EUROPE BIOBANK WEEK

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VIENNA - AUSTRIA

Ilona Reischl : "Clinical trial requirements for medicinal products and medical devices

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European, Middle Eastern & African Society for Biopreservation & Biobanking

Clinical trial requirements for medicinal products and medical devices –

When does your project fall under these legal requirements?

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Disclaimer

EMA: "The views expressed in this presentation are my personal views and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties."

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Core questions:

- Am I systematically investigating a product that falls under the medicinal product or medical device definition? → check legal texts
  - Medicinal product legislation
  - Medical device legislation
- What are the respective legal framework requirements for the conduct of my study?
  - Medicinal product → clinical trial
  - Medical device → clinical investigation
  - In-vitro diagnostic (IVD) → performance evaluation
- What are the respective practical details for approval and conduct of my study? → check guidance documents

Why should you care?

- It is never a good idea to break the law!

- In Austria there is only one legal measure if it is discovered that a clinical study was not conducted according to legal requirements:
  - Interdicting the trial and consequently the use and publication of the generated data!

- Your research applicantions for EU grants (Horizon 2020 etc) are increasingly checked for regulatory compliance
  - Regulatory deficiencies potentially lead to grant rejection!

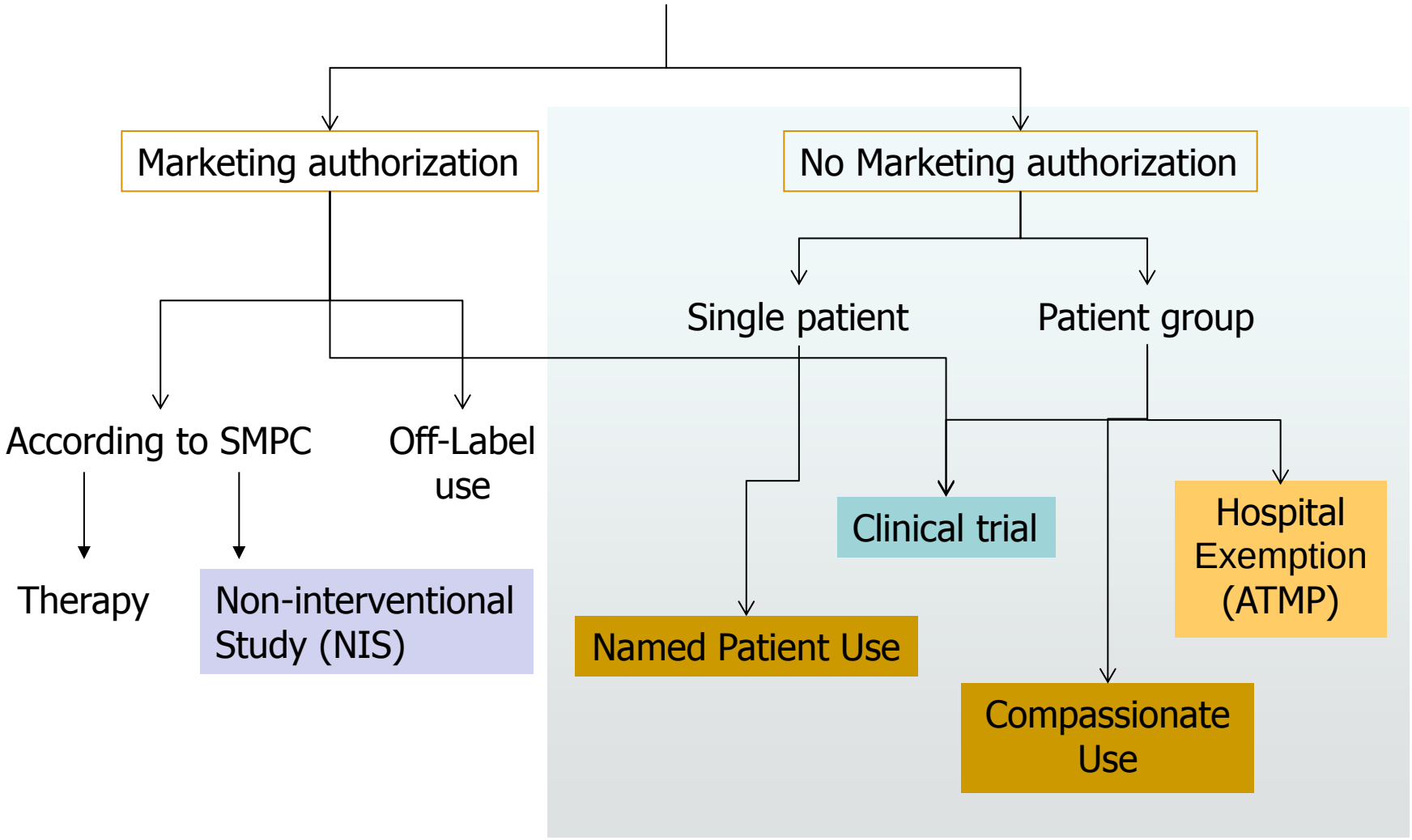
In the context of biobanks

- Am I investigating biomarkers in the context of therapeutic drug intervention? → Clinical trial
- Am I investigating biomarkers in the context of therapeutic device intervention? → Clinical investigation
- Am I developing an IVD for commercial application? → Performance evaluation
- Am I conducting a performance evaluation of an IVD for in-house use? → depending on National legislation; in AT same principles apply for these studies
- Are tissues/cells used as a starting material for manufacture of an Advanced therapy medicinal product (ATMP)? → Procurement and Manufacturing authorization required; clinical trial

Clinical trials for medicinal products

The European Clinical Trials framework is undergoing a complete overhaul

Medicinal Product



Clinical trials framework

- Systematic investigation of a medicinal product that..
  - Is not yet licensed at all/in this indication
  - Is licensed but the study incorporates additional diagnostic or therapeutic measures (including randomization)
- Framework is currently based on Directive 2001/20/EC, but was critisised for disharmonisation between Member states
- is transitioning to the new Clinical Trials Regulation Reg/536/2014/EC

- *Note:* A Directive needs to be incorporated into National law for applicability, a Regulation immediately applies for all member states in ist exact wording

Definition Dir/2001/20/EC

Article 2 (a) 'clinical trial':

- any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or
- to identify any adverse reactions to one or more investigational medicinal product(s)
- and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy;

Non-interventional study – Dir/2001/20/EC

- A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the MA
- The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and
- the prescription of the medicine is clearly separated from the decision to include the patient in the study
- No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data

Classification makes a difference

Clinical Trial

- Insurance requirement
- EU framework
- EU clinical trials register
- Licensed or unlicensed IMP
- High documentation needs
- High cost for conduct

NIS

- No insurance required
- National framework
- National transparency provisions
- Licensed MP according to SmPC (no off-label)
- Routine practice
- Reduced overall cost

www.basg.gv.at/en/medicines/prior-to-authorisation/clinical-trials/
EudraLex Volume 10

Example

- **Title**: Impact of xxx on coronary reserve (licensed MP)

- **Background**: Animal studies demonstrated that xxx has vasodilatoric effects on the coronary arteries and the microcirculation. This has not yet been investigated in humans.
- **Study objectives**: To investigate the impact of xxx on the coronary reserve by PET. As part of the study a PET analysis will be done before taking xxx and 1 month after therapy initiation ..

