EBF Spring Focus Workshop
IVDR: our next Challenge?

Sailing through uncharted IVD waters

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June, 8th 2024

The increasing use of biomarkers for patient selection within argenx clinical trials requiring IVD testing highlights the need to align processes to comply with IVDR

argenx is in uncharted waters within the IVD space
→ finding our way and in doing so gain insights.

IVD team: Multi-disciplinary team supporting & leading early to late IVD discussions, strategy and development.

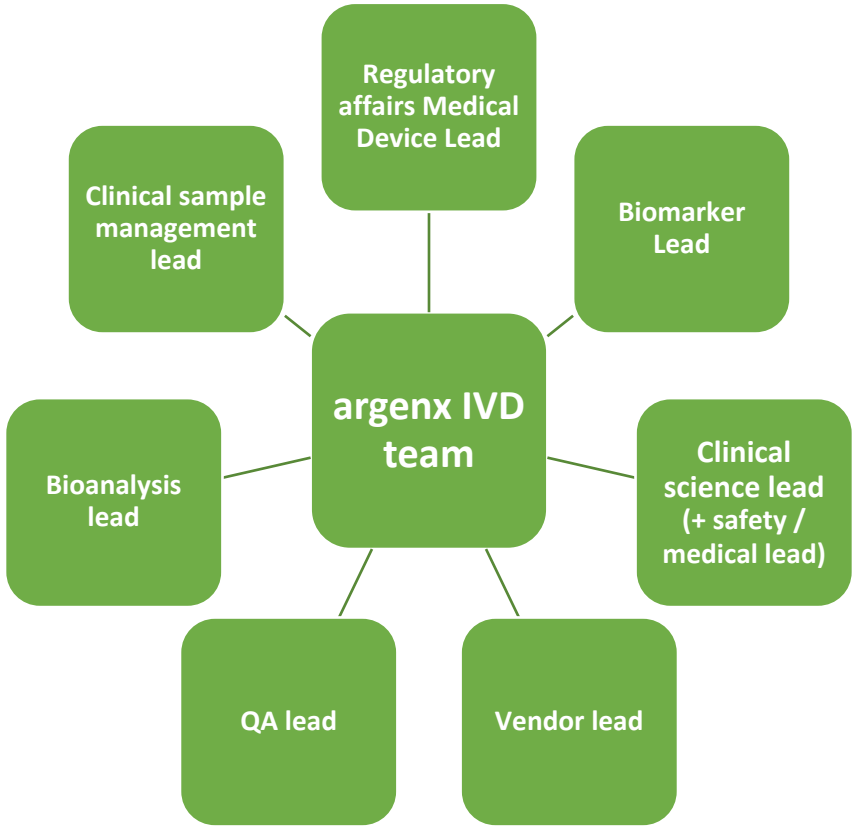
IVD expertise should be "tapped into" early to ensure we

