8 June 2024

# Contradicting advice from national competent authorities when seeking clarity on the use of lab tests in clinical trials: a case study

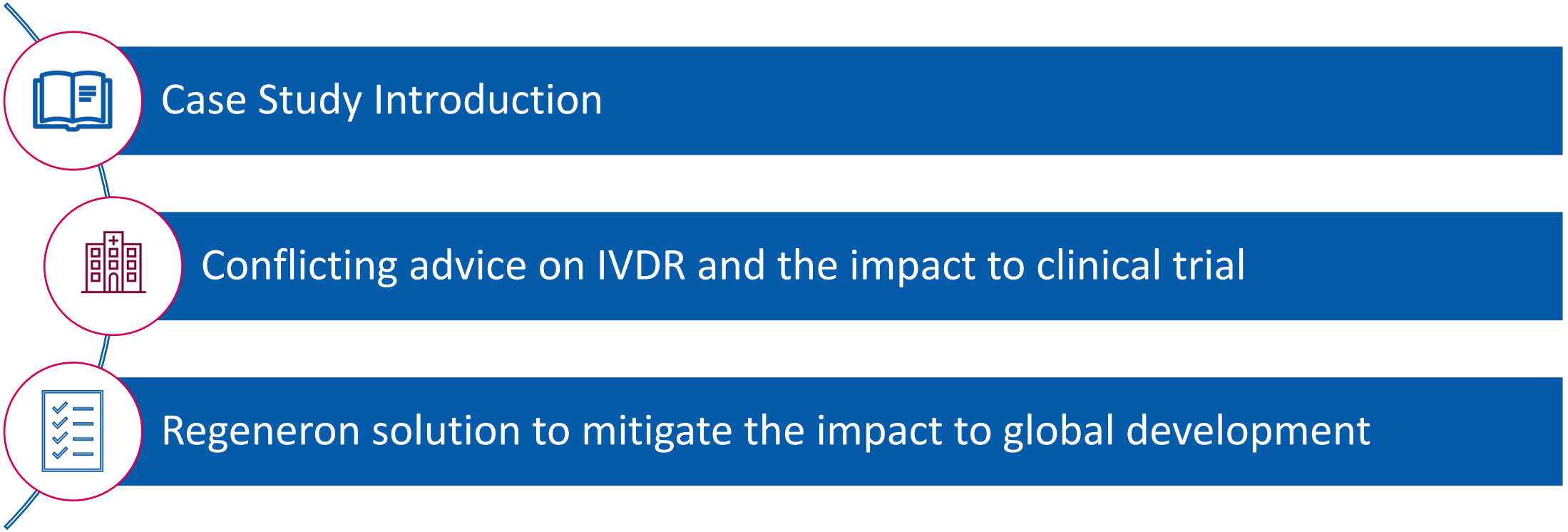
Jason S Simon, Ph.D.