„Investigating the effect of a medicinal product“
Clinical Trial

Example: PET Tracer

- Tracer is the scope of investigation →
  - Clinical trial, Tracer is IMP
- Tracer is used for diagnostic purposes in a CT with a medicinal product →
  - Clinical trial, Tracer is NIMP (non-investigational)
- Tracer is being used for diagnostic purposes in a study without medicinal product e.g Physiotherapy →
  - This does not make the study a clinical trial in the scope of the National Competent Authority
  - Biomedical basic science

Example – Biobank building

- Tissue is routinely collected in the framework of a NIS to build a Biobank
- Tissue samples will be analysed in context of the NIS Results

→ Additional diagnostic measure? → jeopardizes NIS classification

- To which extent are NIS patient and medicinal product data separate from the tissue analysis?
- Depending on protocol details the project might be classified as clinical trial

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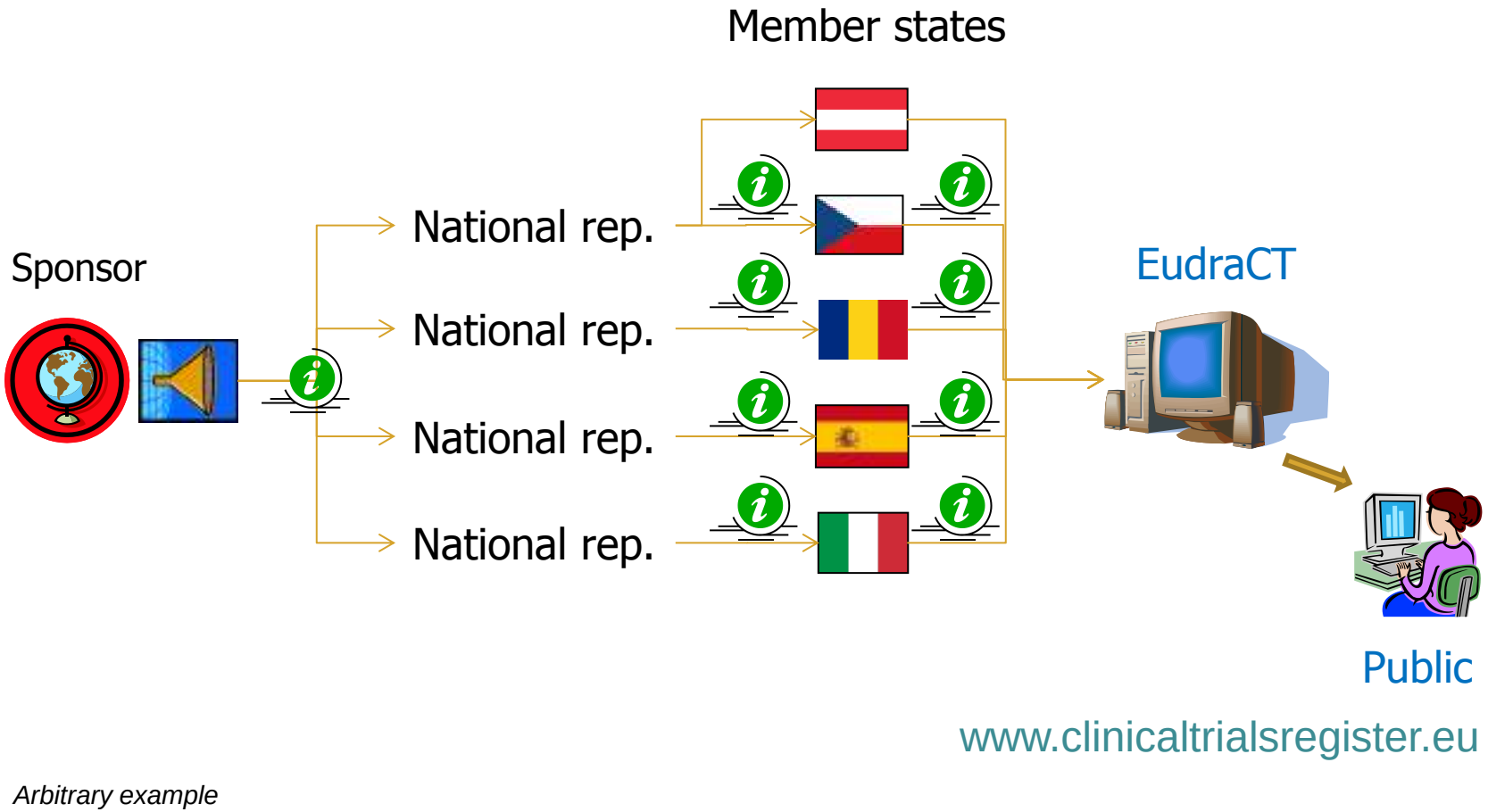
Current Szenario – multinational Study



Arbitrary example

EudraCT/EU CT register

- EudraCT is the EU Database into which the application details for EACH clinical trial approved by agencies are uploaded
- The NCAs add the date of decision for the agency and the EC
- All EU agencies have access to these entries
- CTs for which these dates have been entered will be public in the EU clinical trials register unless they are phase I studies without pediatric population
- www.clinicaltrialsregister.eu
- Clinicaltrials.gov is not a reliable source for EU trials (voluntary entry and no agency oversight). Entry in this database does not fulfill EU requirements

Competent Authority Tasks

- The objective of clinical trial authorisation is to guarantee safety and efficacy for the participant based on a limited dossier

- The objective of marketing authorisation is to guarantee safety and efficacy for a wide patient population based on a full dossier

- Clinical trial authorisation is therefore no guarantee for the suitability of study design and results for marketing authorization

➔ Drug development is the remit of the developer

Official Publication

http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOL_2014_158_R_0001&from=EN

Official Journal of the European Union

L 158

English edition

Legislation

Volume 57

27 May 2014

Contents

I *Legislative acts*

REGULATIONS

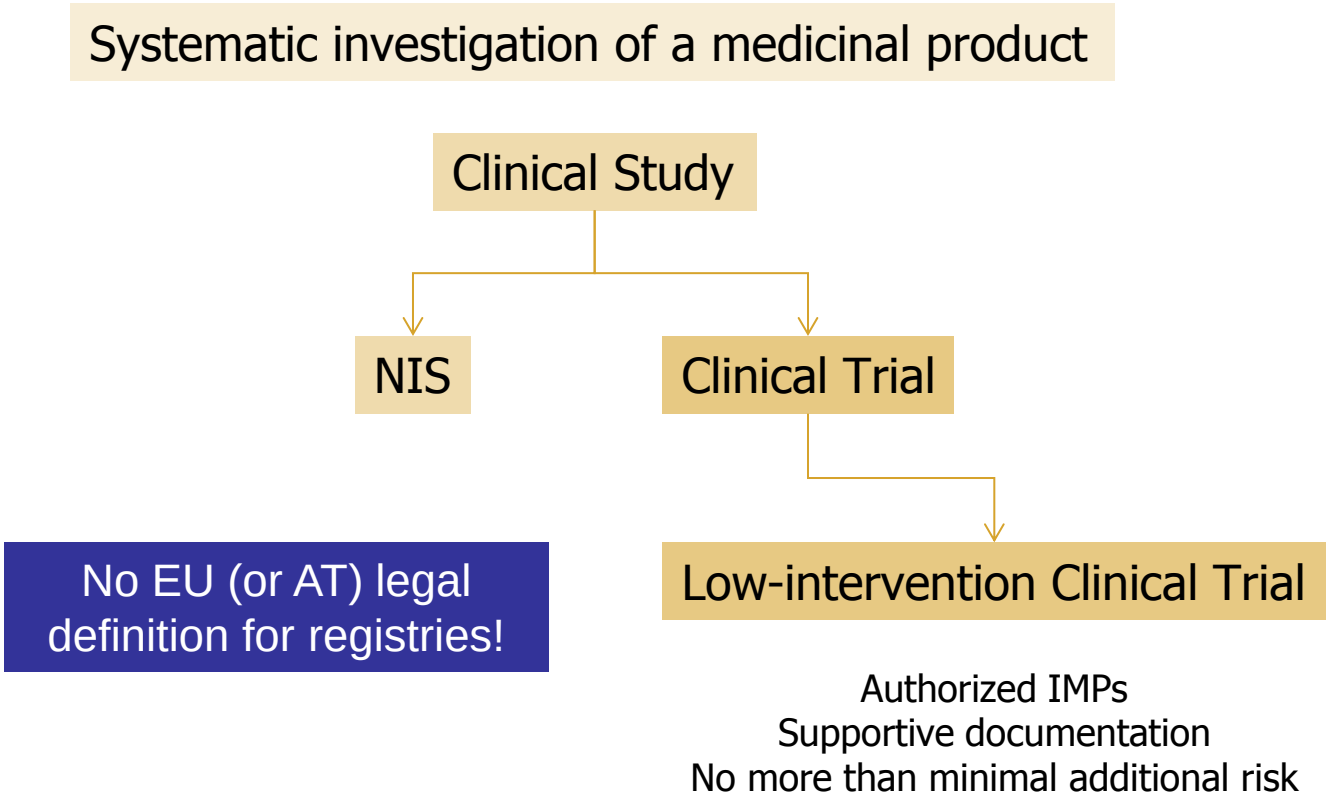
★ Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (1) 1