a) avoid unnecessary IVD burden & highlight risks,

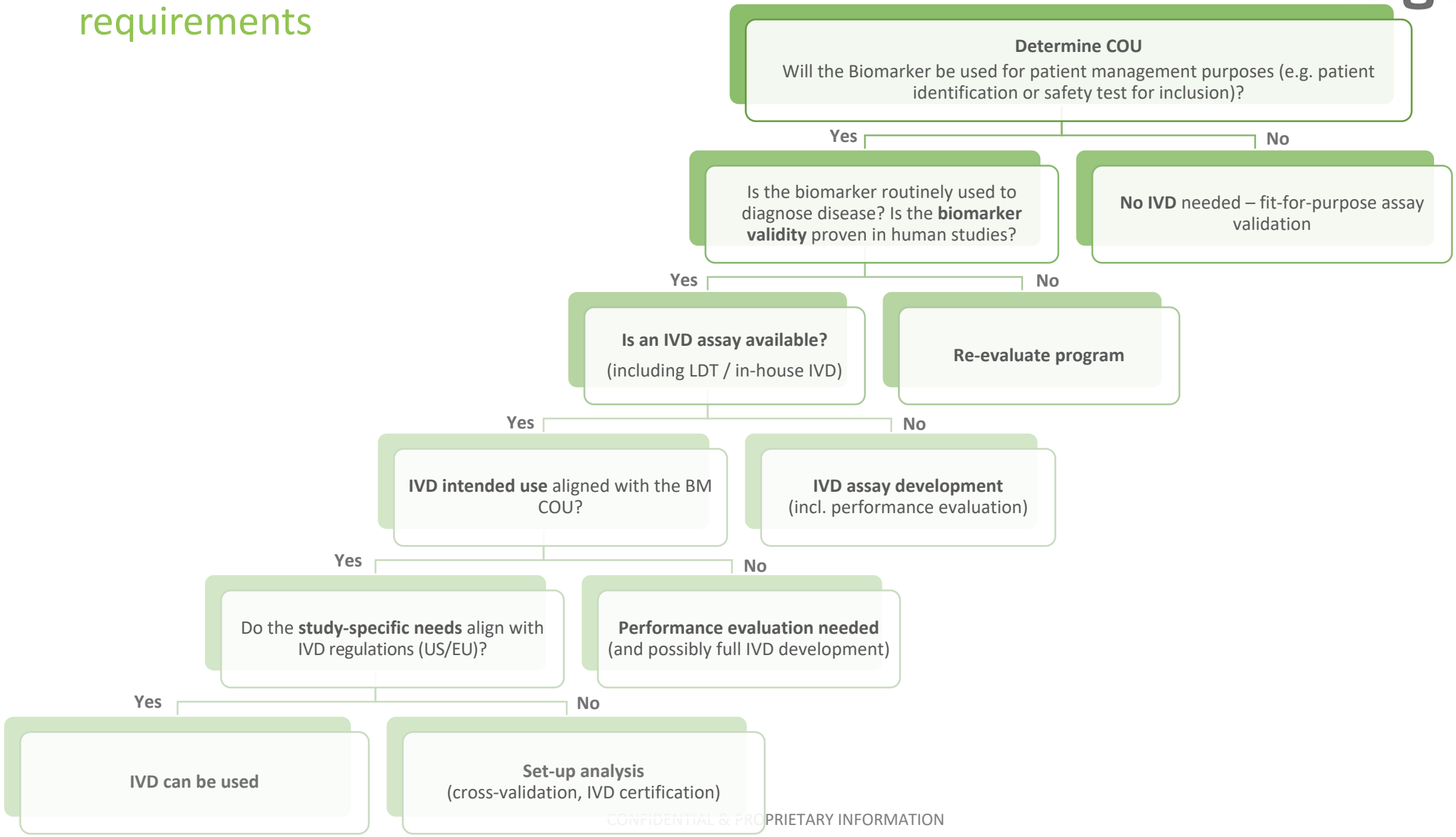
b) optimally deploy regulated tests & IVDs within our clinical studies and,

c) understand the project consequences and have the right guidance to avoid panic scramble

