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3 **Regulatory Science Research Needs**
4 2024 update - DRAFT

Start of public consultation	13 November 2024
End of public consultation	18 December 2024
Please provide comments using this template . The completed comments form should be sent to regulatory.science@ema.europa.eu . To comment on a specific RSRN and priority topic in the table at chapter 2, please refer to the respective RSRN ID (e.g. CT1_1; CT1_2...)	

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24 **Executive summary**

25 Gaps exist in regulatory science that need to be addressed to improve medicine development and
26 evaluation, to ultimately enable access to medicines that address patients' needs. Regulatory science
27 applies scientific disciplines to developing and evaluating medicines and medical devices as well as to
28 advancing regulatory tools, standards and the regulatory system's evolution. Research into regulatory
29 science aims to address repeat issues in development and evaluation as well as gaps that hinder
30 regulatory advancement. The Regulatory Science Research Needs (RSRN) are organised currently into
31 four sections to encompass a wide range of priority topics related to improving clinical research;
32 improving regulatory system evolution; leveraging technologies for development of specific types of
33 medicines; and advancing animal health and the regulation of veterinary medicines.

34 By highlighting these research needs, the goals are to stimulate research in these fields; to encourage
35 researchers to consider in their area of work the regulatory and public health challenges and
36 opportunities; to help researchers identify topics of common interest for interactions such as in the
37 EMA/HMA European Platform for Regulatory science research¹ and for exploring with researchers
38 pathways for translating results into solutions; and to offer the research needs for the awareness of
39 funders so as to support their scoping of funding calls. The list of needs will be further evolved into a
40 living document, updated periodically to ensure ongoing engagement as new topics are identified.

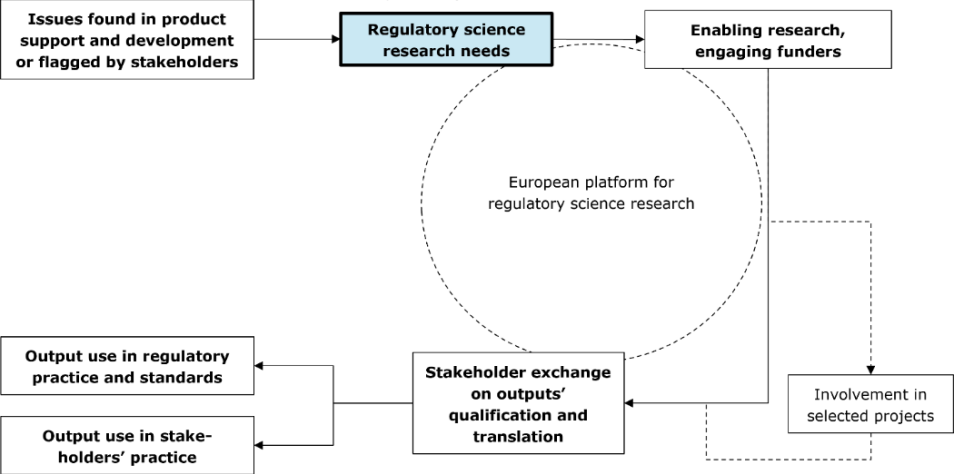
41 **1. Introduction**

42 **1.1. EMA advancing regulatory science**

43 In 2020, the EMA Regulatory Science Strategy to 2025² set the foundation for several initiatives and
44 actions aiming at ensuring that the EU Medicines regulatory network has the regulatory tools to fulfil
45 its mission in face of new scientific challenges. The emergence of new types of medicines, innovations
46 in research and development (R&D), novel methods to perform clinical trials and experiments are
47 examples of opportunities but also of challenges from a regulatory perspective.

48 The Regulatory Science Research Needs (RSRN) initiative aims to identify such challenges and
49 opportunities in order to formulate them as needs for research that could help fill gaps in the
50 regulator's ability to assess medicinal products and deliver public health benefits. The RSRN initiative is
51 part of EMA's activities to systematically advance regulatory science through research (Figure 1).

52 Figure 1: EMA activities to advance regulatory science research



¹ <https://www.ema.europa.eu/en/news-and-events/open-consultations>

² <https://www.ema.europa.eu/en/about-us/how-we-work/regulatory-science-strategy>

The RSRN initiative is part of EMA's activities to systematically advance regulatory science through research (Figure 1) in a concept of a life cycle that has the following steps:

Issues found in product support and development, or flagged by stakeholders. Challenges in medicine development and regulation are identified from several sources, e.g. by screening internal reports, from questions that arise in interactions with medicine and methodology developers, from publications, by horizon scanning activities and from interviews with internal experts, as described in section 3.

Regulatory Science Research Needs. The identified challenges are formulated as research questions which if addressed will help fill the gaps in regulatory science. As part of the systematic approach to formulate the research questions, the type of research gap³ and the type of research activities⁴ that are sought are determined. The research needs are presented in section 2 and are mainly for researchers and funders to support them in delivering research outputs that have relevance also for filling gaps in regulatory science. Researchers and scientists mainly work in the academic sector, with some in the for-profit-sector and at regulatory agencies; the RSRNs will mostly benefit from research that includes collaborations between groups, disciplines and stakeholders.

Enabling research, engaging funders. Enabling research on the identified topics involves different lines of activities:

1. Researchers working on RSRN topics or interested in working on RSRN can engage with EMA, present their research and explore areas of common interest via direct contact with the Regulatory Science and Academia Workstream at regulatory.science@ema.europa.eu (by just clicking on the RSRN ID link);
2. EMA provides technical information on regulatory science upon request to European funders and has raised awareness internationally of funders organisations and structures about the RSRN to support the uptake of relevant topics in considerations for funding calls;
3. EMA invites tenderers for a framework contract on quality, efficacy and safety studies on medicines⁵ which can cover a variety of research in RSRN focus areas to support the delivery of relevant research outputs, such as on translational questions, medicine use in pregnancy and breastfeeding, decision-making in public health and animal health, methodology and statistics, experience of patients and healthcare professionals, risk minimisation measures, non-interventional studies, innovative technologies for manufacturing and quality control, computational methods for comparison of molecular structural features.