Text is finalized!
Guidelines for more detail

The Procedure

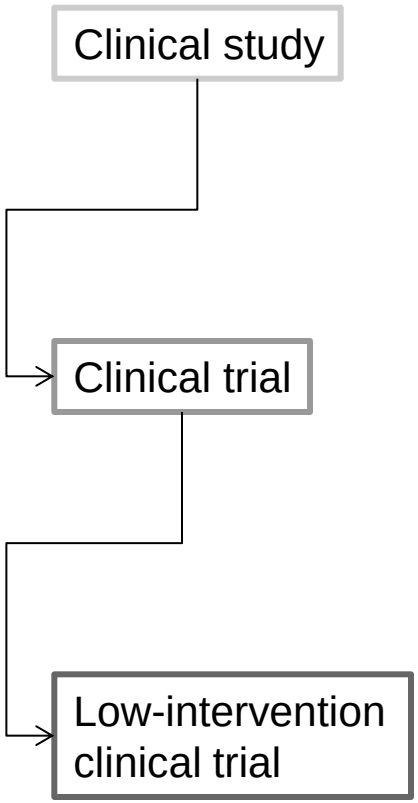
- Single point for submission (EU portal)
- Simultaneous submission for all MS
- Concept of reporting and concerned member states
- Single authorization per MS and trial
- Single contact point per MS
- Single fee per MS
- Coordinated review by competent authority and ethics committee - Organizational setup and internal competences MS responsibility
- `Qualified opt-out' for a MS
- Harmonized dossier requirements

Study Classification



Classification of Studies

Investigation of Medicinal Products (MPs) in Humans



- to discover/verify the clinical, pharmacological or other pharmacodynamic effects
- to identify any adverse reactions; or
- to study absorption, distribution, metabolism and excretion with objective of ascertaining safety

- Assignment of subject to a therapeutic strategy is decided in advance and is not normal clinical practice in the MS
- decision to prescribe the IMP is taken together with the decision to include the subject in the clinical study; or
- diagnostic or monitoring procedures in addition to normal clinical practice are applied

- IMPs, excluding placebos, are authorised
- IMPs used according to SMPC or use is evidence-based and supported by published scientific evidence on safety/efficacy
- additional diagnostic or monitoring procedures do not pose > than minimal additional risk/burden to safety of subjects compared to normal clinical practice in any MS concerned

CT Regulation – Änderung der NIS Definition

Non-interventional study

a clinical study other than a clinical trial

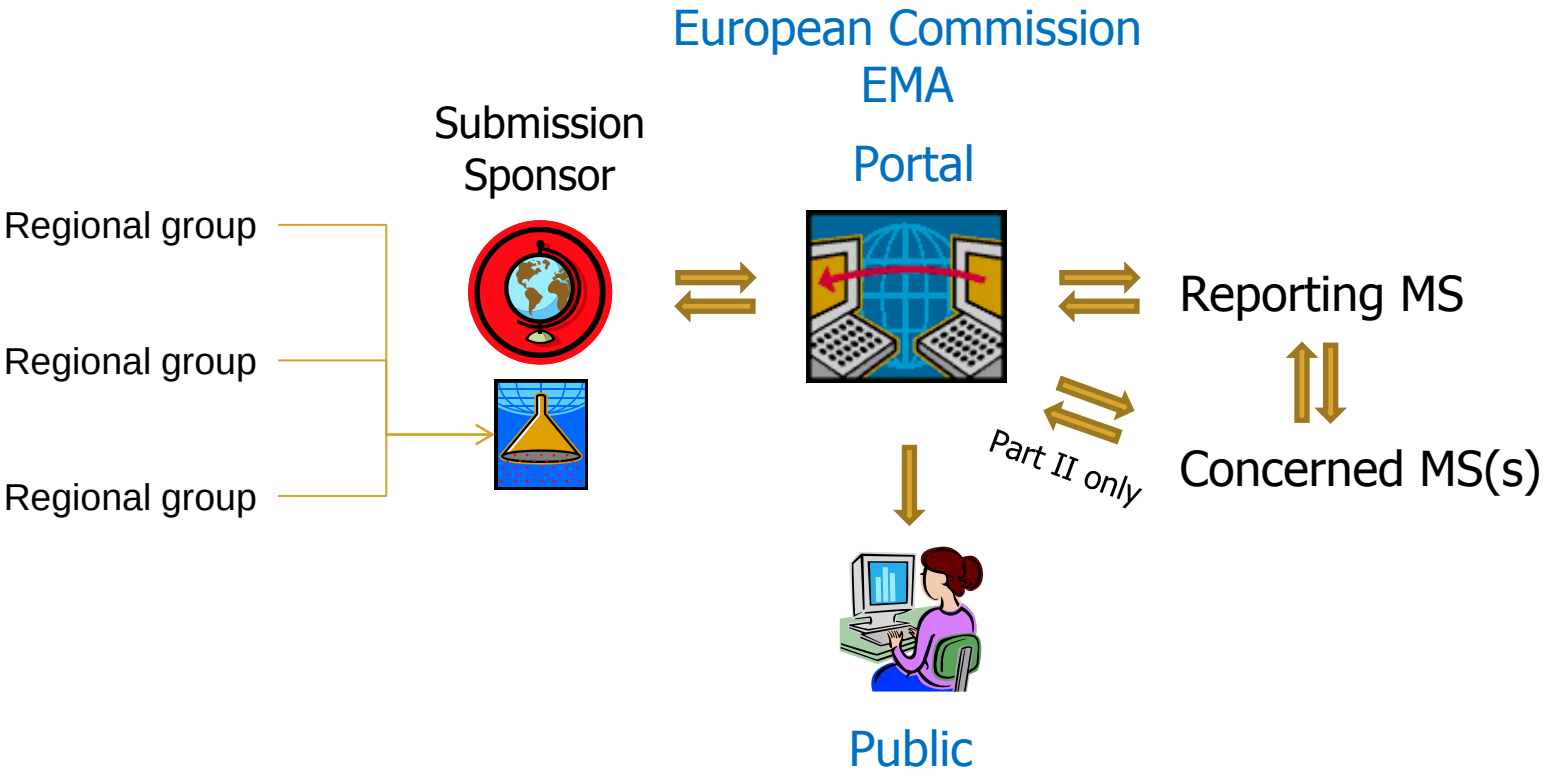
A study
- to discover/verify the clinical, pharmacological or other pharmacodynamic effects
- to identify any adverse reactions; or
- to study absorption, distribution, metabolism and excretion with objective of ascertaining safety

but
- Assignment of therapeutic strategy not pre-assigned
- No additional diagnostic or monitoring procedures