→ Strong case by case situation



Decision tree to support IVD requirements



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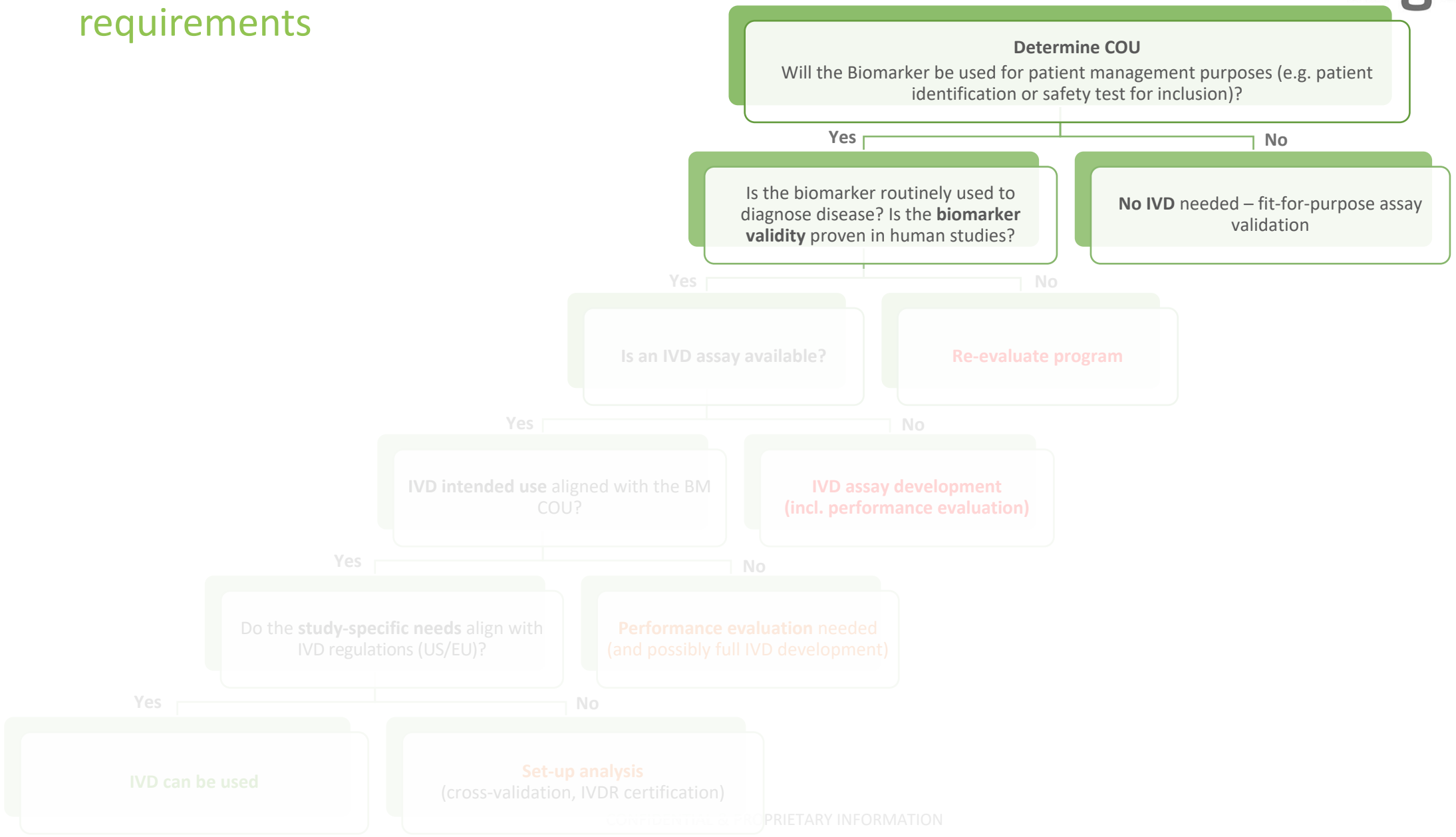
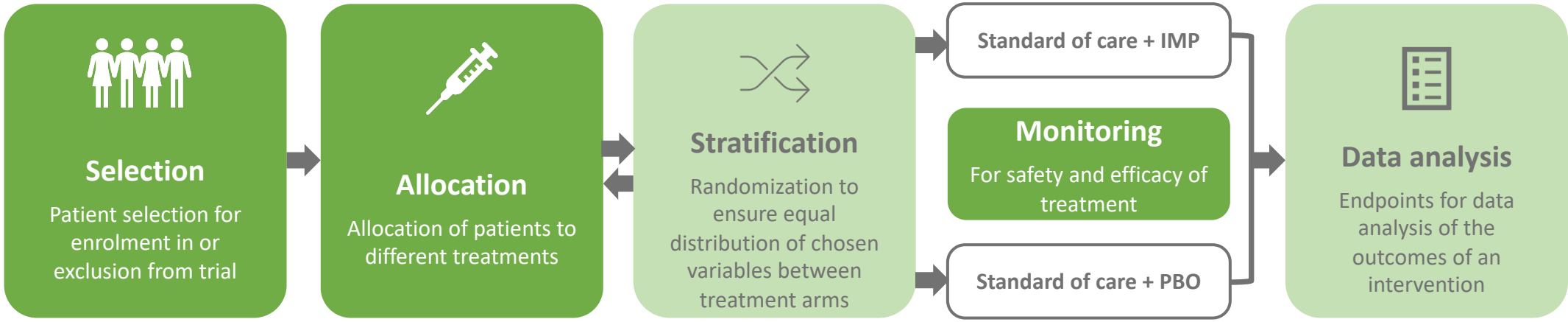


COU determines the need for IVD

COU determines the need for IVD assay

IVD only applies when used for the purpose of **medical management decision making of trial subjects** within the trial, e.g. diagnosis, preventing, monitoring, or treating diseases or other medical conditions in humans



Assays performed for these processes are likely **considered IVD** - reported data going back to the HCP for individual patient decision