Director, Precision Medicine

Diagnostic Strategy Lead

REGENERON®

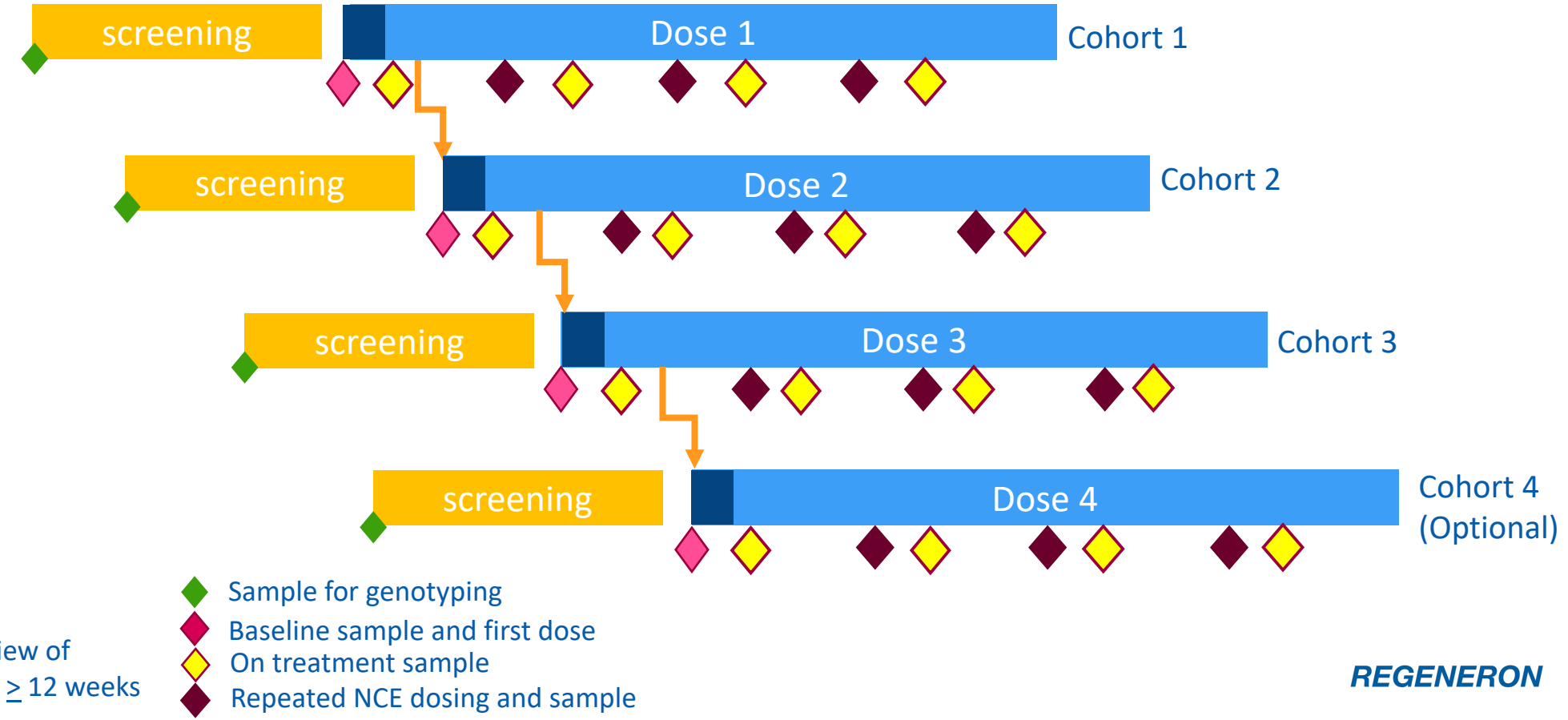
# Presentation Outline



# Case study: Phase 1 placebo-controlled ascending dose trial including 4 assays of note

Adaptation of dosing level and interval based on PD data in early subjects and then after each cohort

- Genotyping for inclusion
- Pharmacodynamic assessment of target engagement
- Surrogate marker of clinical response
- Drug concentration



