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Challenges and opportunities in medicines development - introduction to breakout sessions

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Why this matters?

Residual cardiovascular (CV) risk remains a major challenge

A significant evolution in recent years with new insights into:

- **Biology:** role of inflammation in CV prevention, biomarkers (Lp(a)), early stages of diseases (pre-diabetes, obesity), genetics
- **CV risk**: interest in assessment of lifetime CV risk[1], refining current risk scores (polygenic risk scores, metabolomics[2], U-Prevent[3])
- **Expanding treatment landscape** with new classes of medicinal products targeting **early CV prevention**

This creates a unique opportunity to:

- Identify the most promising **areas for progress**
- Enable stakeholders to **work together**

1 The Global Cardiovascular Risk Consortium N Engl J Med 2025
2 Ritchie SC. EHJ 2025
3 www.U-Prevent.nl

Right population for CV prevention

EMA GDL for CVD prevention: "an accurate definition of the CVD risk of the target population is fundamental"

Integrated global risk scoring models	Risk estimation based on presence of CVD

Challenges:

- identifying high risk patients for primary prevention studies with **evidence of early disease progression** not captured by classic risk models?
- **selecting scores**, biomarkers for precision medicine
- including **underrepresented or underserved populations (women, children[1])**
- **changing targets** in clinical practice guidelines in ongoing clinical studies and labelling
- managing risk of including **heterogenous populations**

1 Primordial prevention: prevent risk factors from developing OR Primary prevention: treat existing risk factors before disease onset (Gillman MW. Circulation 2015; 132:599–600)?

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Trends in selecting patients to studies in cardiometabolic area

More targeted treatment for subtypes of a disease

Studies in **increasingly precise subtypes** of cardiomyopathy, heart failure, diabetes

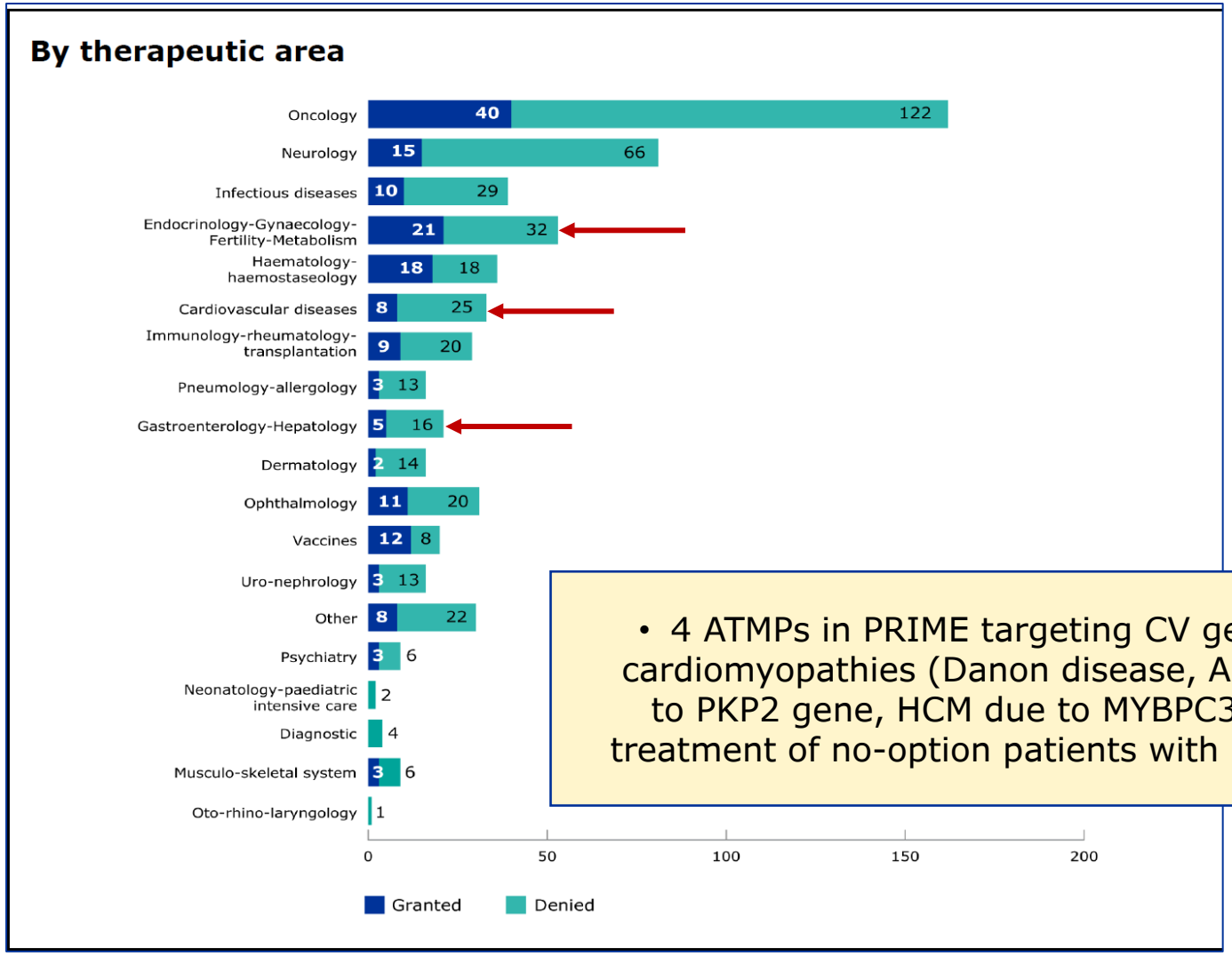
- cardiac myosin inhibitors for hypertrophic cardiomyopathy
- transthyretin (TTR) stabilizers for transthyretin amyloid cardiomyopathy (ATTR-CM)
- immune therapy for early phases of T1DM
- melanocortin 4 (MC4) receptor agonist for obesity
- CV Gene Therapy Medicinal Products (GTMP)