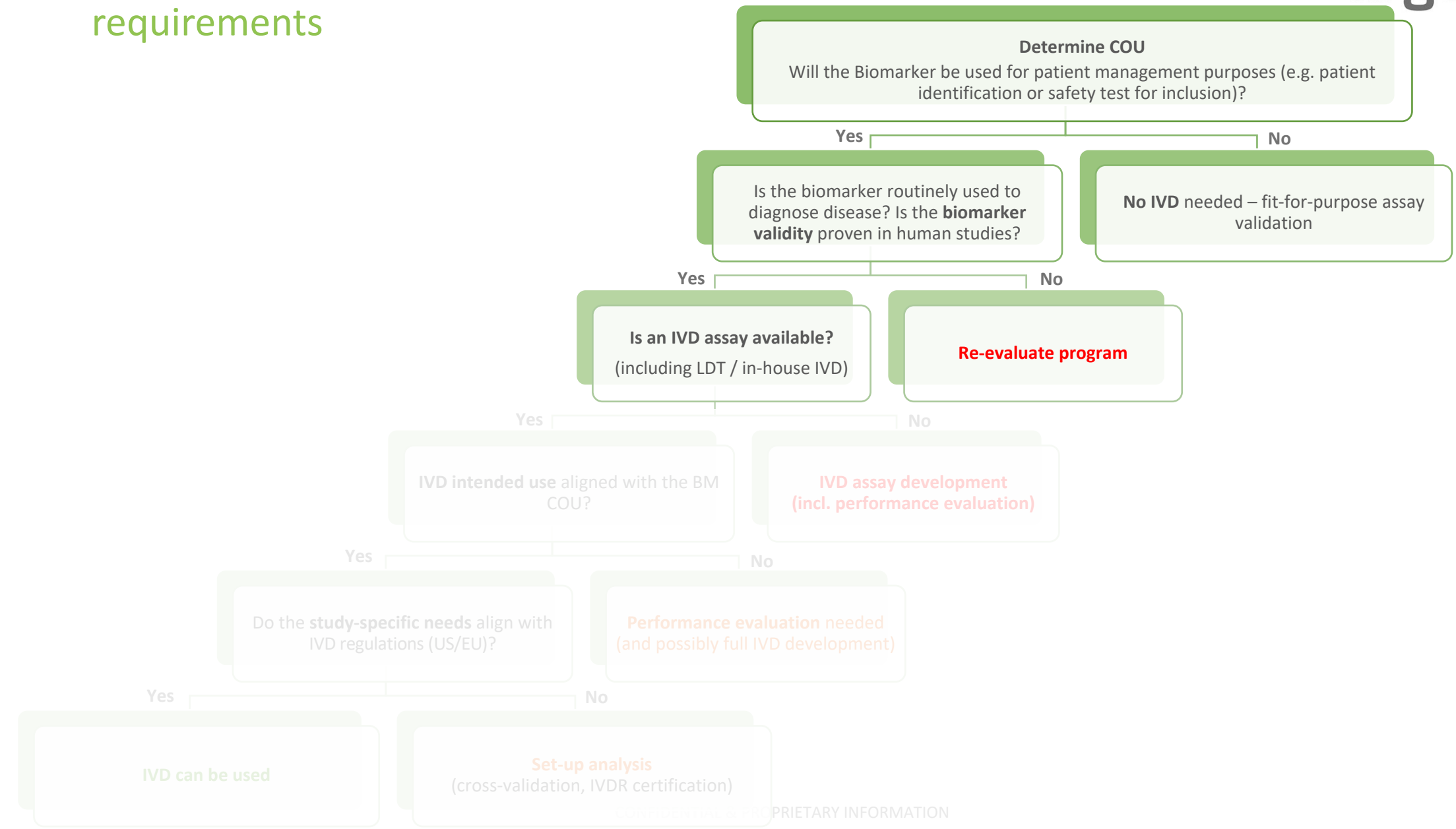
Assays performed for these processes are are likely not to impact patient management decision and hence, **not considered IVD**

argenx examples

- Auto-antibody tests used for patient eligibility
  e.g. anti-AChR Ab in the Ph3 efgartigimod study in MG
- Auto-antibody tests used for patient stratification
  e.g. anti-MuSK Ab in the Ph3 efgartigimod study in seronegative (anti-AChR Ab) MG
- Auto-antibody tests used for PD read-out
  e.g. anti-AChR in the Ph3 efgartigimod study in MG
- All clinical PK and ADA assays

Abbreviations: AChR, acetyl choline receptor; ADA, anti-drug antibody; COU, context of use; MG, myasthenia Gravis; MuSK, muscle specific kinase; PD, pharmacodynamic; PK, pharmacokinetic

Decision tree to support IVD requirements



Questions to ask to understand unmet need (from patient population & test perspective)

Patient population

- How is the target patient population identified?
- Biomarker needed for / to support diagnosis of patient population?

Biomarker

- How is the biomarker used to improve clinical unmet need?
- Is the proposed biomarker established for the patient population?

Test

- Landscape of tests: do existing tests offer solutions that are feasible?
- Is there an IVD test available?