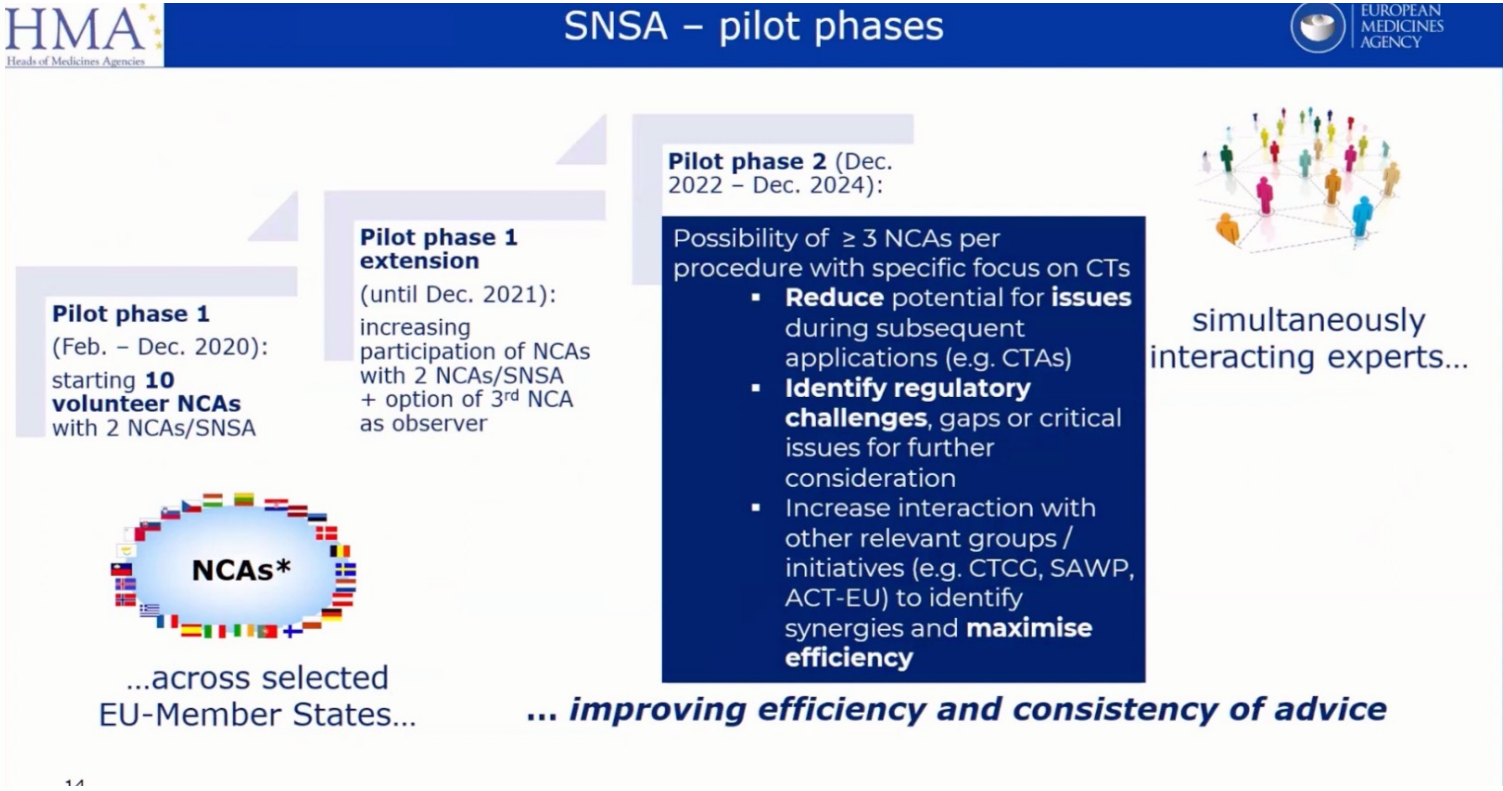



REGENERON

# We sought input on key trial design issues from EU NCA's via the Simultaneous National Scientific Advice (SNSA) process on clinical trial design, including use of lab tests in the study protocol

## Scope

- Scope aligned with national SA
- Can be used to obtain advice for products in an early stage of development
- Specific focus on SA related to CTs
- Complementary to other advice, e.g. EMA SA




Simultaneous National Scientific Advice - information and training webinar | European Medicines Agency (europa.eu)



REGENERON

# IVDR CASE STUDY:

*SNSA feedback yielded conflicting advice*

| | Genotyping | PD Marker | Drug Concentration | Surrogate of Response |
|---|---|---|---|---|
| **Use in study** | Enroll patients with confirmed associated variants | Inform dosing in subsequent cohorts | Inform dosing in subsequent cohorts | 2nd endpoint & partially Inform dosing in subsequent cohorts |
| **Country 1 Feedback** | Acceptable to use previously obtained test results. Central test **subject to IVDR** | Determination of dosing for subsequent cohorts = **medical purpose and subject to IVDR** | Determination of dosing for subsequent cohorts = **medical purpose and subject to IVDR** | Agree Research Use Only (RUO) not subject to IVDR |
| **Country 2 Feedback** | **Any testing** for variants for enrolment criteria is considered medical management and is **subject to IVDR** | Same as Country 1, includes info for future trials | Same as Country 1, includes info for future trials | Determination of dosing for subsequent cohorts = **medical purpose and subject to IVDR** |

# IVDR CASE STUDY:

*EU Simultaneous National Scientific Advice*

| | Genotyping (mostly consistent) | PD marker (consistent) | Drug PK (mostly consistent) | Surrogate of response (inconsistent) |
|---|---|---|---|---|
| **Use in study** | Enroll patients with confirmed associated variants | Inform dosing in subsequent cohorts | Inform dosing in subsequent cohorts | 2nd endpoint & partially Inform dosing in subsequent cohorts |
| **Country 1 Feedback** | Acceptable to use previously obtained test results. Central test **subject to IVDR** | Determination of dosing for subsequent cohorts = **medical purpose and subject to IVDR** | Determination of dosing for subsequent cohorts = **medical purpose and subject to IVDR** | Agree Research Use Only (RUO) not subject to IVDR |
| **Country 2 Feedback** | **Any testing** for variants for enrolment criteria is considered medical management and is **subject to IVDR** | Same as Country 1, includes info for future trials | Same as Country 1, includes info for future trials | Determination of dosing for subsequent cohorts = **medical purpose and subject to IVDR** |
| **Company Response** | **Identified central lab with CE marked genetic Panel** | **Contracted specialty lab with experience submitting PSAs** | **Modified protocol to remove dosing decisions based on drug conc.** | **Dropped Country 2 from study enrolment** |