Involvement in selected projects. EMA is involved in selected publicly-funded research projects, with different roles.⁶ The aim is to contribute to, and closely monitor, relevant research outputs that might directly impact the EU regulatory system by facilitating the adoption of practical solutions that benefit public and animal health.

³ Research gaps in, e.g., problem evidence, theory, concept, knowledge, methodology, empirical data, population

⁴ Type of research activities in, e.g., natural, social, formal or applied sciences; wet- or dry-lab research; desk-based research

⁵ <https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/tender-details/72456246-9cd8-4978-9703-f90cf4e86227-PIN>

⁶ <https://doi.org/10.3389/fmed.2023.1181702>

Exchanging with stakeholders on the qualification and translation of outputs. To ensure that the output of regulatory science research is translated into impactful solutions in regulators' or stakeholders' practices that ultimately support public and animal health, several activities are required to stimulate meaningful changes in the long term:

1. EMA is involved in selected research projects or is exposed to outputs and potential solutions at an early stage, so that EMA can stimulate internal discussions on topics of relevance.
2. EMA maintains a dynamic exchange with trade associations and academic developers on RSRN topics. These discussions allow the development of principles, recommendations, priorities and approaches that can help the translation of research output into practical applications in R&D and improved regulatory standards and practices.
3. To support the relevance of solutions, EMA welcomes developers of regulatory science solutions at an early stage, e.g. via EMA's contact for regulatory science and regulatory science research (regulatory.science@ema.europa.eu), in Academia briefing⁷ or Innovation Task Force briefings,⁸ and scientific and qualification advice.⁹
4. EMA is building collaborations on regulatory science research topics with experts from academia and the not-for-profit sector via the Collaborating Experts programme¹⁰.

European Platform for Regulatory Science Research. EMA and the Heads of Medicines Agencies (HMA) will launch in early 2025 the European Platform for Regulatory Science Research. The platform aims to advance and accelerate regulatory science research, to increase the quality and impact of research and outcomes, thereby improving regulatory practices, standards, medicines development and use. This includes contributing to research needs identification, exchanging experience on methodology and best practices, and fostering translation of results into practical solutions. The platform is also intended to promote dialogue and foster collaboration between regulatory science researchers and regulators across Europe and beyond. More information about the Regulatory Science Research Platform can be found in its Concept paper,¹ under consultation in November 2024.

Converging presentation of research needs. Within EMA's work to advance regulatory science research, this list of cross-topics and cross-agency regulatory science research needs is complemented by lists originating from specific areas of interest, for instance those arising from multistakeholder interactions, such as:

[[Complementary research agendas will be added over time]]

- [Vaccine Monitoring Platform \(VMP\) research agenda](#)
- AI network research priorities roadmap
- ACT EU PA5 Clinical trial analytics research priorities

⁷ <https://www.ema.europa.eu/en/partners-networks/academia>

⁸ <https://www.ema.europa.eu/en/human-regulatory-overview/research-development/supporting-innovation>

⁹ <https://www.ema.europa.eu/en/human-regulatory-overview/research-development/scientific-advice-protocol-assistance>

¹⁰ https://careers.ema.europa.eu/content/Collaborating-Expert/?locale=en_GB

1.2. RSRN opportunities for researchers

The opportunities for researchers are based on the proactive dialogue that EMA is establishing with researchers. These interactions are mutually beneficial, since researchers can receive regulatory orientation and can hear about optimising leveraging their case, while EMA gains early exposure to tools, methods and developments that can help future-proof the regulatory environment beyond the case at hand. By engaging with EMA, researchers can more easily translate their outputs into concrete applications and public and animal health solutions, particularly when the application impacts a medicine's lifecycle or requires regulatory assessment.

Researchers working on specific RSRN and with results mature enough to benefit from discussion with EMA topic experts can use the pre-filled emails available via the RSRN ID link in the list or write to regulatory.science@ema.europa.eu to request such a discussion, referring to the specific topic and research question. Such topic and research question can potentially be brought for discussion to a European Platform for Regulatory Science Research¹ meeting.

1.3. Developments in relation to the RSRN v1 (2021)

Since first published on 15 December 2021, the RSRN v1 list has stimulated interactions with EMA and has allowed various activities to be identified and undertaken in relation to the specific topics. Section 3.2 in the current document provides a preliminary, aggregated summary from ongoing efforts to track activities and outputs that may be related to the RSRN v1. Several categories for the status and progress of activities have been defined for the RSRN v1, with the following consequences for the 2024 update of the regulatory science research needs:

- Some RSRN v1 topics would still stand to benefit from interactions with researchers and have been partly included or reformulated in the 2024 update of RSRN priorities;
- Some RSRN v1 topics with several ongoing related activities may not need further interactions currently and have therefore not been included in the 2024 update;
- Some RSRN v1 topics have been addressed, have generated sufficient outputs, or are no longer considered relevant based on recent activities and have therefore not been included in the 2024 update.

Examples of RSRN v1-related developments include activities conducted as part of:

- EU projects and public-private project consortia, such as funded under Horizon Europe and IHI (with or without involvement of regulatory scientists from the EMA or National Competent Authorities);
- projects delivered through EMA's Collaborating Experts Programme¹¹;
- activities funded through EMA's Framework contract for tenderers of studies into quality, efficacy and safety of medicines.

Examples of EU or global activities that have been informed by the RSRN v1 include:

- Calls for funding proposals;
- EMA focus groups that contribute to leveraging research outcomes (e.g., Focus Group on the Qualification Procedure and the Focus Group on Regulatory Science Research Translation);¹²

¹¹ <https://careers.ema.europa.eu/content/Collaborating-Expert/>, whose outputs are among the scientific publications listed here: <https://www.ema.europa.eu/en/news-and-events/publications/scientific-publications>

¹² <https://www.ema.europa.eu/en/events/tenth-industry-standing-group-isg-meeting>

- Scientific publications or monographs such as on research management,^{13,14} on regulatory support pathways,^{15,16,17} on setting priorities^{18,19} and on improving methods^{20,21} for regulatory research, and on results,²² each referencing the RSRN v1;

The work in relation to RSRN is conducted in concertation with other EMA initiatives and pilots, such as the ATMP pilot, real-world evidence studies, Emergency Task Force activities.