Integration across cardiometabolic diseases

Studies in **populations across diabetes, obesity, cardiovascular and kidney disease**

- GLP1 receptor agonists, nsMRAs, SGLT2 inhibitors

PRIME eligibility recommendations by 21 May 2026



PRIME: aims to support accelerated development of medicines with **major public health interest** and in particular from the viewpoint of therapeutic innovation in areas of unmet medical need.

Potential to **address** to a significant extent **an unmet medical need**

- 4 ATMPs in PRIME targeting CV genetic cardiomyopathies (Danon disease, ARVC due to PKP2 gene, HCM due to MYBPC3 gene, treatment of no-option patients with PAD/CLI)

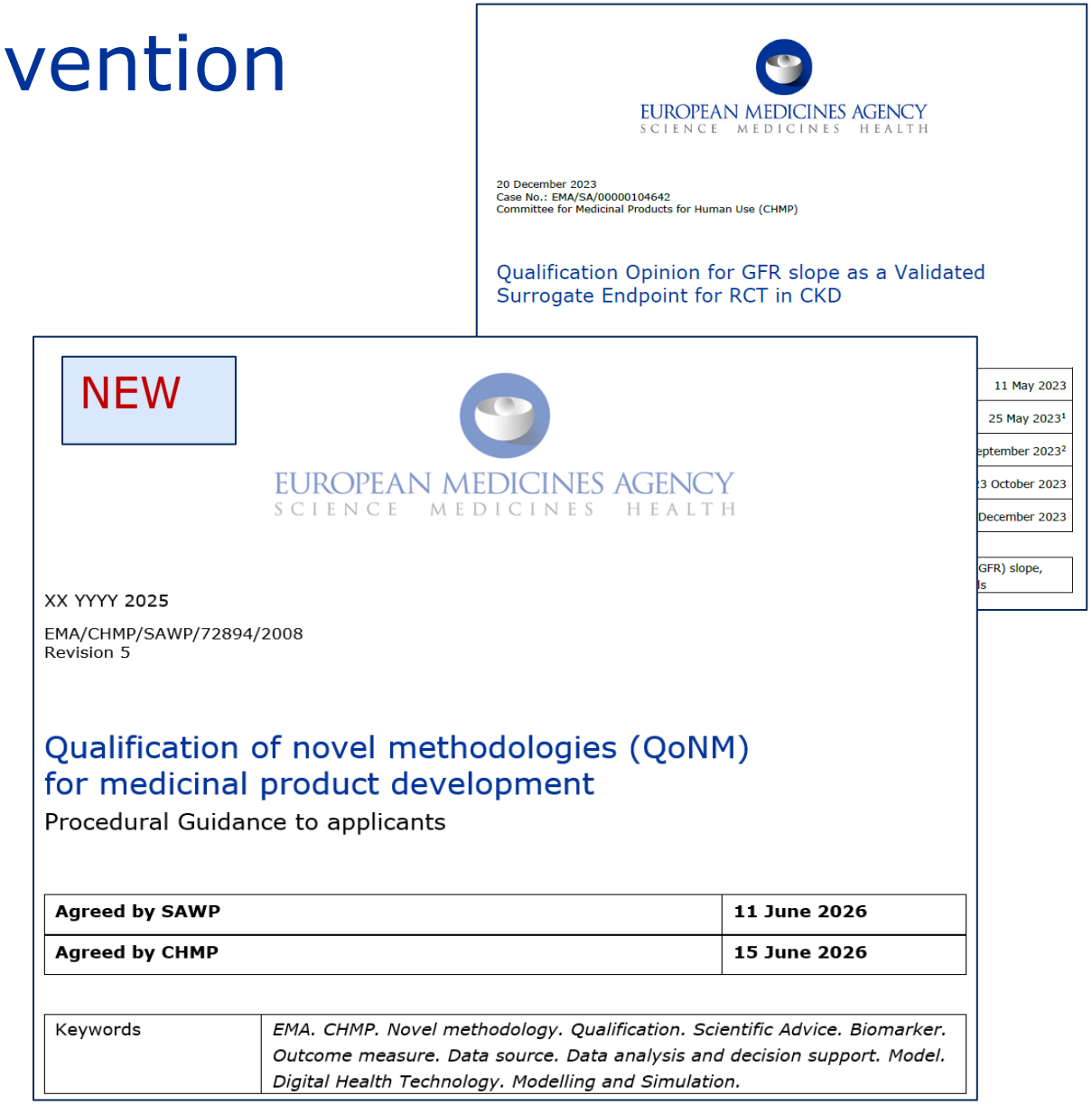
Early access pathways in CV and metabolic fields

IMA	Abbreviated Indication	CMA	MA under EC	PRIME
2019	familial chylomicronemia syndrome (FCS) and at high risk for pancreatitis	X		
2019	reversal of anticoagulation due to life-threatening or uncontrolled bleeding	X		
2025	noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH)	X		
2021	homozygous familial hypercholesterolaemia (HoFH)		X	
2018	complications of leptin deficiency in lipodystrophy		X	
2023	treatment of hyperargininemia in Arginase 1 Deficiency (ARG1-D)		X	
2024	treatment of PAH			X
2021	acquired hypothalamic obesity (aHO)/obesity with rare genetic conditions			X
2005	treatment of PAH		X (switch)	
2003	treatment of pulmonary hypertension		X (switch)	
2013	homozygous familial hypercholesterolaemia (HoFH)		X	
2000	hyperphosphataemia in patients receiving haemodialysis or peritoneal dialysis		X (switch)	
2001	Fabry disease		X (switch)	
2002	treatment of pulmonary hypertension		X (switch)	
2026	non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH)	X		
2026	delay the onset of stage 3 type 1 diabetes (T1D)			X

Novel biomarkers in CV prevention

- How to identify and validate the most promising **biomarkers?**
  - Biological plausibility?
  - Link to clinical outcome (MACE)?
  - Which patients benefit most?
  - Established CVD or primary prevention?
  - How should cut-off thresholds be defined?
  - How reliable and standardized is measurement?