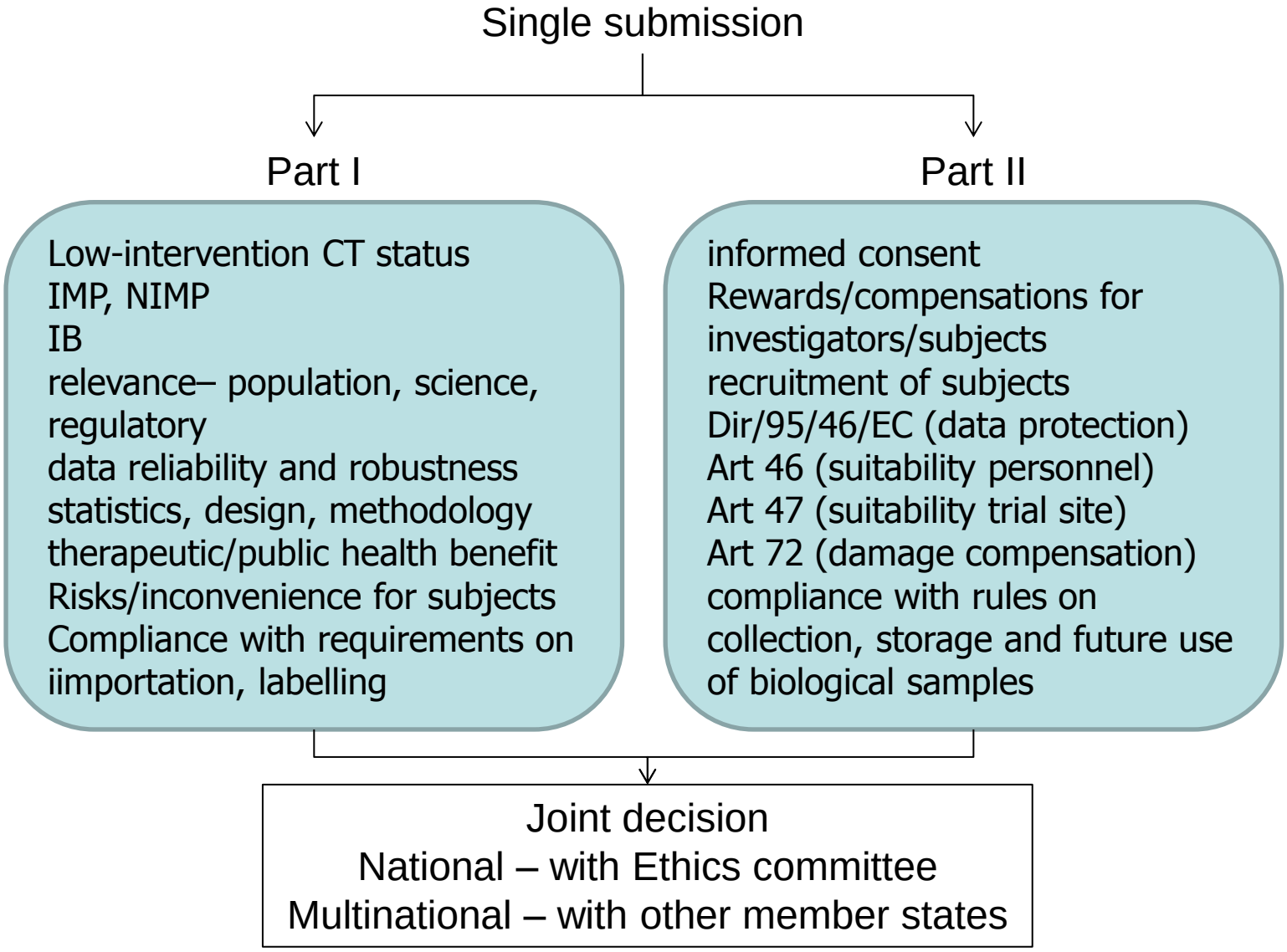
Comment:
No reference to “within SmPC” in contrast to current legal definition Dir/2001/20/EC

AT: National legislation needs to be adapted

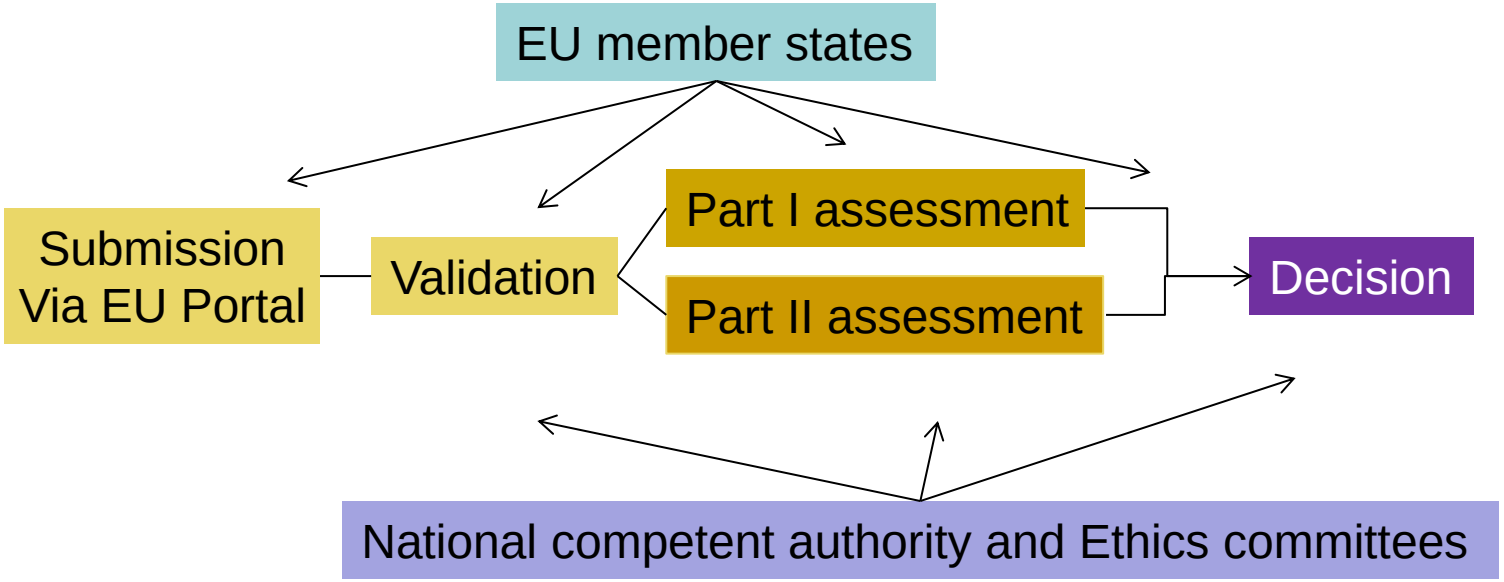
Future Szenario for multinational trials