argenx example

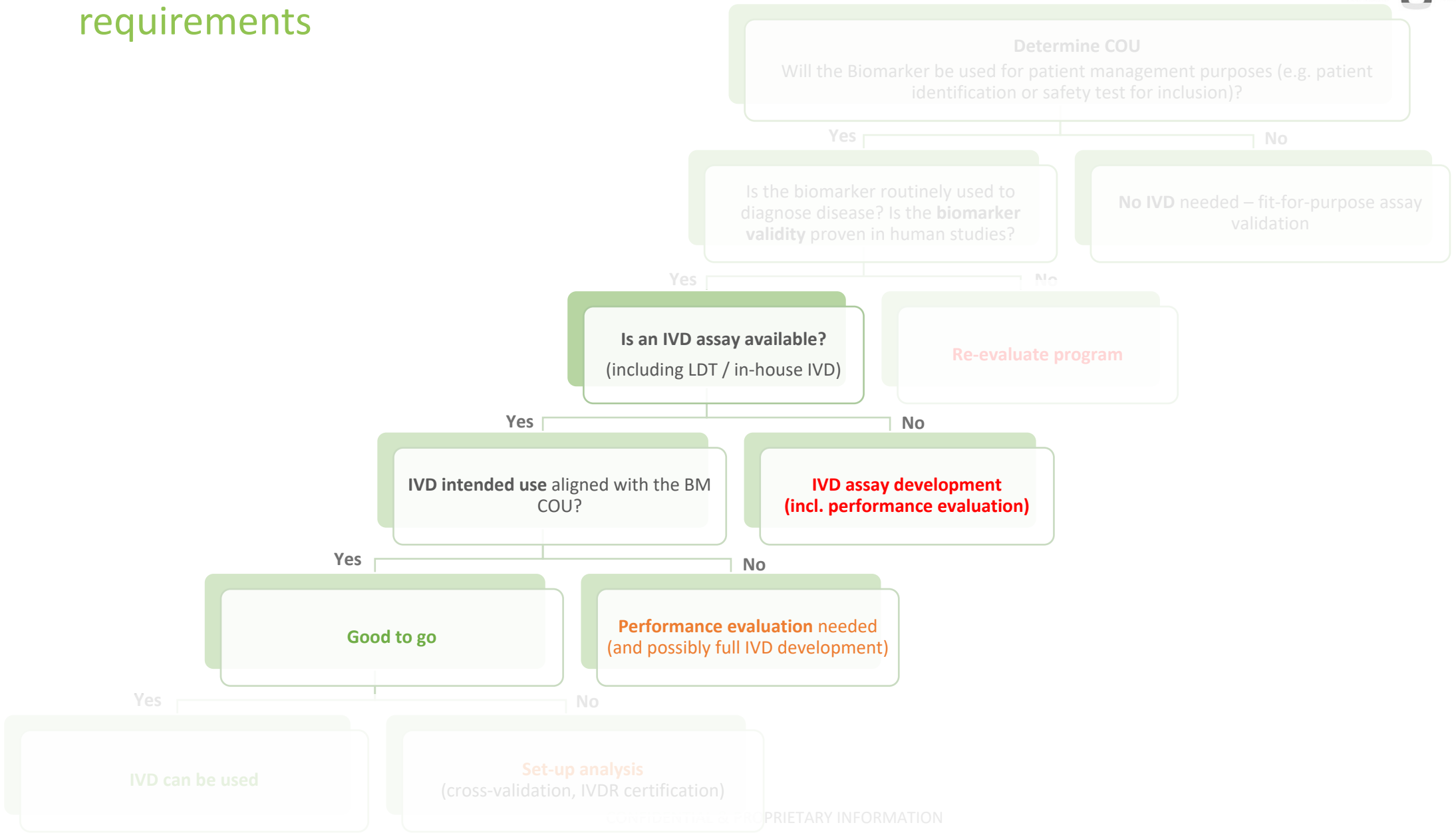
Anti-AChR Ab test used to support MG diagnosis – selection of AChR positive MG subpopulation

AChR autoAb targeting NMJ are key mediators of MG pathology and are present in ~85% of MG patients

IVD test available

Abbreviations: AChR, acetyl choline receptor; IVD, in vitro diagnostic; MG, myasthenia Gravis; NMJ, neuromuscular junction

Decision tree to support IVD requirements



IVD intended use

Critical to check whether the biomarker COU aligns with the intended use of the IVD

Does the intended use of the IVD match with the intended use of the biomarker?

Yes → You can use the IVD

No → If you want to use an IVD outside of its prescribed intended purpose → perform a **performance study** to confirm scientific validity and analytical / clinical performance

argenx example

anti-AChR autoAb IVD test in the Ph3 efgartigimod study in MG

anti-TSHR autoAb IVD test: team considered to use as eligibility criterion in the Ph3 efgartigimod study in TED but IVD assay is not FFP (Graves' disease)

At argenx very often a **biomarker is used for different COU** e.g. auto-antibody tests → **different assay needed**!