- Qualification framework:
  - Support development of new ways to develop drugs
  - e.g. more efficient endpoints for clinical trials



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20 December 2023
Case No.: EMA/SA/00000104642
Committee for Medicinal Products for Human Use (CHMP)

Qualification Opinion for GFR slope as a Validated Surrogate Endpoint for RCT in CKD

NEW

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XX YYYY 2025

EMA/CHMP/SAWP/72894/2008
Revision 5

Qualification of novel methodologies (QoNM) for medicinal product development

Procedural Guidance to applicants

Agreed by SAWP	**11 June 2026**
Agreed by CHMP	**15 June 2026**

Keywords	*EMA. CHMP. Novel methodology. Qualification. Scientific Advice. Biomarker. Outcome measure. Data source. Data analysis and decision support. Model. Digital Health Technology. Modelling and Simulation.*

Study design: benefit-risk consideration

Efficacy challenges

Demonstrating meaningful CV risk reduction within feasible timelines (events are rare)

Role of traditional CVOTs and alternative approaches (e.g. surrogates, RWE, pragmatic trials)

Quantifying benefit in multimorbid & heterogenous populations

Guidance on use of real-world data: questions and answers

NEW

Questions and **answers** are available to clarify and facilitate understanding of certain regulatory aspects addressed by existing EMA guidance on the use of **real-world data**.

These aspects refer to definitions, contexts of use, data quality, transparency and methodological implications of planning and conducting **clinical studies** using real-world data.

Safety challenges

Safety in patients with multiple comorbidities (polypharmacy, drug interactions)

Long term safety of life-long prevention

Preventing unnecessary early treatment

EMA Collaboration in cardiometabolic field

- **International Regulators** cluster in **Cardiometabolic field**
- EMA experts contributing to workshops i.e. ESC Cardiovascular Round Table since 2005
- **Bilateral meetings with Learned Societies** (EMA/ESC 2024, 2025, EMA/EASD 2025)
- Learned Societies and Patients' Organisations:
  - continuous source of experts for **Scientific Advisory Group on CV Issues**
  - Input into **CHMP early dialogue**
- From Jan 2025 **ATMP in cardiometabolic area in scope of**