¹³ Arnouts S et al. Technology Readiness Levels for vaccine and drug development in animal health: From discovery to life cycle management. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9811140/>

¹⁴ Berkner S et al. Too advanced for assessment? Advanced materials, nanomedicine and the environment.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9378259/>

¹⁵ Kallio MJ et al. Translating Academic Drug Discovery Into Clinical Development: A Survey of the Awareness of Regulatory Support and Requirements Among Stakeholders in Europe. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10099080/>

¹⁶ Massella M et al. Regulatory Considerations on the use of Machine Learning based tools in Clinical Trials.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9638313/>

¹⁷ Saesen R et al. Advancing academia-driven treatment optimisation in oncology: Launch of the EMA Cancer Medicines Forum. [https://www.ejcancer.com/article/S0959-8049\(22\)00169-1/fulltext](https://www.ejcancer.com/article/S0959-8049(22)00169-1/fulltext)

¹⁸ Pasmooij AMG et al. The Evolution of Drug Regulatory Sciences in the Netherlands: More than a Country Report.

<https://onlinelibrary.wiley.com/doi/abs/10.1002/cpt.3275>

¹⁹ Reddy N et al. Regulatory landscape of alternatives to animal testing in food safety evaluations with a focus on the western world. <https://www.sciencedirect.com/science/article/pii/S0273230023001381>

²⁰ Stevens ER et al. Enhancing the quality and efficiency of regulatory science literature reviews through innovation and collaboration with library and information science experts.

<https://www.frontiersin.org/journals/medicine/articles/10.3389/fmed.2024.1434427/full>

²¹ Barrett JS et al. Generation and interpretation of big data in pediatric drug development. In: Essentials of Translational Pediatric Drug Development. <https://www.sciencedirect.com/science/article/pii/B9780323884594000122>

²² Whittaker HR et al. Eligibility of patients with chronic obstructive pulmonary disease for inclusion in randomised control trials investigating triple therapy: a study using routinely collected data. <https://doi.org/10.1186/s12931-024-02672-x>

2. List of regulatory science research needs: 2024 update

2.1. Structure and overview on research needs and types of research

This part of the document details the regulatory science research needs, in sections of those needs that 1) improve clinical research; 2) improve regulatory system evolution; 3) foster technologies for development of specific novel medicines; and 4) advance specifically animal health and the regulation of veterinary medicines. In line with the One Health approach, some of this topics also reflect a holistic perspective that recognises the interconnection of human, animal and environmental health.

Each **section** has several **focus areas** with several **research needs** encompassing several **priority topics**. Specific identifiers such as **RSRN-2024-CT1-1** indicate the version update (2024), the research need (CT1) and the priority topic (1).

Each **research need** is associated with keywords and domains of impact of the research, which can help to navigate the list and find topics of interest.

Additionally, each **priority topic** is associated with letters that define the **type of research** that is thought relevant for addressing the topic. Multiple letters mean that the topic touches different or overlapping research fields, or that it might benefit from complementary or synergistic research approaches. The types of research are categorised as follows:

- **(A) Natural sciences:** disciplines such as biology, chemistry, physics, which make use of rigorous scientific methods, including observation, controlled experiments, analysis, mathematical models and empirical evidence.
- **(B) Social sciences:** fields such as sociology, political science, economics, policy science, which mainly employ qualitative methods (such as interviews, focus groups, etc.), and analyse policy and social dynamics, societal patterns and matters relating to decision-making.
- **(C) Formal sciences:** fields such as logic and mathematics, which make use of language tools and abstract structures.
- **(D) Applied sciences:** disciplines such as medicine, biomedical engineering and genetic epidemiology, where scientific knowledge and research are applied to achieve tangible goals, solve real-world problems and improve systems and technologies.
- **(E) Wet-lab research:** experimentation in laboratory settings.
- **(F) Dry-lab research:** computational and theoretical research, in other words by using computer systems, coding and data analysis to generate new information and data outputs.
- **(G) Desk-based research:** literature reviews, synthesis of relevant existing data and analysis of existing information, often from published sources or retrievable under request.

The following provides an overview as counts of research needs and their priority topics within the respective needs section.

Table 1: Overview on 2024 updated of RSRNs

Sections with Research needs to ...	Number of research needs	Number of priority topics
2.2. ...improve clinical research	9	24
2.3. ...improve regulatory system evolution	9	23
2.4. ... foster technologies for development of specific types of medicines	14	35
2.5. ... advance specifically animal health and the regulation of veterinary medicines	15	27
Total	49	109

2.2. Research needs to improve clinical research

This section includes 9 research needs and 24 priority topics to develop clinical trial methodologies and advance clinical trial design, thereby enhancing the flexibility, speed, and quality of clinical trials.

The needs in this list touch upon statistical analysis in clinical trials, innovative approaches in clinical trial design and the optimisation of clinical trials in specific therapeutic areas.

RSRN ID	Research need	Priority topic	Keywords	Impacted domain
Focus area: Statistical analysis in clinical trials				
CT1	Research on use of the estimand framework ICH E9(R1)	1. Develop principles for aligning estimation methods with targeted estimands for intercurrent event strategies, including hypothetical scenarios (C; D; F) 2. Develop principles for applying causal inference approaches to clinical trials in the estimand framework (C; D; F) 3. Generate recommendations on how the estimand framework and frameworks for HTA assessment (e.g., PICO) could be aligned based on methodological principles (C; D; G)	• Study design • Statistical analysis • Estimands	Human and Veterinary medicines Health technology assessment
CT2	Research to enhance robustness of non-randomised studies	1. Develop a framework of multiple dimensions and criteria for the rigor and quality of non-randomised clinical trials (RCT) (C; D; G)	• Statistical analysis • Non-RCT • Clinical trials	Human medicines
CT3	Research on analytical methods for clinical trials	1. Perform a review of elicitation and data-driven methods for priors for Bayesian analyses of clinical trial results to inform clinical and regulatory decision-making, and identify use-cases that	• Statistical design • Statistical analysis • Rare diseases • Several therapeutics areas • Orphan medicines • Clinical trials	Human medicines