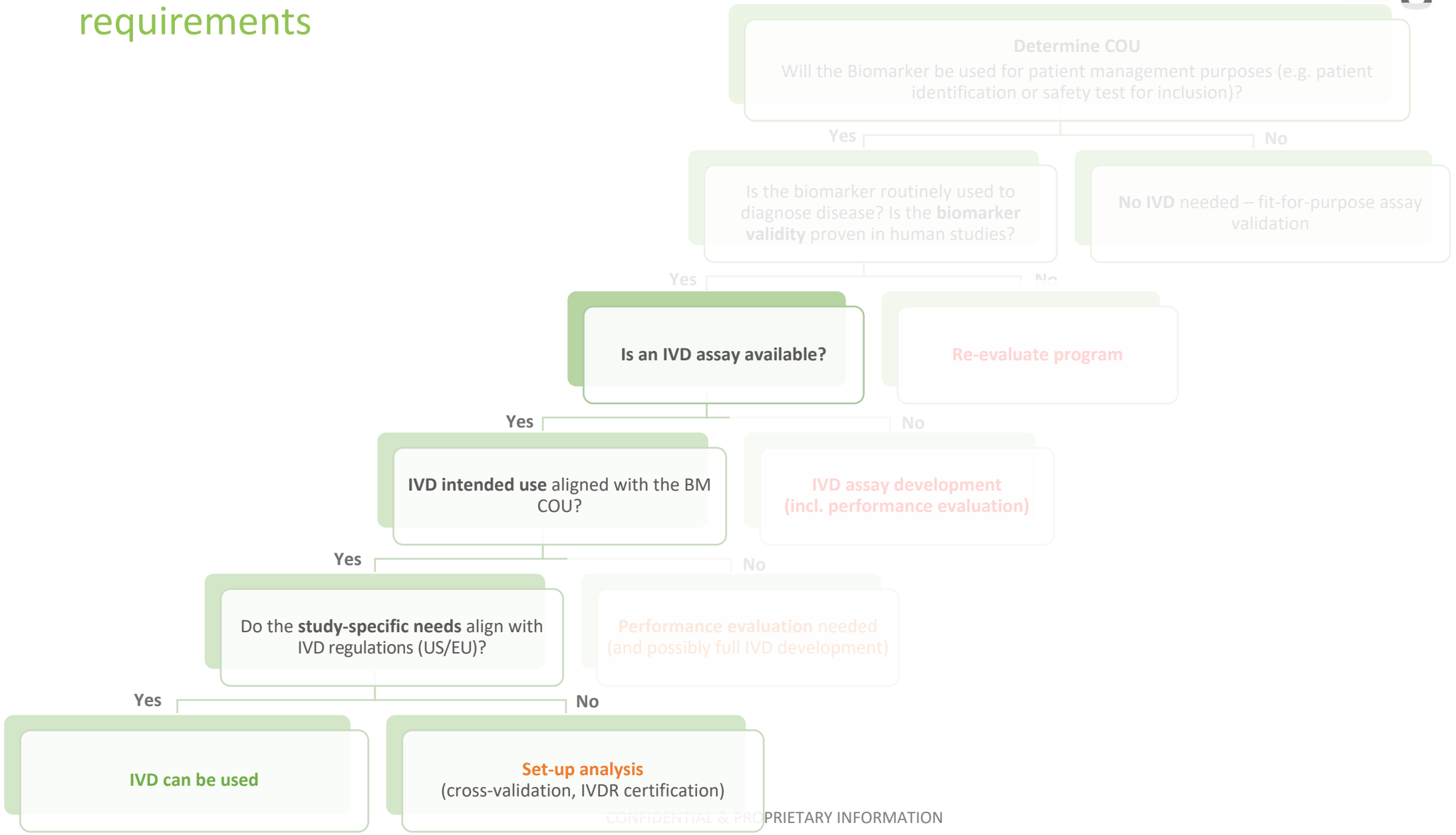
- Diagnostic / patient eligibility purpose: IVD kit needed with qualitative read-out
- Pharmacodynamic purpose: ROU / GCLP assay needed with relative quantitative read-out

→Different assay characteristics required thus different assay validation needs to be done

→Different lab requirements

Abbreviations: AChR, acetylcholine receptor; FFP, fit for purpose; GCLP, good clinical laboratory practice; IVD, in vitro diagnostic; MG, myasthenia Gravis; RUO, research use only, TED, thyroid eye disease

Decision tree to support IVD requirements



IVD regulations

Impact of EU IVDR for argenx clinical studies

Risk assessment process

Ongoing clinical study (submitted before May 2022)

New clinical study (EU / part of global study)

Tests not used for medical decision making

Tests used for medical decision making

No change

CE marked IVD under IVDR for intended purpose, or, under IVDD (and holding its validity under the IVDR transition period) or qualified in-house IVD

IVD not (yet) CE marked under IVDR or IVDD or no in-house IVD that complies with IVDR article 5(5)

CRO is CE marked IVD user
Good to go

Re-evaluate – assess what needs to be done
Cross-validation / certification / performance study needed / exclude EU (member states)?