joint clinical assessment (JCA)/joint scientific consultation (JSC) with HTA

- Comments on **EMA Guidelines in cardiometabolic field:**

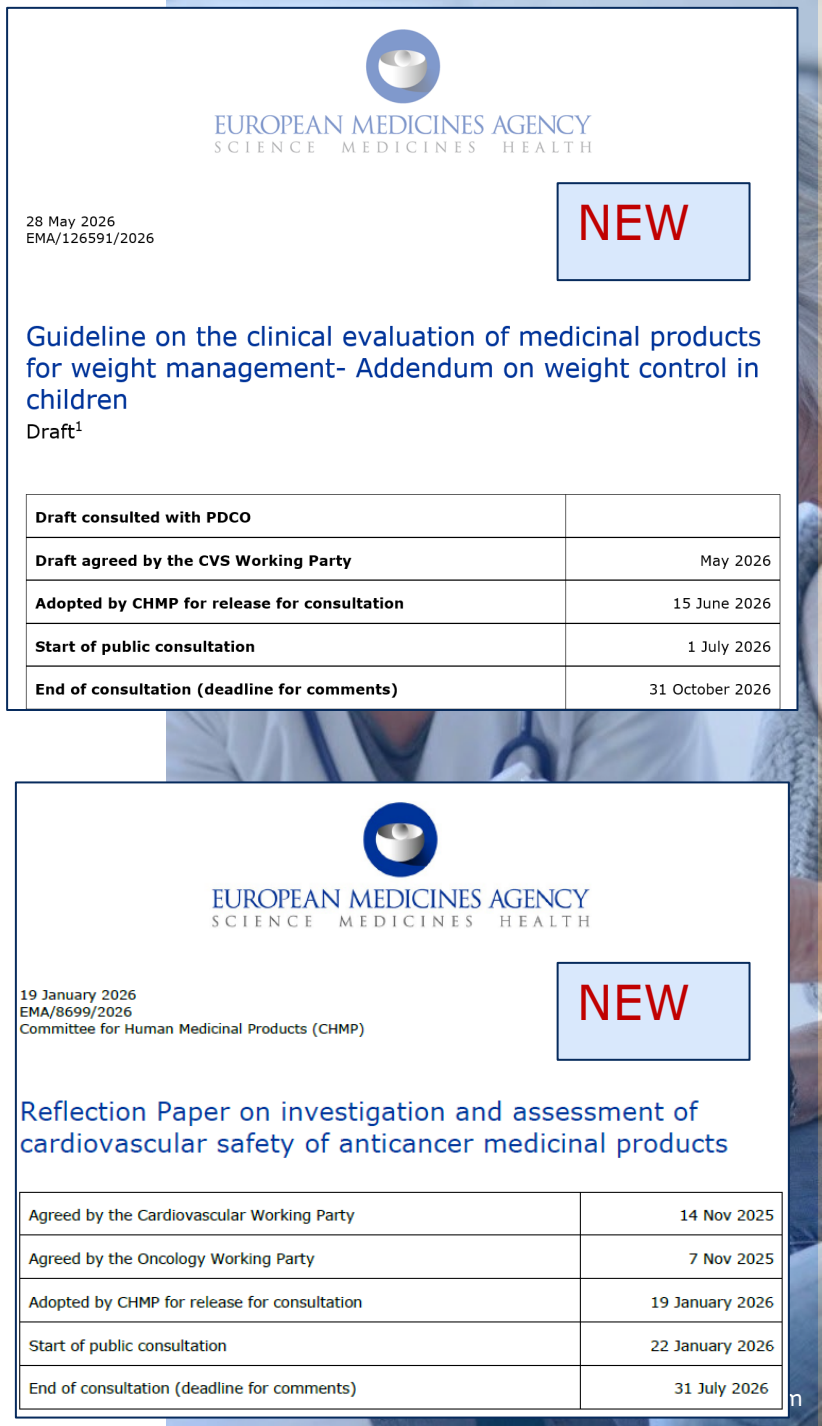
https://www.ema.europa.eu/en/human-regulatory-overview/research-development/scientific-guidelines/clinical-efficacy-safety-guidelines/clinical-efficacy-safety-guidelines-cardiovascular-system

Source: https://www.escardio.org/events

EMA Guidelines with focus on CV prevention

Guideline on [products for]

- cardiovascular disease prevention (2009)
- weight management (2017)
- lipid disorders (2017)
- **hypertension (2017, under revision)**
- development/slow progression of chronic renal insufficiency (2017)
- diabetes mellitus (2023)
- non-alcoholic steatohepatitis (NASH) (2024, RP)
- peripherial arterial occlusive disease (2026) NEW



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28 May 2026
EMA/126591/2026

NEW

Guideline on the clinical evaluation of medicinal products for weight management- Addendum on weight control in children

Draft[1]

Draft consulted with PDCO	
Draft agreed by the CVS Working Party	May 2026
Adopted by CHMP for release for consultation	15 June 2026
Start of public consultation	1 July 2026
End of consultation (deadline for comments)	31 October 2026

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19 January 2026
EMA/8699/2026
Committee for Human Medicinal Products (CHMP)

NEW

Reflection Paper on investigation and assessment of cardiovascular safety of anticancer medicinal products

Agreed by the Cardiovascular Working Party	14 Nov 2025
Agreed by the Oncology Working Party	7 Nov 2025
Adopted by CHMP for release for consultation	19 January 2026
Start of public consultation	22 January 2026
End of consultation (deadline for comments)	31 July 2026