# Pathways to Placing a Test on Market / In Service in EU*

**Placing in service in the EU also includes testing performed in a US lab on EU patient samples*

## In Scope of IVDR

### CE Marking

Commercial Product

Requires Conformity Assessment by EU Notified Body/EMA

Intended use must match protocol use

### Device for Performance Study

Non-CE marked device intended to be used in a performance study

Requires Performance Study Application

### In-house IVD (LDT)

An IVD manufactured and used within a single health institution

Needs to meet conditions of IVDR Article 5(5)

Central and specialty labs used for clinical trial testing cannot claim in house status

### Research Use Only

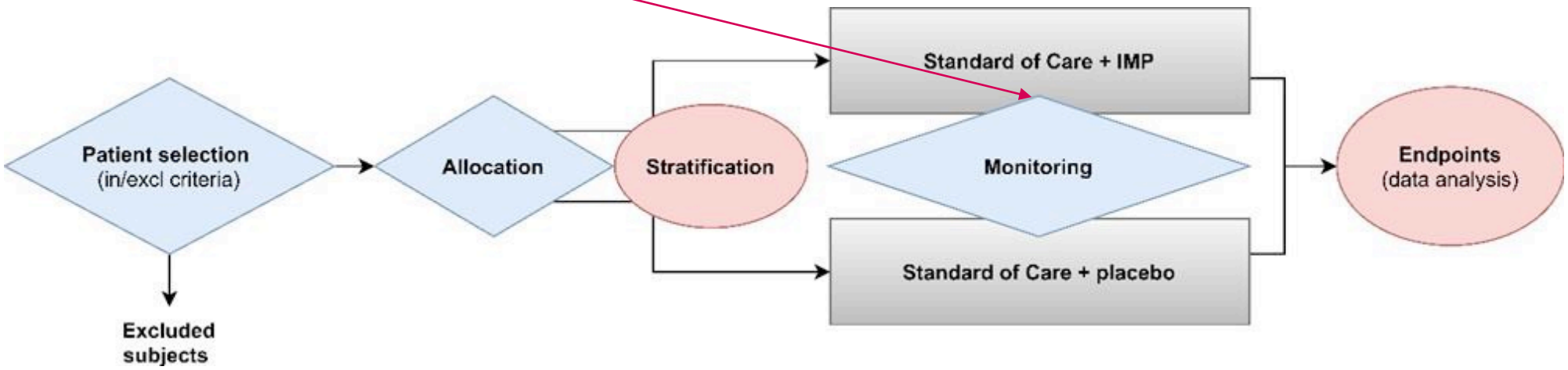
RUO

Used to study all aspects of human life in order to better understand underlying mechanisms…
**in a manner that does not have an intended medical purpose**

# Interventional Performance Study - Definition

**Interventional Study:** Clinical performance study where the test results may influence patient management decisions and/or may be used to guide treatment

**Intervention/**
**Medical Purpose**




*Guidance MDCG 2022-10*



REGENERON

# Device for Performance Study

*Authorization Requirements*

**Article 58: Authorization required by each participating member state for any performance study:**

a. In which **surgically invasive** sample-taking is done only for the purpose of the performance study;

b. That is an **interventional** clinical performance study as defined in point (46) of Article 2 or

c. Where conduct of the study involves additional **invasive procedures** or other risks for study subjects

