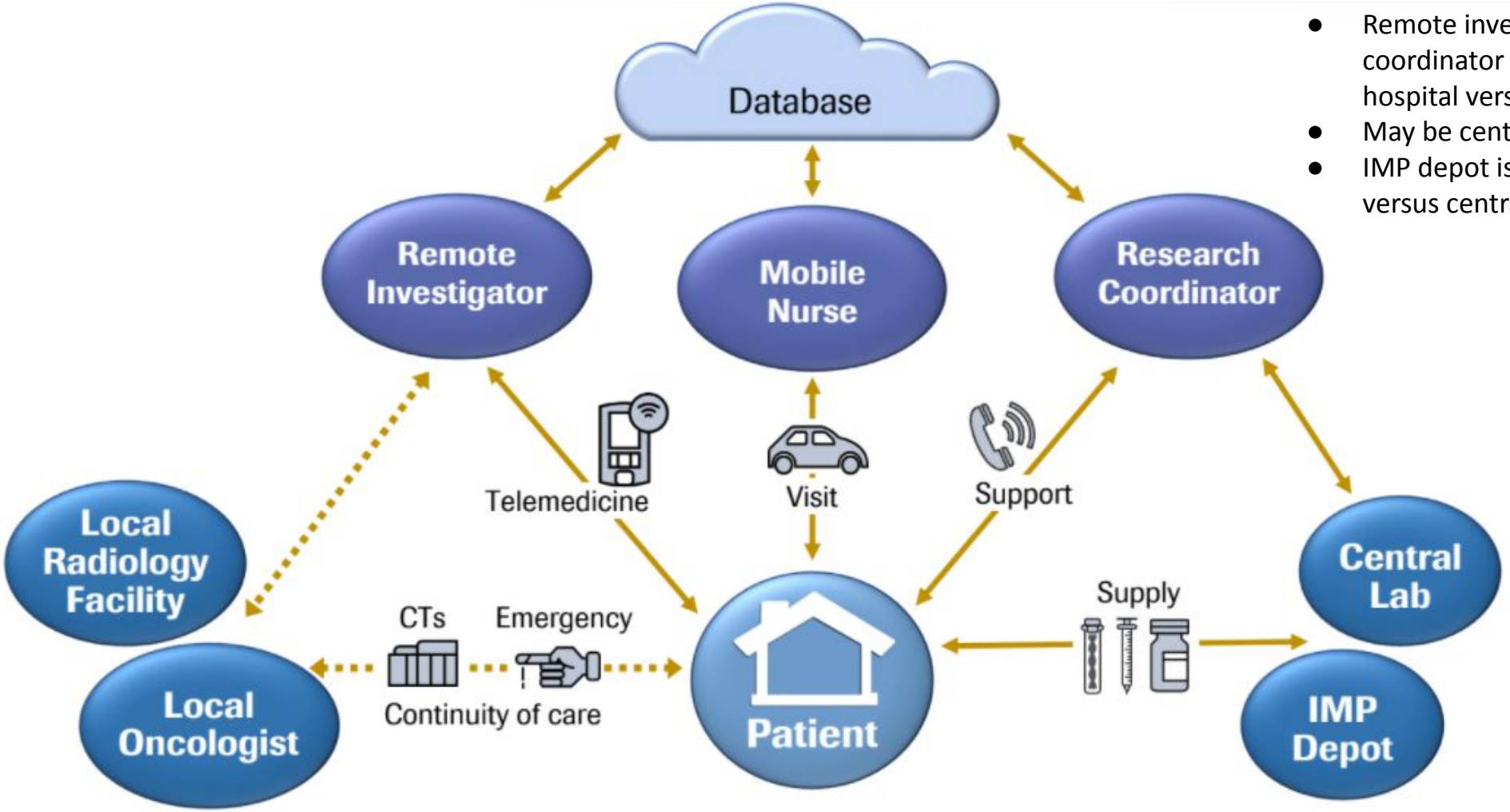
2. "**Three-party" TC** between FMI, Science 37 (including Study Investigator) and the Local Oncologist

3. **Ordering Physician informs the patient** of the possibility to participate in the study and obtains agreement to move forward

4. **Science 37 contacts patient and ordering physician** to initiate enrolment procedures and the Ordering physician **releases the patient's medical records** to Science 37

5. If the patient is considered **potentially eligible**, the Study Investigator (S37) obtains the Informed Consent Form (**ICF**) from the patient to start screening procedures

ALpha-T Operational Workflow in the US



In the EU:

- One physical hospital site per country versus one virtual site in the US
- Remote investigator and research coordinator must be working at the hospital versus for virtual site in the US
- May be central or local lab
- IMP depot is at the hospital pharmacy versus central pharmacy in the US

Patients' safety in ALpha-T
Mostly similar oversight to traditional clinical trial

- Safety of Alecensa is **well-established**
- Oral drug, administered at home, **IMP accountability** performed by a mobile nurse
- **Eligibility criteria** have been designed to exclude patients at higher risk for toxicities
- **Safety monitoring** of the patients during study via an Internal Monitoring Committee (IMC)
- The investigator and mobile nurse or clinical research coordinator are responsible for ensuring that all **adverse events** are recorded and reported to the Sponsor