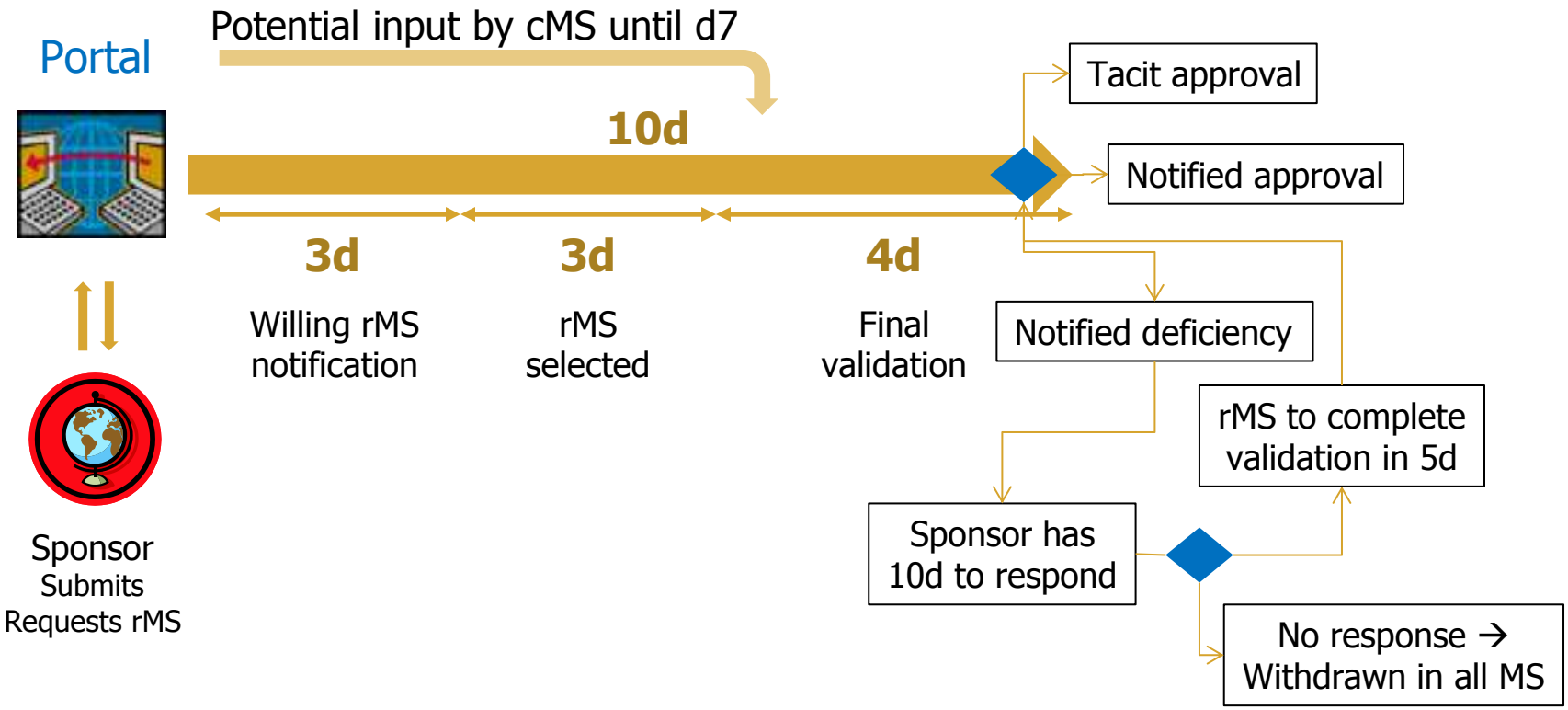
Assessment


Single submission
Part I
Part II
Low-intervention CT status
IMP, NIMP
IB
relevance– population, science, regulatory
data reliability and robustness
statistics, design, methodology
therapeutic/public health benefit
Risks/inconvenience for subjects
Compliance with requirements on iimportation, labelling
informed consent
Rewards/compensations for investigators/subjects
recruitment of subjects
Dir/95/46/EC (data protection)
Art 46 (suitability personnel)
Art 47 (suitability trial site)
Art 72 (damage compensation)
compliance with rules on collection, storage and future use of biological samples
Joint decision
National – with Ethics committee
Multinational – with other member states

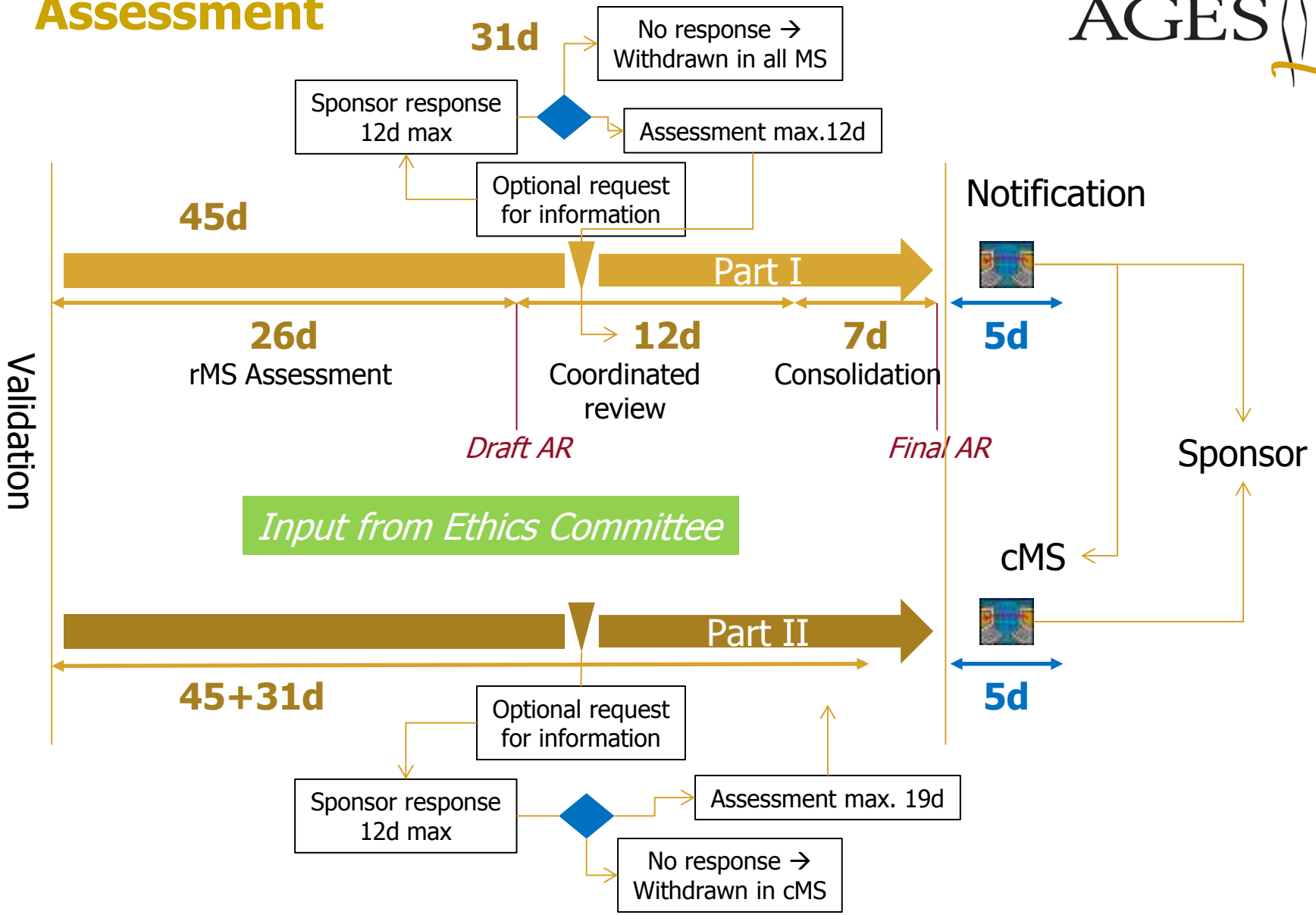
Assessment process



Validation


Portal
Potential input by cMS until d7
10d
3d
3d
4d
Willing rMS notification
rMS selected
Final validation
Tacit approval
Notified approval
Notified deficiency
rMS to complete validation in 5d
Sponsor has 10d to respond
No response → Withdrawn in all MS
Sponsor
Submits
Requests rMS

Assessment


31d
No response → Withdrawn in all MS
Sponsor response 12d max
Assessment max.12d
Optional request for information
45d
Notification
Part I
26d
rMS Assessment
12d
Coordinated review
7d
Consolidation
5d
Validation
Draft AR
Final AR
Sponsor
Input from Ethics Committee
cMS
Part II
45+31d
5d
Optional request for information
Sponsor response 12d max
Assessment max. 19d
No response → Withdrawn in cMS