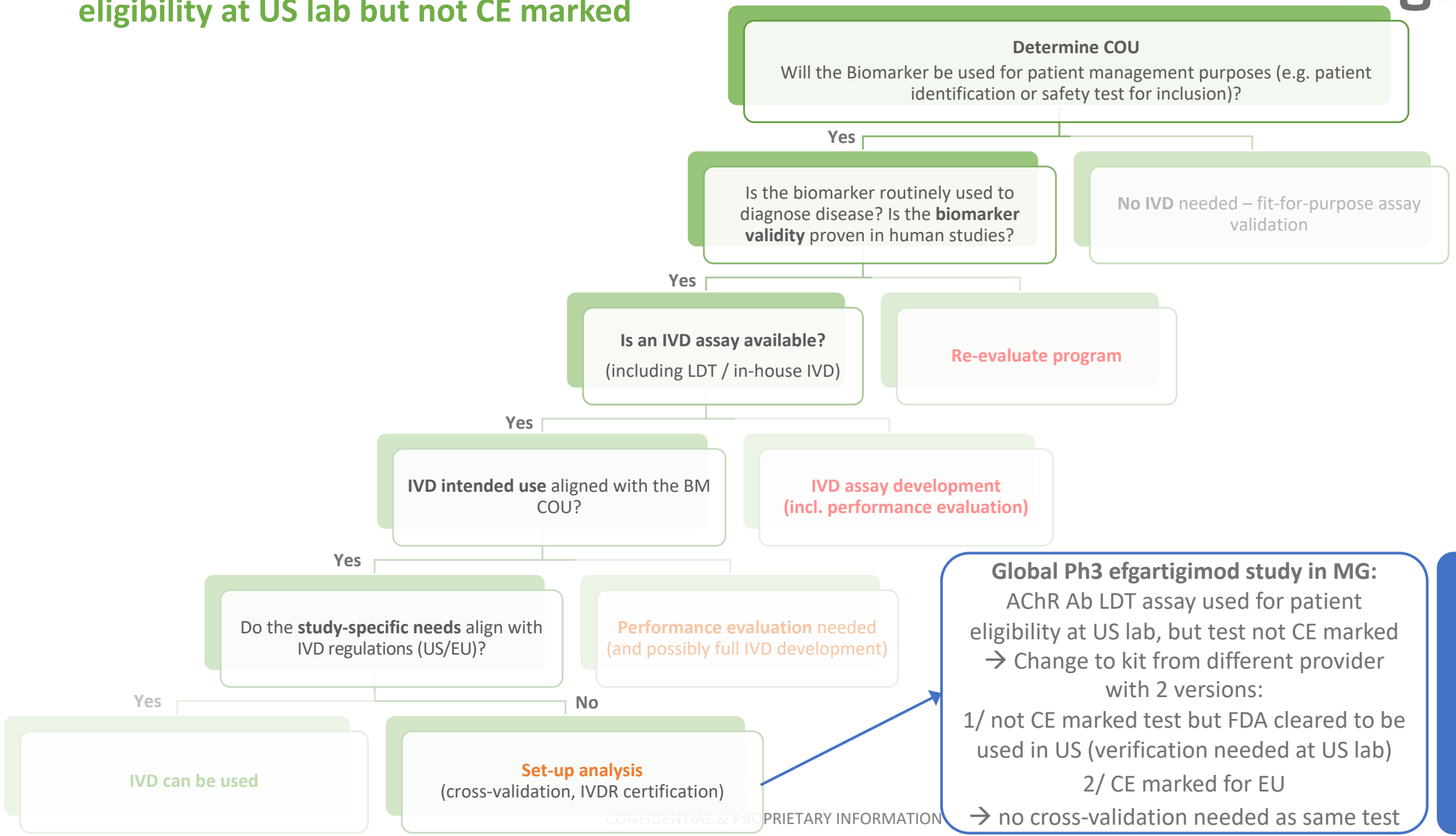
General trends

- All trials approved before May 26, 2022 can continue
- Generally, new clinical studies are not supported if no CE-marked test available
- Some uncertainties remain, e.g. intend of manufacturers to apply for IVD certification, exemption for in-house IVD, etc.

Sponsor is responsible for CRO oversight

Argenx IVD team is mapping IVD needs in our clinical studies and compliance of IVD assays