RSRN ID	Research need	Priority topic	Keywords	Impacted domain
		would particularly benefit from using such priors (focus on ultra-rare diseases) (B; C; G) 2. Research multiple bias modelling in evidence synthesis and analysis, to inform regulatory decisions (C; G)		
Focus area: Innovative approaches in clinical trial design				
CT4	Research on methods to improve efficiency of design and analysis methodologies for trials	1. Perform a comparison of methods to use non-concurrent arms, including handling time trends, in platform trials (G) 2. Research hierarchical / multi-level modelling approaches for analyses of efficacy endpoints in complex or personalised treatment trials (C; D; G) 3. Conduct a review of features of medicines and of trial participants that are relevant for expressing their independency with respect to considerations for "type 1 error control" (e.g., when included in arms, periods, groups or other elements of platform trials) (G) 4. Develop with stakeholders a protocol for, and prepare the conduct of a multi-stage or platform trial that establishes a new early efficacy endpoint(s) and uses this endpoint in future participants in the trial to investigate the efficacy of an investigational product(s) (G) 5. Research ways of constructing ordinal endpoints that include functional improvements or impairments and favourable or detrimental events, and simulate its impact on trial efficiency using past trials (F; G) 6. Perform an analytical comparison of designs for first-in-man oncology studies in terms of efficiency and patient benefit-risk (F; G) 7. Review stakeholder positions and arguments (covering ethics, policies, pharmacology, medicine) concerning diversity, equity and inclusion, analyse the impact and implications for	• Clinical trials • Platform trial • Complex trials • Oncology • First-in-man studies	Human medicines

RSRN ID	Research need	Priority topic	Keywords	Impacted domain
		various activities in particular clinical research and medicine development (B; G)		
CT5	Research on EU capacity and operational aspects of clinical trials	1. Develop a mapping and quantification of key challenges for sponsors (commercial and non-commercial) to efficiently plan, resource, set-up and conduct multinational clinical trials in the EU (and beyond) (B; G) 2. Perform gap analysis and quantify capacities and competencies (e.g., researchers, organisations, infrastructure) in the EU for carrying out master protocol-based trials, large, simple pragmatic or low interventional clinical trials in the EU (and beyond; to include aspects of health care systems, health professionals formation etc.) (B; G) 3. Map clinical trials with decentralised elements (e.g., over time, geography, therapeutic area, types of elements) and perform trend analyses to describe challenges and opportunities (if possible, including the impact of the EU DCT recommendations²³; B; G) 4. Research including a survey and interviews into the local, regional and country-specific availability and usability of existing electronic health care record, hospital and medical practice IT systems for screening persons and recruiting subjects into clinical trials (B; G)	• Clinical trials • Network capacity • Decentralised clinical trials	Human medicine
Focus area: Clinical trials optimisation in specific therapeutic areas				
CT6	Research on innovative clinical trial designs to support medicines development	1. Review complex clinical trials in rare diseases and perform analyses to evaluate design choices, opportunities and avenues to address challenges of drawing conclusions from them (B; G) 2. Research into efficiency of broader options for clinical trial design, broader inclusion of study populations, stratification	• Clinical trials • Advanced therapy medicinal products • Rare disease • Platform trials • Complex trials • Obesity • Neurology	Human medicine

²³ <https://www.ema.europa.eu/en/news/facilitating-decentralised-clinical-trials-eu>

RSRN ID	Research need	Priority topic	Keywords	Impacted domain
		approaches and analyses, e.g. in obesity and diabetes (G) 3. Research into efficient options for organising and designing clinical research in pre-symptomatic stages of neuro-degenerative diseases for documenting clinical benefits (B; D; F; G) 4. Research to develop non-invasive markers for MASH suitable for clinical trials for regulatory purposes (D; E; G)		
CT7	Research on safety documentation in clinical trials	1. Perform an analysis of clinical trials to inform principles and requirements for collecting and reporting cardiovascular toxicities by using case studies from the following therapeutic areas: 1) oncology; 2) neurology; 3) psychiatry (B; D; G)	- Clinical trials - Side effects - Cardiovascular toxicity	Human medicine
CT8	Research on natural history studies to support medicines development for rare diseases	1. Design protocols and conduct natural history studies to 1) propose and define endpoints for clinical trials in rare diseases lacking authorised medicines and 2) explore their use as comparative groups for clinical trials in understudied rare diseases without internal control (D) 2. Develop approaches that model measurement uncertainty, random and systematic fluctuation (C; F)	- Clinical trials - Natural history - Rare diseases - Orphan medicines	Human medicine
CT9	Research to optimise evidence generation	1. Review clinical trials conducted to support marketing authorisation of medicines to treat solid cancers or malignant haematological conditions to gauge inclusiveness of the concerned populations and identify approaches for effective inclusiveness (including but not limited to factors such as age, ethnicity, sex; B; G)	- Clinical trials - Age - Haemato-oncology - Representativeness	Human medicine

210

211 **2.3. Research needs to improve regulatory system evolution**

212 This section includes 9 research needs and 23 priority topics that aim to improve the Agency's
213 regulatory methodologies, standards and practices, thereby optimising the processes and oversight
214 needed to ensure efficiency of the medicines regulatory system. This is expected to help maintain an
215 adaptive and dynamic regulatory system that fosters growth and innovation, while ensuring public
216 trust and reliability.

217 The needs in this list touch upon research that goes beyond current regulatory pathways, as well as
 218 research into the handling of shortages of medicines and medical devices, communication strategies
 219 and data management.