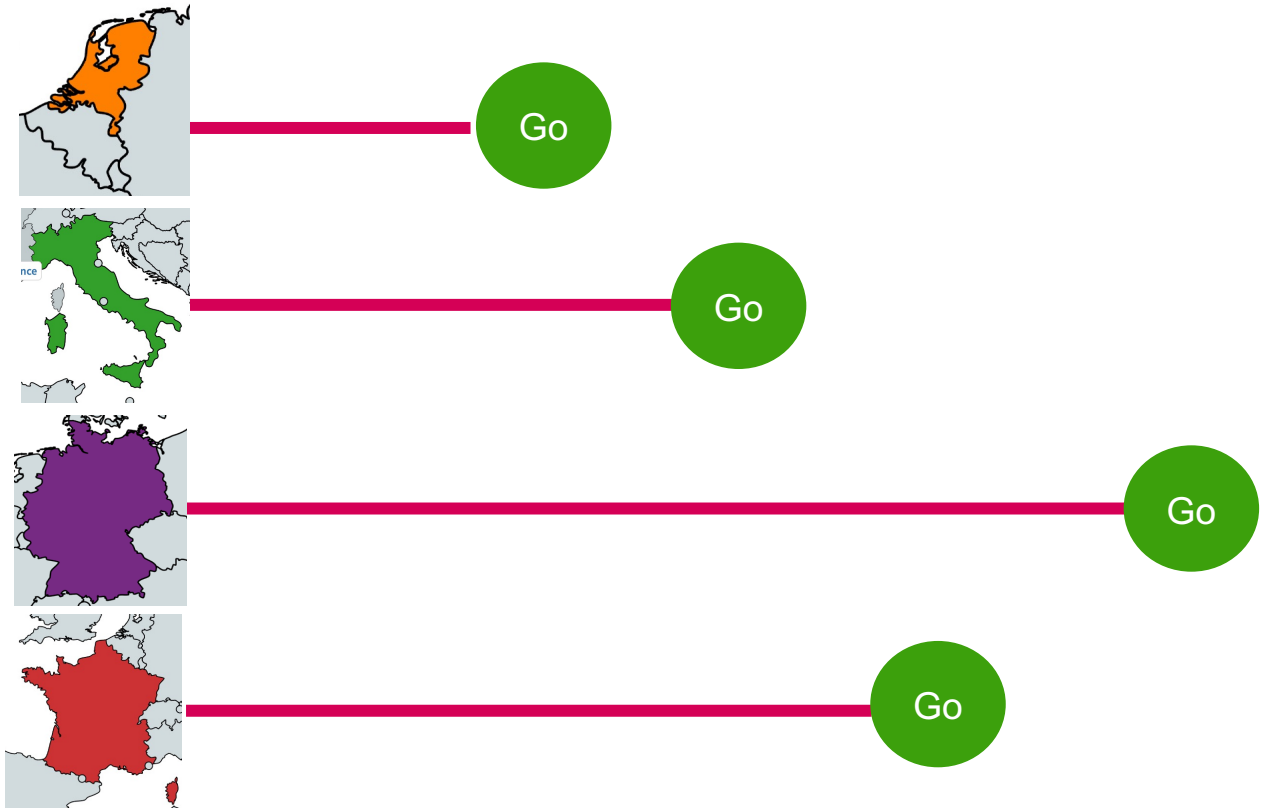
**Performance studies that meet criteria of Article 58 require prior authorization via a Performance Study Application to each country from which patients are being enrolled**

# Performance Study Application – Challenges

*Uncoordinated Review Across EU Countries*

## Variability of IVDR Interpretation


## Variability of Review Timelines




**Average PSA Review Timeline = 3 – 7 months**



REGENERON

# IVDR has changed REGN management of clinical trial design, initiation and execution

- Each clinical trial undergoes an IVDR IMPACT ASSESSMENT to identify **every** clinical lab test to determine:
  - Type of assay/assay technology
  - Is the assay in question CE marked?
  - Location of testing (local lab, central lab?)
  - Purpose of assay (enrollment, stratification, dosing decision, safety, PD assessment, endpoint assessment etc)
- Assays considered to be supporting medical management which are not available as CE marked kits AND for which local lab testing is not desirable are identified and suitable solutions are developed
  - contract CRO for assay development/PSA submission
    - contract regulatory CRO to perform monitoring of device
  - identify single in-house lab to support global clinical testing
- Search for a compliant EU solution is exhausted prior to making decision to perform trial Ex-EU member states (and non-EU member states that have adopted IVDR regulations)
- Timeline for readiness of assays in the EU are communicated to clinical trial operation team and senior management

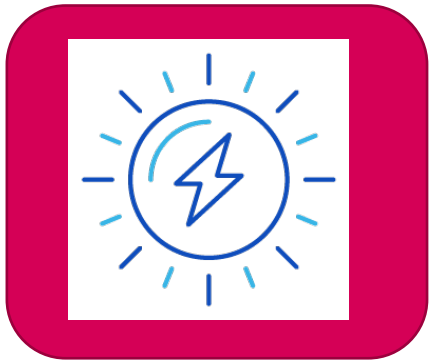
# Summary

EU Regulation 2017/746 (IVDR) imposes new requirements for assays used within Drug Clinical Trials. Assays used for medical purpose may need authorization from EU Competent Authorities prior to study start

The lack of EU member state coordination and delay in EUDAMED resulted in variable IVDR interpretation was highlighted by the SNSA feedback

REGN initiated a robust clinical protocol review process (and staff training) to ensure early identification of assays that would require PSAs to minimize risk of study delays

# Proposal for discussion



Given the disruption to clinical development caused by IVDR regulations, a ‘Safe Harbor’ for certain assays used in early clinical trials may be warranted.

For Example:

Bioanalysis of drug concentration is often used to inform dose escalation in clinical development. These assays are validated to GLP and GCP and FDA/EMA/ICH standards, but are almost never developed/intended to be used as commercially IVD tests. The use of these data in clinical trial uses should be exempt from IVDR regulation