Assessment

- Should address in particular:
- Anticipated therapeutic and public health benefits (**relevance**)
  - Trial recommended or imposed by regulatory authorities in charge of the assessment of medicinal products and the authorization of their placing on the market and
  - whether used surrogate end-points are justified
- Risk and inconvenience for the subject
- Unless otherwise justified in the protocol, the subjects should represent the population groups, that are likely to use the medicinal product investigated (gender and age groups)

Assessment

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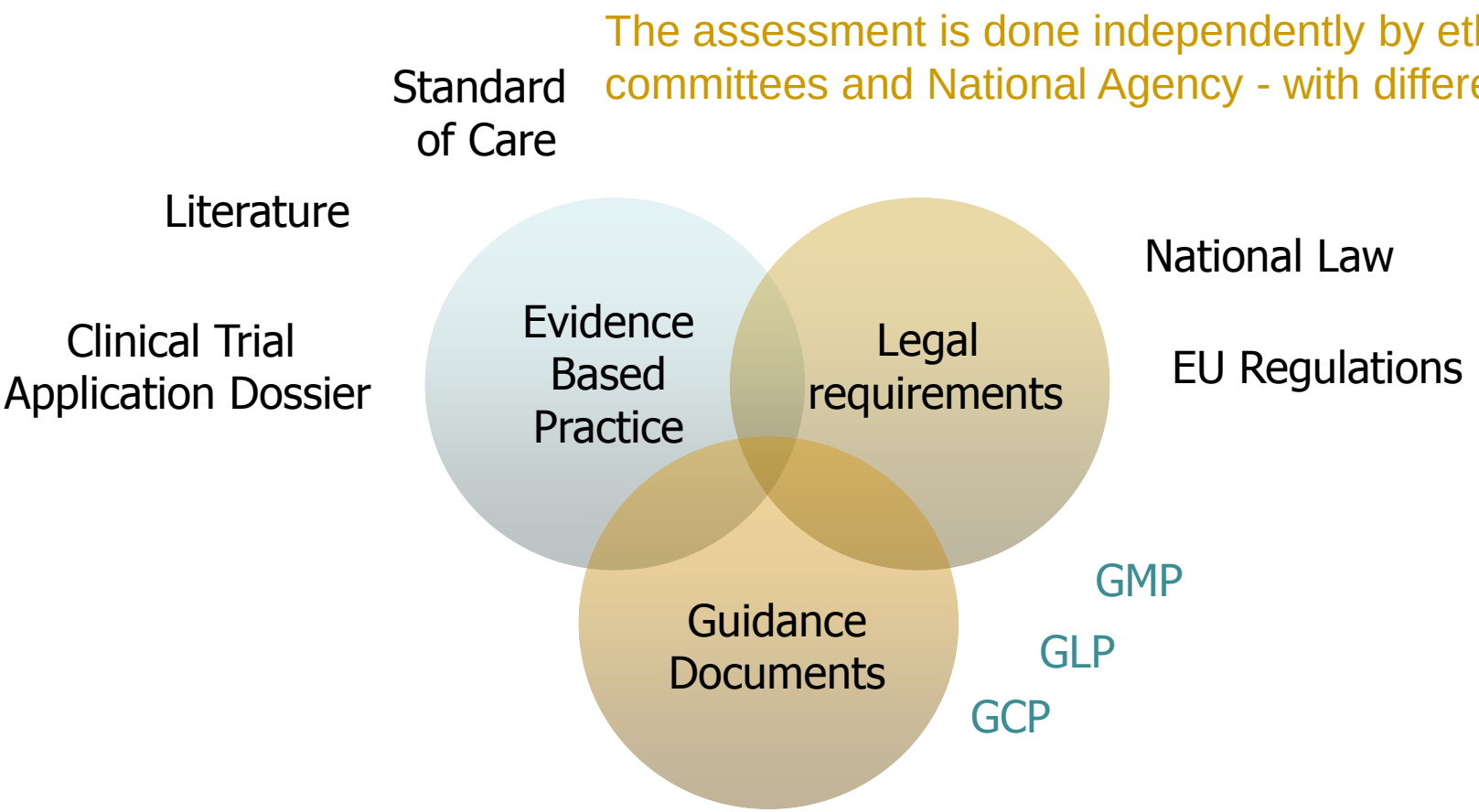
Decision Criteria Competent Authority

The assessment is done independently by ethics committees and National Agency - with different focus



Biobanking

- ANNEX I APPLICATION DOSSIER FOR THE INITIAL APPLICATION
- D. PROTOCOL

The protocol shall at least include:

- a description of the arrangements to comply with the applicable rules for the collection, storage and future use of biological samples from clinical trial subjects, where applicable,
- unless contained in a separate document

→ *All biobanking aspects need to be described in detail*

Further use of data

- It is appropriate that universities/research institutions, in accordance with data protection, can collect data from CTs to be used for future scientific research (medical, natural or social sciences research)
- Necessary that subject gives consent to use his or her data outside protocol of CT - has right to withdraw consent at any time
- Necessary that research projects based on such data be made subject to reviews that are appropriate for research on human data, for example on ethical aspects, before being conducted

→ Data to be collected after consent, within a protocol, and further use subject to review

Outlook

- Timelines will be shorter for all parties involved
- Implementation is a challenge for member states
- Intense communication is a prerequisite and requires ..
    - functional IT systems (EU Portal and Nationally)
- Increasing transparency of process, decisions and documents
- Increased transparency for the public
- "Relevance" of the clinical trials will be a discussion point

Medical devices

Currently different framework for clinical trials but the upcoming Regulations will bring the frameworks much closer together