RSRN ID	Research need	Priority topic	Keywords	Domain of impact
Focus area: Going beyond current regulatory pathways				
RP1	Research on the impact of medical devices and medicinal product/ medical devices combinations on the medicine's lifecycle and the regulatory system	1. Review and describe the evidence framework and methodological principles for generating scientific evidence underpinning medical devices, medicines and their combination (G)	• Medical device/drug combination • Combination product • Clinical trials • Regulatory framework	Human medicine
RP2	Research on regulatory pathways for medicines and drug development tools	1. Investigate the needs and opportunities for new drug development tools (and technologies) to be supported through new expressions of regulatory endorsement (B; G) 2. Research to develop criteria to inform the regulatory evaluation and assessment of transmission-blocking agents (D; G) 3. Conduct research to identify parameters that influence regulators' reliance on others' assessments globally (B; G) 4. Deepen the research on methodologies, including Bayesian, for indirect comparisons of effects on clinically relevant endpoints between medicines, including use cases in the field of rare diseases (D; F)	• Drug development tool • Regulatory science • Reliance • Rare diseases	Human and Veterinary medicine
RP3	Research on impact of classifications/definitions on regulatory environment	1. Perform a mapping and review of international classifications and assessment frameworks of borderline products to describe their impact on different stakeholders (B; G) 2. Perform a review of criteria used globally for biosimilar assessment, including clinical development (type and amount of data) and critical quality attributes (G) 3. Perform a global, quantitative, geographic and time-related analysis of types of health-related clinical research, covering and going beyond regional	• Clinical trials • Clinical research • International harmonisation • Classifications • Borderline products	Human medicine

RSRN ID	Research need	Priority topic	Keywords	Domain of impact
		regulatory definitions (e.g., "studies", "trials", "low-intervention trials", trials in the health system) to provide a landscape of research, a synopsis of research classifications / terminology, and an overview of types of designs and links with the health system (A; D; G)		
RP4	Research on pharmacological commonalities and the potential for leveraging mechanism of action for studying interventions	1. Perform a descriptive analysis of pharmacological commonalities across diseases and subtypes to leverage a mechanism-of-action approach for investigating therapeutic interventions (G) 2. Perform a scoping review to explore how the mechanism of action-approach can be developed from oncology to other therapeutic areas (in particular neurology, unmet medical needs), taking into account experience with paediatric medicine development (e.g., EU paediatric investigation plans, U.S. required podiatric assessments and written requests) (G)	• Mechanism of action • Paediatric investigation plan • Neurology • Unmet medical needs	Human medicine
Focus area: Shortages				
RP5	Research on shortages of medicines and medical devices globally	1. Perform comparative analysis of different jurisdictions globally in terms of handling shortages of medicines and medical devices (B; G) 2. Perform a qualitative and quantitative analysis of the clinical use patterns of the most used critical medicines in hospital settings across the EU (D; G) 3. Perform quantitative analysis of the rate of export of critical medicines outside the EU (G)	• Shortages	Human and veterinary medicine
RP6	Research on availability of critical medicines and medicines for unmet medical needs	1. Research to update 'white spots'²⁴ in pharmaceutical development pipelines, of unmet medical needs with a particular focus	• Shortages • Social media • Rare disease • Unmet needs • Communication	Human and veterinary medicine

²⁴ <https://doi.org/10.1586/17512433.2015.1028918>

RSRN ID	Research need	Priority topic	Keywords	Domain of impact
		on rare metabolic diseases (B; G) 2. Develop methodologies and perform an analysis of the impact of social media on key medicines' availability, identify factors determining the impact and develop suggestions for suitable interventions or best practices of prevention (B; G)		
Focus area: Communication				
RP7	Research on approaches to improve communication and engagement on medicines to better address public needs	1. Develop criteria and measurable parameters for credibility and for public trust relevant for EMA (B; G) 2. Develop methods and approaches relevant for EMA to identify and address fake news and misinformation (B; D; F; G) 3. Perform an in-depth analysis of how misinformation on vaccines and population hesitancy is impacting public health (B; G) 4. Analysis of stakeholders knowledge, needs and perceptions on antimicrobial resistance (AMR)/One Health (B; G) 5. Analysis of stakeholders' knowledge, information needs and perceptions implications concerning gene therapies and other advanced therapy medicinal products (ATMPs) (B; G) 6. Analysis of stakeholders' needs for biosimilar uptake, such as educational needs, in particular on interchangeability (B; G) 7. Analysis of EMA communication output on vaccines (including any new communication materials), including through user testing (G)	• Communication • Public trust • Misinformation	Human and Veterinary medicine
Focus area: Data management				
RP8	Research to improve understanding of data processing opportunities	1. Perform a comparative analysis to inform the development of principles for harmonisation of data protection strategies	• Data management	Human medicine

RSRN ID	Research need	Priority topic	Keywords	Domain of impact
		across regulators and stakeholders (B; G)		
RP9	Research on tools to improve the use of scientific data	1. Review the most used and impactful models/tools to link and optimise use of heterogeneously structured scientific data (G) 2. Explore best methodological practices for data management and analysis of regulatory metadata (i.e., information about medicines, development tools, clinical trials, application of standards such as OMOP and ISO), covering descriptive and inferential uses, visualisation and prediction (C; F; G) 3. Explore use of modelling and simulation methods for the analysis of historical data from regulatory submissions for cross-product meta-analysis, including disease progression models to support scientific advice/marketing authorisation applications and regulatory guidance (C; F)	• Data management • Scientific data • Regulatory metadata • Modelling and simulation	Human and Veterinary medicine

220

221 **2.4. Research needs to foster technologies for development of specific types of medicines**

222 This section includes 14 research needs and 35 priority topics that aim to generate scientific evidence
 223 to improve efficacy, safety and protocol optimisation related to development of novel technologies or
 224 tools used across medicine lifecycle.

225 The needs in this list touch upon research on platform technologies and vaccines, tackling antimicrobial
 226 resistance, non-animal models and 3Rs-related developments, advanced therapeutic medicinal
 227 products (ATMPs), real world data/real world evidence and biomarkers.