Regulatory Evolution – considerations for RP

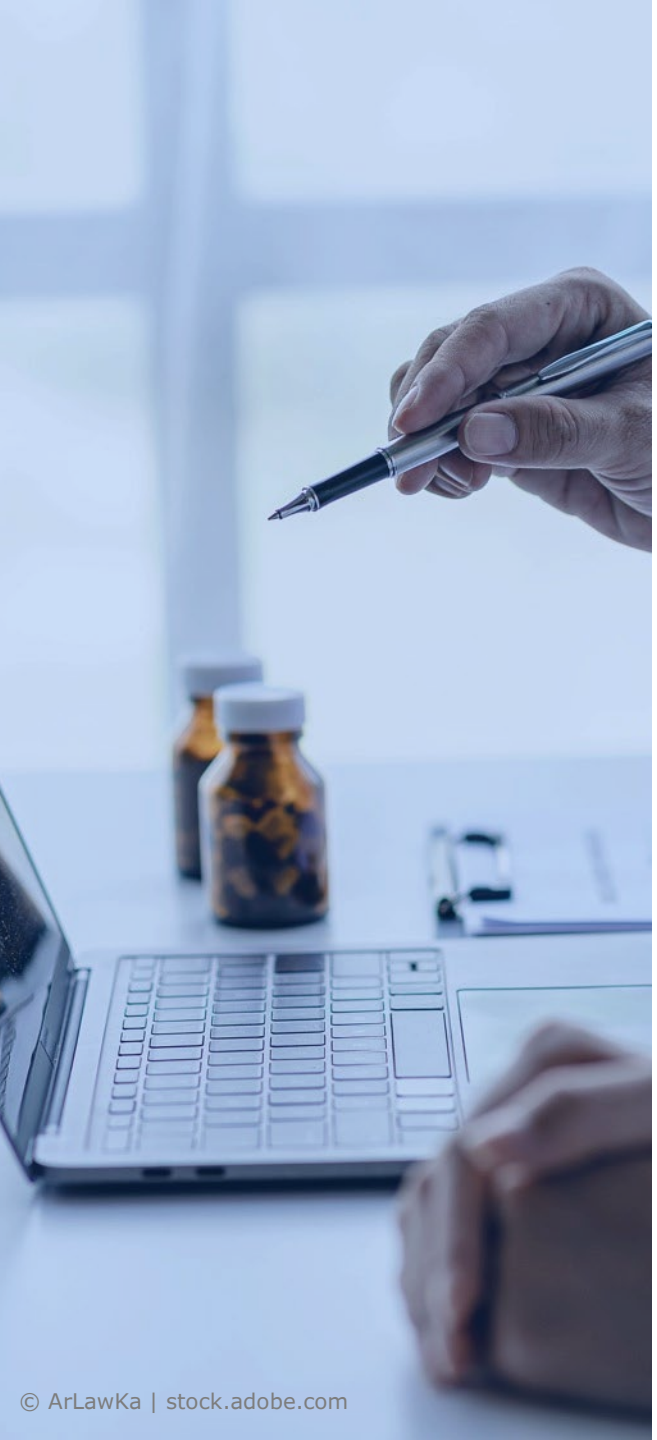
- Stakeholders' consultation of the CVS WP Work Plan 2025: proposal to develop a

  Reflection Paper (RP) on overlapping aspects of CV, kidney and metabolic diseases

- Need from **clinical perspective** is recognized[1]:
  - Improve recognition of CVD and kidney disease in patients with metabolic disorders
  - Improve recognition of metabolic disorders in patients with cardio-renal diseases

- Questions from **regulators perspective:**
  - understanding overlapping pathways
  - interpretation of inconsistent eligibility definitions
  - explain benefits to patients and stakeholders
  - which aspects could be reflected in the future RP?

1 Cosentino F, EHJ 2023;
Koskinas KC, Eur J Prev Cardiol 2025;
Ndumele, 2026 AHA/ACC/ADA/ASN Guideline for the Prevention, Detection, Evaluation, and Management of Cardiovascular-Kidney-Metabolic Syndrome. JACC 2026,
ESC CRT workshop on Cardiometabolic disease 18-19 Mar 2026



Key questions for breakout sessions

For CV prevention trials across the cardiometabolic spectrum:

- How would we identify the **target population** for research and practice (including high-risk, underrepresented and underserved populations)?
- What are the **key regulatory challenges**?
  What **guidelines** should be developed/revised?
  What aspects of **collaboration** could be improved?
- How would we **evaluate the intervention**?
  What novel study approaches could be considered?
- What are the **priorities** within **research** and **regulatory frameworks** to encourage innovative development in medicines?

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