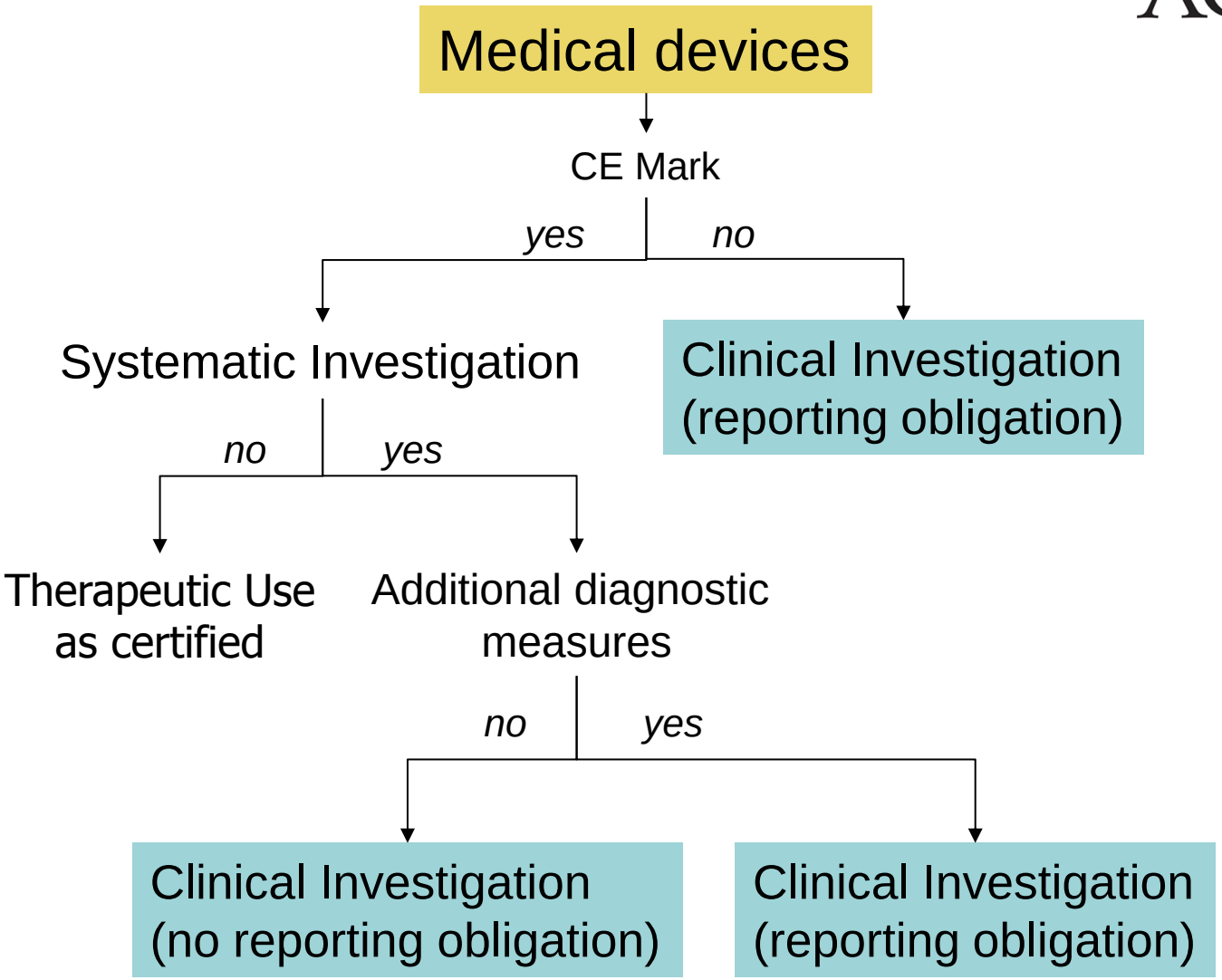
Medical devices

- Current legislation is based on Directives
- Regulations are in preparation for medical devices and IVDs

  → be prepared to see the Clinical trials Regulation timelines and basic concepts applied to medical devices

  → Same concept for a public database of clinical investigations

- Different paths to market compared to medicinal products


Medical devices
CE Mark
yes
no
Systematic Investigation
Clinical Investigation
(reporting obligation)
no
yes
Therapeutic Use
as certified
Additional diagnostic
measures
no
yes
Clinical Investigation
(no reporting obligation)
Clinical Investigation
(reporting obligation)

Core questions:

- Am I systematically investigating a product that falls under the medical device definition? → Check legal texts

- What are the respective legal framework requirements for the conduct of my study ? → check legal texts
  - Medical device → clinical investigation
  - In-vitro diagnostic (IVD) → performance evaluation

- What are the practical requirements for the approval and conduct of my study? → check guidance documents

EU - Definition of medical device

Dir/93/42/EEC article 1(2) (a)

- "Any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:
    - diagnosis, prevention, monitoring, disease treatment/alleviation
    - diagnosis, monitoring, treatment, alleviation of/compensation for injury or handicap,
    - investigation, replacement or modification of anatomy/ physiological process,
    - control of conception
- and ..

EU - Definition of medical device

Dir/93/42/EEC article 1(2) (a)

- … which does **not** achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means;
- In deciding whether a product falls under the MDD, particular account shall be taken of the **principal mode of action**
- Typically, MD function is achieved by **physical means** (including mechanical action, physical barrier, replacement of or support to organs or body functions **...**).
- The principal intended action of a MD may be deduced from the scientific data regarding mechanism of action and the manufacturer's labelling and claims

Definition of medical device
Dir/93/42/EEC article 1(2) (a)

- Categorizing requires scientific rationale
  - **"Pharmacological means"** is understood as an interaction between the molecules of the substance in question and a cellular constituent, usually referred to as a receptor, which either results in a direct response, or which blocks the response to another agent. Although not a completely reliable criterion, the presence of a dose-response correlation is indicative of a pharmacological effect.
  - **"Immunological means"** is understood as an action in or on the body by stimulation and/or mobilisation of cells and/or products involved in a specific immune reaction.
  - **"Metabolic means"** is understood as an action which involves an alteration, including stopping, starting or changing the speed of the normal chemical processes participating in, and available for, normal body function.

Definition CI

- A Clinical trial is the systematic investigation of a medical device except IVDs on study participants with the goal of

1. evaluating the performance of a medical device or to verifying if the performance of the medical device in normal conditions of use conforms with those stated by the manufacturer or other sponsor
2. investigating adverse events according to type, severity and frequency under normal conditions of use and if those can be considered as acceptable risks in the context of the stated performance.
3. identifying the mechanisms of action and the suitable clinical use of a medical device to determine its safety and efficacy

In vitro-Diagnostic
Dir/98/79/EEC

- **IVD**: Any MD which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment or system used alone or in combination intended for the examination of specimens including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information, concerning
    - physiological or pathological state
    - Congenital abnormality
    - Safety/compatibility with potential recipients
    - Monitor therapeutic measures
- Specimen receptacles are IVDs
- Notified Body involvement only needed for IVDs whose correct performance is essential to medical practice and whose failure could cause serious risk to health

Definition PE

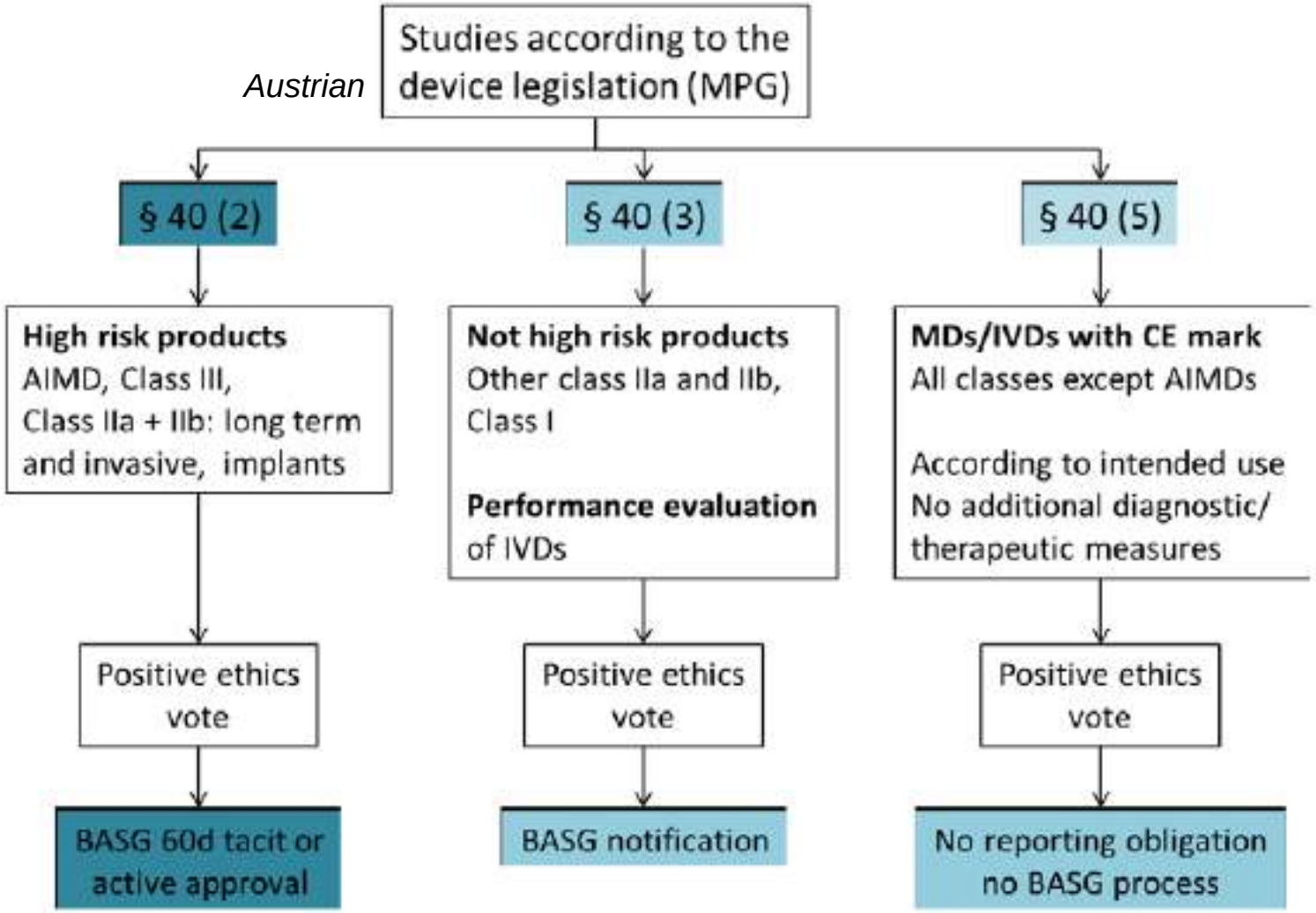
- A performance evaluation is the systematic investigation of an in vitro diagnostic (IVD) on samples of study participants, including blood and tissue samples in medical laboratories or other institutions with the goal of:

1. determining or verifying the performance of the IVD, or determining of the performance of the in vitro diagnostic conforms with the performance under normal conditions of use as stated by the manufacturer or other sponsor
2. investigating risks under normal conditions of use according to type, severity and frequency and if those can be considered as acceptable risks in the context of the stated performance or
3. determining the capacity and suitable clinical use of the IVD to determine the safety and performance of the IVD

EUDAMED

- EU database for all medical device aspects
- Currently not public
- Data entry is required for National Agencies
- Currently not comparable to EudraCT
- CIE number for all clinical investigations after first entry
- First member state for multinational CIs should communicate CIE number to applicant

Medical Device Clinical Investigations



www.basg.gv.at/en/medical-devices/clinical-trials-with-medical-devices/

Notification requirements

- Performance evaluations according to § 65a (2) MPG – specific for IVDs
- Prerequisites: pos. EC opinion;
  no notification requirement to the agency, no insurance requirement
- The clinical study is not associated with a specific sampling in type or amount from study participants or with additional medical diagnostic or therapeutic measures or there are no therapeutic consequences for the study participants

Competent Authority Tasks

- The objective of clinical trial authorisation is to guarantee safety and efficacy for the participant based on a limited dossier

- Notified bodies are in charge of CE certification for introduction to market or for certain products, the manufacturer affixes the CE mark

- Clinical trial authorisation is no guarantee for the suitability of study design and results for certification by Notified bodies/declaration of conformity

➔ Device development is the remit of the developer

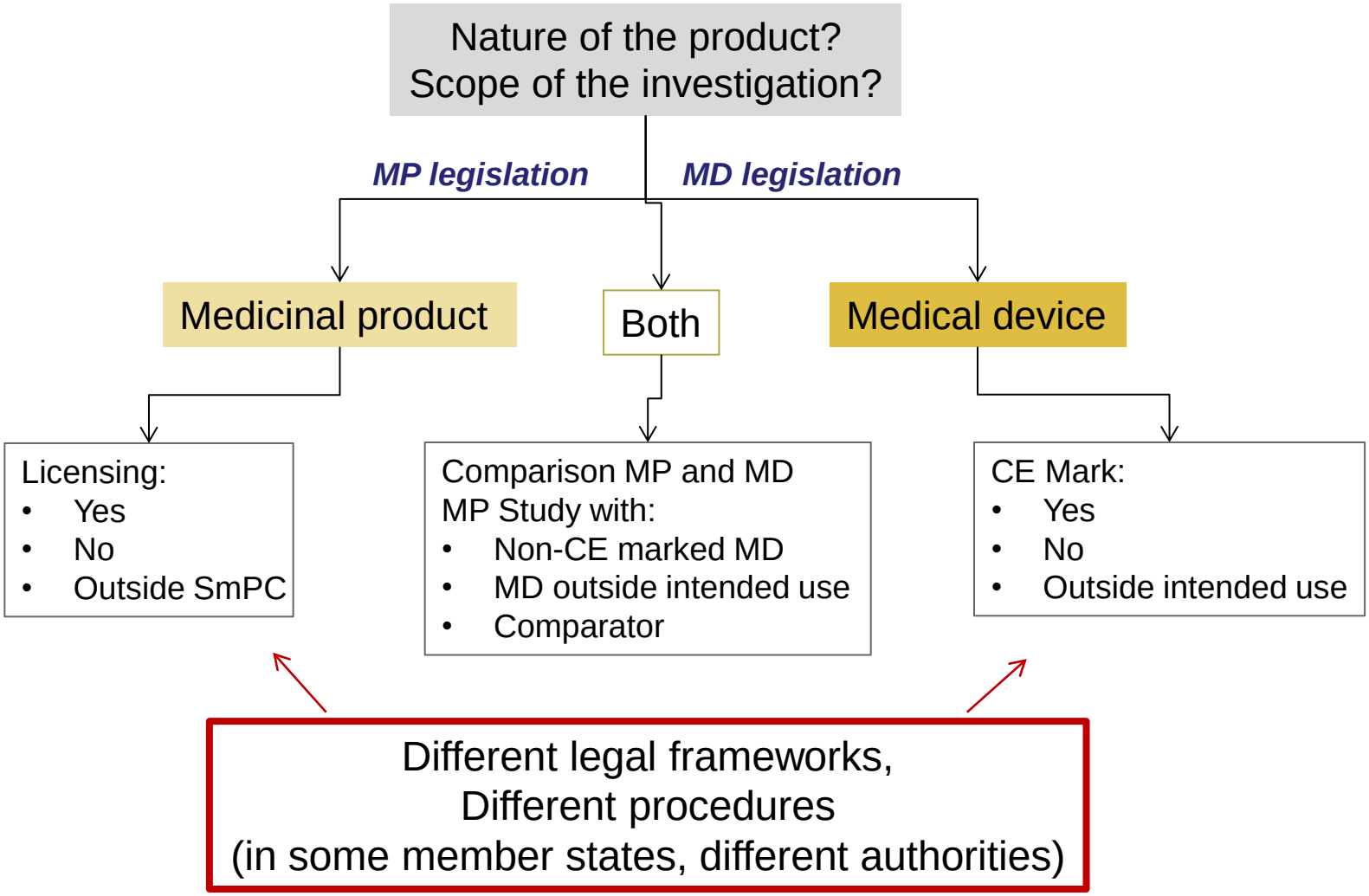
After medicinal products and medical devices –

What next?

Combined clinical trials

No separate path – both frameworks apply

Legislative framework clinical trials



Example

- In a clinical trial a medicinal product under development is being investigated, e.g. an antibody
  → clinical trial

- In addition a companion diagnostic for an enzyme mutation is being investigated, that does not carry a CE mark and is intended to be commercialized with the antibody e.g. an IVD
  → performance evaluation

- Both aspects have a reporting requirement → combined trial requirements of both legislations apply

Outlook

- Combined clinical trials need to be submitted to the agencies responsible for drug and device trials
  → in Austria within the same division

- The future framework will address combined studies in a more detailed way

- As procedures will be aligned (timelines) current administrative difficulties will be eased

In conclusion

- Conducting systematic investigations of medicinal products or/and medical devices requires regulatory knowledge
- Guidance is provided on National Agencies‘ websites
  → AT: www.basg.gv.at
- Increased transparency means that deficiencies will be more transparent in the future
- Conduct of studies under appropriate requirements will be verifiable via public EU databases (clinicaltrials.gov does NOT qualify)
- The legislative framework is changing for medicinal products and medical devices
- Consider regulatory requirements in your grant applications!

Thank you for your attention
Questions?

GDPR status of biological samples

- Recital 24 clarifies that information derived from the biological sample would be consider as personal data
  - → The sample could be considered as a data storage medium.
- Considering the definition of personal data of GDPR, biological samples that are labeled in such a way that the subject from which the sample was obtained can be identified:
  - are personal data concerning health
  - if in possession of an entity having the access to technology allowing retrieval of that personal data.