RSRN ID	Research need	Priority topic	Keywords	Domain
Focus area: Platform technologies and vaccines				
NT1	Research on mRNA-based medicines across therapeutic areas with a focus on oncology and rare diseases	1. Generate scientific evidence on efficacy and safety as determined by the type of mRNA (e.g., self-amplifying, trans-amplifying, circular) considered for future medicines in comparison to mRNA types used in authorised medicines (A; D; E)	• Platform technology features • mRNA • Oncology • Rare diseases	Human and Veterinary Medicine

		2. Generate scientific evidence on how molecular features (e.g., coding sequence, backbone, structure), chemical modifications and synthesis pathways are related to clinical safety and efficacy of mRNA-based medicines and can be used for comparing authorised with investigational medicines (A; D; E) 3. Generate scientific evidence on the safety and efficacy as determined by different delivery systems and routes of administration of mRNA-based investigational or authorised medicines (D; E; F)		
NT2	Research on reactogenicity and immunogenicity for novel vaccines combining an increasing number of antigens for different pathogens using the same platform technology (e.g., mRNA-based)	1. Perform studies to define best administration approaches with respect to immunogenicity and reactogenicity in consideration of regulatory assessment requirements (E; G) 2. Comparative studies of the impact of different numbers and types of combined antigens on immunogenicity and reactogenicity and their relation (E; F)	• Vaccines • Immunogenicity • Platform technologies	Human and Veterinary medicine
NT3	Research to inform regulatory assessment of platform technologies	1. Perform a quantitative analysis of how and which changes in platform technologies could impact results of non-clinical and clinical testing of medicinal products (E; G) 2. Explore opportunities and challenges of platform technology approaches for monoclonal antibodies and analyse their potential impacts on regulatory assessment (G) 3. Develop scientific methods to simulate and predict the impact of changes in a platform technology on clinical safety and efficacy (C; D; F; G)	• Platform technologies • Active substance • Monoclonal antibodies • Computational modelling • Machine learning	Human and Veterinary medicine
NT4	Research to strengthen scientific evidence in the field of mRNA vaccines and novel vaccines technologies	1. For a broader set of rare adverse events, perform studies to describe mechanistic, pharmacodynamic and pathophysiological	• Vaccines • Immunisation • Adverse drug reaction	Human and Veterinary medicine

		pathways and causal aspects 2. Perform studies to characterise aetiology and pathophysiology of rare adverse events for mRNA vaccines and novel vaccines technologies (A; D; E)		
NT5	Research on potential modifiers of treatment effects	1. Perform appropriately designed clinical trial(s) using different types of vaccines to robustly evaluate and quantitatively estimate how their treatment effect on immunogenicity depends on and varies with factors such as: 1) gut microbiome; 2) time of the day for administration; 3) age; 4) ethnicity; 5) pharmacogenomics; 6) epidemiology of circulating pathogens (A; D; E)	• Vaccines • Immunogenicity	Human medicine
NT6	Research on optimisation of post-authorisation study design	1. Perform a comparison of a set of possible vaccine study designs in the post-authorisation setting with respect to efficiency and robustness (G)	• Vaccines • Post-authorisation studies • Infectious diseases	Human and veterinary medicine
Focus area: Antimicrobial resistance				
NT7	Research to establish standards for phage-based therapies	1. Perform studies to identify elements that determine the potency of phage-based therapies (A; D; E) 2. Perform studies to develop quality standards for phage-based therapies, including to compare and address fixed mixtures as well as mixtures adapted to different therapeutic targets) (A; D; E; F) 3. Perform studies to define manufacturing standards of phage-based therapies (G)	• Bacteriophages • Antimicrobial resistance	Human and Veterinary medicine

NT8	Research on development of novel antibiotics	1. Using a multistakeholder approach, develop standards for assays to allow high-throughput screening libraries for new antibiotics (E; G) 2. Using a multistakeholder approach, develop methods to identify potential candidate antibiotics from novel sources such as human and animal "microbiomes" (E)	• Antimicrobial resistance • Antibiotics	Human and Veterinary medicine
Focus area: Non-animal models (NAMs) / 3Rs				
NT9	Research to improve regulatory acceptance of 3R methods / NAMs	1. Perform analytical comparison of approval criteria across regulators for NAMs (EDQM, EMA...) and identify elements to foster regulatory harmonisation (G) 2. Develop scientific evidence of clinical predictivity of NAMs for <i>in vivo</i> pathophysiology (A; E; F) 3. Perform studies to support use of modelling and simulation towards 3Rs and translational modelling for first-in-man studies (D; F)	• 3Rs • Non-clinical models • <i>In vitro</i> models • Modelling and simulation	Human and Veterinary medicine EU regulatory system
NT10	Research on impact of medicines on pregnancy, breast-feeding, neonates	1. Develop non-clinical models to predict transfer of medicines to human breast milk and uptake by the neonate (A; D; E; F) 2. Develop modelling approaches including physiologically based pharmacokinetic (PBPK) models to predict transfer of medicines to human breast milk and uptake by the neonate (A; D; E; F) 3. Review and provide an analytical comparison of the available <i>in vitro</i> models that fit the purpose of measuring the impact on pregnancy, breast feeding, neonates (G) 4. Conduct studies to better understand the effects of using HIV anti-retrovirals during pregnancy and breastfeeding on the foetus and newborn (including a better understanding of U=U)	• 3Rs • Non-clinical models • Pregnancy • Neonatal medicine • Breast-feeding • <i>In vitro</i> models • HIV • Modelling and simulation	Human medicine

		levels on breastfeeding) (E; F; G)		
NT11	Research on modelling and simulation methods to support regulatory decisions	1. Develop models and designs for characterisation of exposure response throughout drug development to support dose selection and posology claims in SmPC, with a focus on special populations (F; G) 2. Perform studies to develop optimal PK (and PD) designs in children to support extrapolation from adults (A; D; E; F) 3. Develop modelling approaches including PBPK for renal/hepatic impairment in elderly patients (A; D; E; F) 4. Develop methods to quantify and report uncertainties in complex models, such as diagnostic and reporting tools to facilitate regulatory decision based on these models (D; F)	• Modelling and simulation • Dose selection • Posology • Special populations	Human medicine
Focus area: Non-animal models / ATMPs				
NT12	Research on methods to improve regulatory acceptance of ATMPs	1. Perform studies to develop non-clinical efficacy models for therapies based on genome editing (A; E; F) 2. Develop methods to validate predicted or observed off-target effects of genome editing, especially effects on regions with unknown functions (A; E; F)	• 3Rs • Non-clinical models • ATMPs • Genome editing • Side effects	Human and veterinary medicine
Focus area: Real-world data (RWD) / Real-world evidence (RWE)				
NT13	Research on methods to improve use of RWE in decision-making	1. Perform studies on the application of causal inference methods to RWE for medicines, contributing to effective and efficient decision-making (C; D; F; G) 2. Develop/explore methods to assess the robustness of RWE-derived claims for centrally authorised medicinal products (F) 3. Develop methods to understand and possibly mitigate the impact of heterogeneity between	• RWD, RWE • Causal inference	Human and Veterinary medicine