- Investigator does not see the patient in person (telemedicine). Mobile nurse is at home with the patient. Local physician provides continuity of care
- Protocol provides guidelines for managing adverse events, dosage modification and treatment interruption or discontinuation
    - e.g. eliciting adverse event information and causal attribution guidance

IMP = investigational medicinal product

Data collection in ALpha-T

Data integration
to de-risk the data integrity elements of the study
(GCP compliant)

- eCRF data is collected in Science 37 Platform (NORA) which **mimics RAVE eCRF's**
- **Real time** eCRF data integration from Science 37 Platform to RAVE
- **Process in RAVE is as per usual clinical trial for:**
  - Data Management and Science data review and query
  - Coding
  - Serious Adverse Events (SAE) reporting and reconciliation

Note: In the EU, data will be entered directly into the clinical database

GCP = Good Clinical Practice; Nora = Network Oriented Research Assistant

Data quality in a DCT

- Good first DCT in oncology to learn from
  - rare disease, unmet need, randomised (RCT)/ real world (RWE) not feasible
  - single arm study, simplified with respect to randomization, blinding
  - small sample size with 50 patients

- Potential impact on the variability of the data?
  - **Local vs central labs** assessments:
    - Already accepted in trials if patients are unable to go to central lab
  - **Imaging** assessments: possibility for a local and/or central facility for a given patient
    - Need to ensure the local radiology facility is performing scans to the quality required and follows target lesions consistently with the central site assessments (training, list of trial-related tasks)
  - Use of **telemedicine** instead of clinic visits:
    - Nurse at home with the patient and investigator always online (qualified, clinical trials standards)

- Potential impact on the integrity of the data?
  - (?) more diverse trial population
  - (?) increased patient retention into the study
  - (?) missing visits, out of window (flexibility of phone call vs clinic visit)
  - (?) dose modification / AE-SAE rates
  - (?) NORA as both source and CRF in the US

Regulatory landscape
Health Authority interactions: key milestones for ALpha-T

2020		2021				
Sep	**Oct**	**Feb**	**March**	**April**	**May**	**June**
ALPHA-T IND clearance (1st Sept)	**EMA ITF Meeting** (15 Oct.)	**Swissmedic/ Swissethics meeting** (10 Feb)	**Euro DIA session on DCTs** (16 March)	**Danish Agency Scientific Advice** (14 April)	**Spanish Agency Informal meeting** (innovation office) (26 May)	**Danish Agency Follow up Scientific Advice** (10 June)
	FDA OCE Meeting (26 Oct.)				**Swedish Agency Scientific Advice** (27 May)	**UK Agency Scientific Advice** (15 June)

IND = Investigational New Drug; ITF = Innovation Task Force; OCE = Oncology Center of Excellence; DIA = Drug Information Association; DCT = Decentralised Trial

Regulatory landscape
Health Authority interactions: key general feedback

Thinking is still evolving
(EMA ITF and FDA OCE)

- **Application of decentralized trials must be considered on a case-by-case basis** (decentralized approach for a molecule with a well-established safety profile would be more likely to be acceptable).
- **No systematic approach can be employed yet and level of decentralisation may vary across country due to legal or healthcare operating model constraints.**
- **However** both EU and US Health Authorities demonstrated a high interest and willingness to remove or minimise obstacles and to find ways to be more flexible !

ALPHA-T
Key EU feedback

Key topic discussed: Principal Investigator (PI)/Local oncologist relationship, telemedicine/mobile nurse, digital tool (e.g. eICF), **Data Source,** Monitoring, local imaging center

- Remote vs local activities: ensuring that **roles and responsibilities are clear** as well as ensuring a **two way data exchange** between the different stakeholders is paramount
- Adequate data audit trail is needed as multiple **data source** will be employed + Patient **data protection** needs to be ensured
- Activities performed remotely should stay as close as possible to **standard practice**
- Ensure good **drug distribution** practice are in place (i.e. right medication to the right patient, enough drug shipped in the event of delay in visit, check damage and label)

Sweden - Decentralised and virtual interventional clinical trials Q and A (June 2021)
Denmark - Guidance on the implementation of decentralised elements in clinical trials with medicinal products (May 2021)

Regulatory landscape
Health Authority interactions: summary

ALPHA-T Key feedback

Overview of HA acceptance on key topics

	Telemedicine /Mobile nurse	**Informed Consent Form (ICF) e-signature**	**Drug shipment at home**
Spain	✅	✅ during pandemic	✅
Sweden	❌(Medical doctor needed)	✅	✅ but via Pharmacist or Principal Investigator
Denmark	❌ (Medical doctor needed)	✅ if accepted by the ethics committee	✅
UK	✅	✅	✅
Switzerland	✅	❌ (alternative remote paper sig.)	Depend on the canton
FDA	✅	✅	✅

Advantages of a decentralised clinical trial

- Performed **at or close to the patient's home** and fits around their day to day life
- Allows access to the patient, **irrespective of where they live**
- Allows **continued connection** to the medical team that the patient is already familiar with
- More diverse & representative patient population

Doing now what patients need next