AChR Ab LDT assay used for patient eligibility at US lab but not CE marked

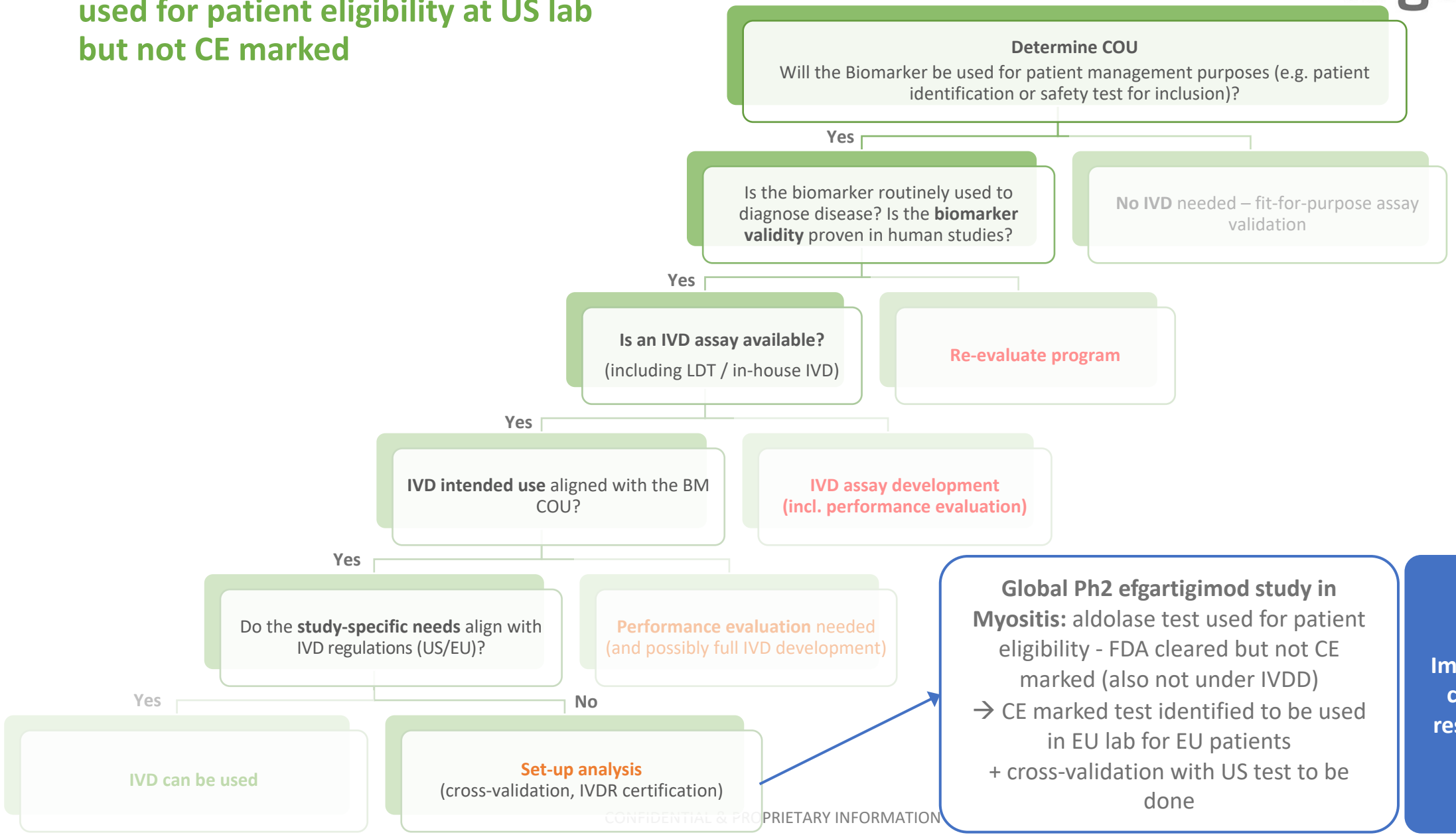


Global Ph3 efgartigimod study in MG:
AChR Ab LDT assay used for patient eligibility at US lab, but test not CE marked
→ Change to kit from different provider with 2 versions:
1/ not CE marked test but FDA cleared to be used in US (verification needed at US lab)
2/ CE marked for EU
→ no cross-validation needed as same test

Impact on clinical study timelines

Case study

Aldolase IVD test used used for patient eligibility at US lab but not CE marked



Global Ph2 efgartigimod study in Myositis: aldolase test used for patient eligibility - FDA cleared but not CE marked (also not under IVDD)
→ CE marked test identified to be used in EU lab for EU patients
+ cross-validation with US test to be done

Impact on clinical resources

Case study

Conclusions

- As a result of the recent developments in IVD regulations and the increasing use of biomarkers for patient selection **at argenx**, we felt there was the **need to align processes**.
- A **cross-functional working group** has been formed to provide support and guidance to teams to ensure consistency and efficiency
- A **comprehensive flowchart** was developed to streamline the process of identifying the need of an IVD assay based on the context of use.
  - The flowchart guides users in assessing the availability and suitability of an IVD assay
  - It supports the evaluation of the compatibility of the assay and its certifications with study-specific requirements
  - It outlines necessary steps in case of discrepancies
- Assessment of IVD assay availability and suitability should be done in close **collaboration** with clinical CROs and diagnostic labs.

Acknowledgements

Argenx IVD team

- Mayank Choudhary
- Leentje De Ceuninck
- Isabelle Dewaele
- Jean-Philipe Lecocq
- Amandine Berthet Le Flohic
- Titilayo Majekodunmi
- Marlies van den Ende
- Jamie McKay
- Marqus Hamwright

Clinical project teams represented by

- MG team: Sophie Steeland & Delphine Masschaele
- Myositis team: Leentje De Ceuninck
- TED team: Estefanía Urdániz