		RWD sources on the choice of analytical approaches and designs used to take into account this heterogeneity, with a focus on: sample composition; prognostic / risk factors specific to therapeutic areas; nature / type of the data source (C; D; F; G) 4. Perform mapping of medical ontologies and develop cross-dictionary phenotyping to assess the impact of their differences on RWE use and value (G)		
Focus area: Biomarkers				
NT14	Research on predictive biomarkers for patient-tailored treatment of frequent diseases	1. Develop studies for discovering and confirming biomarkers that may predict response to a medicine, with a focus on frequent or chronic diseases such as cardiovascular diseases (A; E; F)	• Biomarkers • Personalised medicine • Cardiovascular diseases	Human medicine

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229 **2.5. Research needs to advance specifically animal health and the regulation of veterinary** 230 **medicines**

231 This section includes 15 research needs and 27 priority topics that aim to ensure the safety and
232 efficacy of veterinary medicines, safeguarding both animal and public health.

233 The needs in this list include research on non-animal models and 3Rs-related developments,
234 environmental risk assessment, antiparasitic and antimicrobial resistance, pharmacovigilance methods,
235 novel therapies and innovation, vaccines and veterinary big data.

RSRN ID	Research need	Priority topic	Keywords	Domain of impact
Focus area: Non-animal models / 3Rs				
VET1	Research to develop 3Rs-compliant methods for regulatory testing of veterinary medicines and establishment of maximum residue limits	1. Develop methods for quantitative <i>in vitro</i>/<i>in vivo</i> extrapolation modelling (A; E; F) 2. Develop <i>in silico</i> models specifically for veterinary medicines (F) 3. Develop microphysiological / cellular models specifically for veterinary medicines (A; E; F) 4. Develop <i>in vitro</i> models for the assessment of toxicity and potency of novel therapies, particularly nanoparticles and	• 3Rs • Non-clinical models • <i>In vitro</i> models • Maximum residue limit • Computational biology • Nanoparticles	Veterinary medicine

		RNA-based veterinary medicinal products (A; E; F)		
Focus area: Environmental risk assessment				
VET2	Research to generate data for regulatory decisions on environmental safety of veterinary medicinal products	1. Develop methods to reliably estimate, measure and analyse environmental concentrations of substances used in veterinary medicinal products (A; D; E; F) 2. Develop methods/produce data to inform the assessment of public health risks related to antimicrobial resistance acquired via the environment resulting from the use of a veterinary medicinal product (A; D; E; F; G) 3. Conduct a gap analysis of the availability of environmental risk assessment (ERA) data for veterinary medicinal products and propose new models to update ERAs (e.g., addressing water pollution effects of veterinary products) (G)	• Environmental risk assessment • Veterinary medicinal products	Veterinary medicine
VET3	Research on approaches to monitor environmental risk	1. Develop tools and strategies to monitor environmental risks arising from the release of bacteriophages used to treat food-producing animals (including in aquaculture). This includes validation of methods to detect interactions between antibiotics and bacteriophages that might affect antibiotic activity (C; D; F; G)	• Environmental risk assessment • Bacteriophages • Antibiotics • Antimicrobial resistance	Veterinary medicine
Focus area: Antiparasitic resistance				
VET4	Research to increase scientific knowledge on antiparasitic resistance	1. Perform studies to identify the mechanisms of antiparasitic resistance development and transmission (A; E) 2. Develop methods to estimate and accurately predict the level of antiparasitic	• Antiparasitic resistance • Risk assessment	Veterinary medicine

		resistance depending on parasite and antiparasitic substance class (A; C; E; F)		
VET5	Research to ensure control and prevention of antiparasitic resistance	1. Perform studies to determine the types of data and the minimum level of evidence necessary to ensure reliable assessment of antiparasitic resistance (F; G) 2. Perform mapping and gap analysis of measures necessary for the control and prevention of antiparasitic resistance globally (G)	• Antiparasitic resistance • Risk assessment	Veterinary medicine
Focus area: Pharmacovigilance				
VET6	Research on approaches to leverage data for improved pharmacovigilance	1. Perform studies to establish the data landscape of pharmacovigilance-related information (including species population, data on treatment) at the level of veterinary practice and husbandry in the different Member States (G) 2. Perform an analysis of data in the union pharmacovigilance database to identify potential biases in terms of product type population that may affect data warehouse analyses and suggest appropriate measures to improve the robustness and consistency for signal management (C; F; G)	• Pharmacovigilance • Data management • Union pharmacovigilance database	Veterinary medicine
VET7	Research on approaches to facilitate and improve reporting of adverse events related to veterinary medicines	1. Perform analysis on the sales data relative to the reporting of adverse event in the different Member States 2. Develop new methods (and review relevant existing methods) to increase the reporting rates of adverse events for veterinary medicinal products (to cover technologies such as mobile devices and apps) (D; F) 3. Investigate and develop methods to	• Adverse drug reaction • Adverse event	Veterinary medicine

		optimise the dissemination of updated safety information to practising veterinarians and animal owners (food-producing animals and companion animals) (B; G)		
Focus area: Novel therapies and innovation				
VET8	Research on identification of regulatory bottlenecks for novel manufacturing	1. Review novel manufacturing methods and delivery approaches (including devices) with a focus on related regulatory limitations and bottlenecks (G) 2. Review and perform an analysis on the approach underpinning novel manufacturing regulation in the devices field, highlighting learnings that could translate into medicine regulation (G)	• Advanced manufacturing	Veterinary medicine
VET9	Research on novel methodologies for quality control of veterinary medicines	1. Develop or optimise methods entailing deep sequencing for testing of contaminants, to inform limit-setting for veterinary use, such as blood products, cell products (D; E; F)	• Quality control • Pharmaceutical quality • Product quality issue • Deep sequencing	Veterinary medicine
Focus area: Vaccines				
VET10	Research on vaccines for priority diseases	1. Perform an analysis to identify challenges, opportunities and potential synergies to foster the development of veterinary vaccines for therapeutic gaps in the market (e.g., specific target species, limited markets, zoonotic and emerging diseases) (G)	• Vaccines • Priority diseases • Limited market • Zoonosis • Emerging diseases	Veterinary medicine
VET11	Research on methods to ensure highest quality of vaccines	1. Perform an analysis to discover opportunities offered by novel methods for the detection of nucleic acids applied to the quality control of veterinary vaccines (e.g., in the detection	• Quality control • Vaccines	Veterinary medicine

		of contaminating material and vaccine strain characterisation) (G) 2. Develop approaches to investigate process- and product-related impurities in veterinary vaccines (D, E, F)		
Focus area: Antimicrobial resistance				
VET12	Research on data generation for regulatory decisions on antimicrobials	1. Develop models to support the initial or the maintained marketing authorisation of antimicrobials of public health relevance. The models might take into account the following elements: 1) off-patent veterinary antimicrobials; 2) modelling and extrapolation using PK/PD; 3) dose optimisation (B; F; G)	• Antimicrobial resistance • Dose optimisation • Pharmacokinetic study • Pharmacodynamic study	Veterinary medicine
VET13	Research on methods for reporting data on antimicrobial use	1. Develop methodologies to establish defined daily dose and defined course dose (DDDvet/DCDvet) for reporting of antimicrobial use in different animal species (A; D; E; F)	• Defined daily dose • Defined course dose • Antimicrobial resistance	
VET14	Research on diagnostics to support prudent use of antimicrobials	1. Develop and establish/validate point-of-care/companion diagnostics for veterinary antimicrobial sensitivity tests (D)	• Antimicrobial resistance • Point-of-care testing • Diagnostics	Veterinary medicine Notified bodies
Focus area: Veterinary big data				
VET15	Research on big data activities on the veterinary domain	2. Perform a review and highlight differences and opportunities of big data initiatives (e.g., to further explore availability of data sources on animal health, data integration and analytics solutions) to support the Veterinary Big Data strategy (B; G)	• Veterinary Big Data strategy	Veterinary medicine

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3. Methods

3.1. Identification and formulation of new research needs

Between February and May 2024, more than 20 interviews were conducted with internal experts across various EMA departments and workstreams to obtain relevant input and feedback on challenges in their area of work. The interviews identified over 90 critical topics relating to daily operations, handling of assessment procedures and feedback from scientific committees and working parties. These topics were evaluated and used to inform the updated RSRN list.

Regulatory challenges that might benefit from further research were also identified through screening of different sources:

- Procedure reviews. Selected procedures were reviewed and gaps reviewed across different therapeutic areas and quality, non-clinical and clinical domains (e.g., CHMP initial marketing authorisation day 120 overview reports). The procedure reviews were so far exploratory to inform and complement the expert interviews.
- Horizon scanning activities. To enable EMA and the EU regulatory network to proactively respond to forthcoming challenges and opportunities, EMA conducts horizon scanning activities in collaboration with experts and groups such as the EU-IN. The horizon scanning reports include recommendations how to adapt the network, minimise regulatory bottlenecks, support developers and facilitate innovation reaching patients. Challenges and recommendations found in the reports were analysed to inform the updated RSRN list.
- Regulatory interactions at early stages. EMA provides developers with opportunities for interaction, to create a supportive environment for anticipating regulatory aspects while exploring opportunities related to new developments. Academia briefings, Innovation Task Force briefings and Portfolio & Technology Meetings of recent years have been used to collect relevant non-product-specific questions and to inform the updated RSRN list.
- Enquiries from academia. EMA interacts with academic developers in several ways, including through direct interaction facilitated by EMA's academia liaison and enquiries sent via AskEMA or to academia@ema.europa.eu. While providing answers to requesters, EMA takes the opportunity to flag and identify recurrent topics that might benefit from regulatory science research.

The identification of RSRNs showed some priority topics were recurrent, across interviews or several information sources. A small number of the identified challenges were not suitable to be formulated as priority topics for the attention of external researchers. The research needs and opportunities were further divided into sections that represent major clusters of research with several focus areas.

3.2. Investigating and tracking progress on research needs

The documentation of progress of activities addressing research needs is highly work intensive, and it appears that it could not yet be done systematically and continually by any stakeholder. The efforts documented here were made mainly to explore methods, given limited resources.

- A manual literature search was performed to find relevant studies in specific RSRN fields. Additionally, for each specific RSRN, a set of keywords has been tested. Sequential searches were run to first isolate topic-specific publications and to subsequently isolate those reporting on solutions from a regulatory perspective. A manual literature search was only conducted on a subset of research needs according to upcoming priorities and specific interactions with relevant developers.

- EMA also started to explore automating search strategies to track outcomes of regulatory science research. The aim was to explore text mining and AI approaches for the retrieval of publications that likely address questions expressed in the RSRN list.
- EU-funded projects (with or without involvement of EMA) have been screened to identify relevant research on RSRN. Several have progressed to in-depth interactions with EMA to leverage research outputs.

As a conceptual framework for investigating and documenting the progress of RSRNs, consecutive stages have been identified in the life cycle of regulatory science research (Figure 2). A preliminary and incomplete summary of the progress on the RSRN v1 is provided in Table 2. It is planned to provide for most entries in the RSRN v1 an update on the stage of progress, in 2025.

[[The information in table 2 will be added over time and an update will be provided in the finalized document after public consultation on the 2024 updated list]]

Table 2: Stages of progress (preliminary)

Stage number	Stage end November 2024	Number of RSRN v1
1	Research needs that seem addressed with outputs translated in changed regulatory standards or practices or changes in R&D practices	
2	Research needs that seem addressed even though outputs may not or may not yet have changed regulatory standards or practices (yet)	
3	Research needs that have relevant outputs and may have been addressed but not yet advanced to translation	
4	Research needs with some outputs available	
5	Research needs with specific ongoing activities	
6	Research needs that still stands to benefit from activities	
7	Research needs for which it is unclear or could not be clarified if and which activities are ongoing	
	Sum	

Figure 2: Stages of progress mapped onto the life cycle of regulatory science research

