STARS
STRENGTHENING
REGULATORY
SCIENCE

STARS Common Strategy: Regulatory Support and Advice for Academia

Analysis and Recommendations by the STARS Consortium

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Foreword

In addition to the activities to combat the Corona pandemic, the rapid developments in recent years have revealed that academic groups play an essential role in the development of new drugs, vaccines and (digital) medical devices. However, on the way to the patient, a large translational gap is revealed since not all academic-driven research activities will pass the scrutiny of the regulatory authorities. In order to close this translational gap, the STARS initiative increases the regulatory efforts in supporting academic health researchers.

STARS is a collaboration of 21 partners from 18 countries, including the majority of the European national competent authorities (NCA), the European Medicines Agency, and the DLR Project Management Agency focussing on strengthening training of academia in regulatory science (STARS) in Europe. The project is supported by the European Commission's (EC) Framework Program for Research and Innovation Horizon 2020 and runs from 2019 until 2022.

The STARS activities aim to improve the regulatory impact of academic-driven health research in order to accelerate innovation for the benefit of patients and society by sharing knowledge on regulatory science. This has been identified as a deficiency by the EC and many national funders across Europe and beyond.

Therefore, the regulatory awareness and knowledge of academic institutions, groups and individual scientists working in biomedical and health research is crucial and needs to be enhanced. This can be achieved for example by optimising existing or establishing new education and targeted training programmes. Additionally, tailored activities and offers can be developed, such as support to ensure successful outcomes in scientific advice procedures. This may further enable academic health research to achieve its full impact for the patients and the society.

To this end, STARS pursued specific activities, including support tools such as a comprehensive inventory to assist European academic drug developers in finding support on regulatory affairs, recommendations on curricula to be implemented in (bio)medical educational programmes, a white paper that highlights key steps towards improved regulatory dialogue among academia, funding bodies and regulatory authorities, as well as three pilot projects to support academia to demonstrate that selected support activities can be implemented efficiently. Also, from the perspective of the NCAs a better understanding of the needs and challenges of academic researchers and an improved communication strategy should be foreseen.

This present document highlights the achievements of STARS and focusses on the opportunities to strengthen regulatory science and knowledge. Based on the various STARS activities, the current status was described and recommendations were developed together with key stakeholders. Bringing these key players of drug development together, resulted in this strategic document, the "STARS Common Strategy". This document is the STARS road map for the implementation of support activities and training programmes, with the goal to strengthen regulatory sciences and improve successful outcomes from innovative and academic-driven clinical research projects.

The CSA STARS Consortium

Executive Summary

The EU-funded project **S**trengthening **T**raining of **A**cademia in **R**egulatory **S**ciences (STARS) aimed at improving regulatory education and support activities to enhance success and outcome during regulatory scientific advice procedures. The project consequently addressed three major aims:

- improving general knowledge on regulatory issues in the academic world,
- improving the dialogue and communication between relevant stakeholders, and
- strengthening the support for successful outcomes during regulatory scientific advice with direct regulatory impact of academic driven research.

STARS is a collaboration between 19 European national competent authorities (NCAs) from 18 countries, four associate countries, the European Medicines Agency (EMA) and the DLR Project Management Agency (Chapter 1).

In this document, STARS elucidates the European and national aspects of regulatory science and support for academia (Chapter 2) and a comprehensive analyses of the current landscape of regulatory science, gaps and best practices (Chapter 3). During the project's lifetime, STARS coordinated efforts between the NCAs and European partners, relevant initiatives and stakeholders, and the academic research community on the national and European level. The STARS consortium carried out different activities to reach these objectives, including

- several targeted surveys in stakeholder groups,
- three specific pilot projects on best practices and novel support activities,
- development of curricula concepts,
- development of a pre-grant scientific advice concept,
- two stakeholder workshops, and
- publication of a "white paper" (Chapter 4) as well as the submission of a manuscript about the STARS surveys.

Finally, the lessons learned from these activities, the results of two stakeholder workshops and the analysis of the STARS survey data provided the basis for 21 recommendations with the aim to improve the regulatory knowledge, awareness and skills of academia across Europe (Figure A-C and Chapter 5).

In conclusion, implementation of the proposed recommendations will require action from all stakeholders, with including the regulatory authorities in Europe, academic researchers and institutions, as well as the European Commission, national ministries and funders (Figure A). Most of the recommendations relate to aspects in the general communication, which is in line with the STARS communication framework elaborated in the STARS white paper (Starokozhko et al., 2021). With regard to the implementation time, most recommendations can be implemented in the medium term (Figure C).

Figure A: Key Thematic Areas of Recommendations

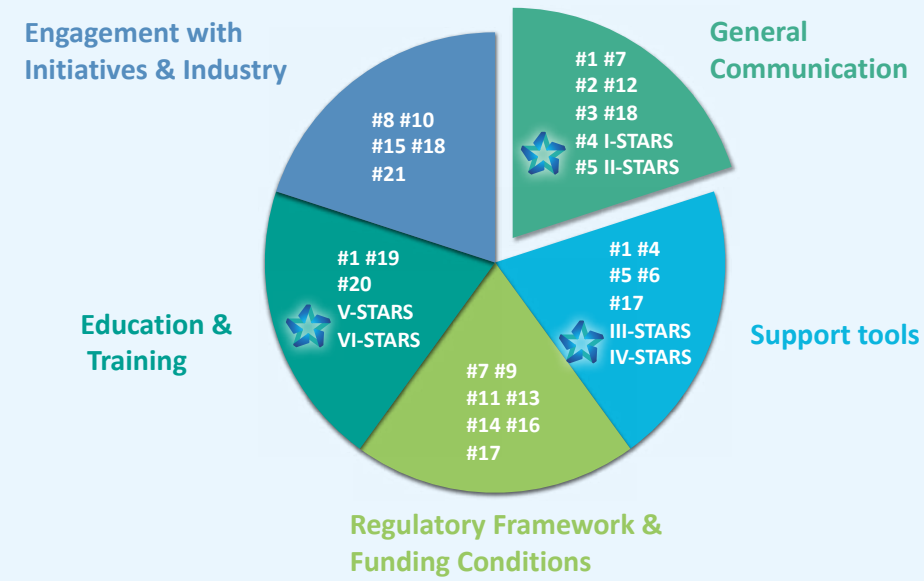


Figure A: Key thematic areas of STARS recommendations (#1-#21). The Roman numerals refer to the individual STARS activities which have been carried out during the project. For more information on single recommendations, refer to Chapter 5.

Figure B: Target Groups of Recommendations

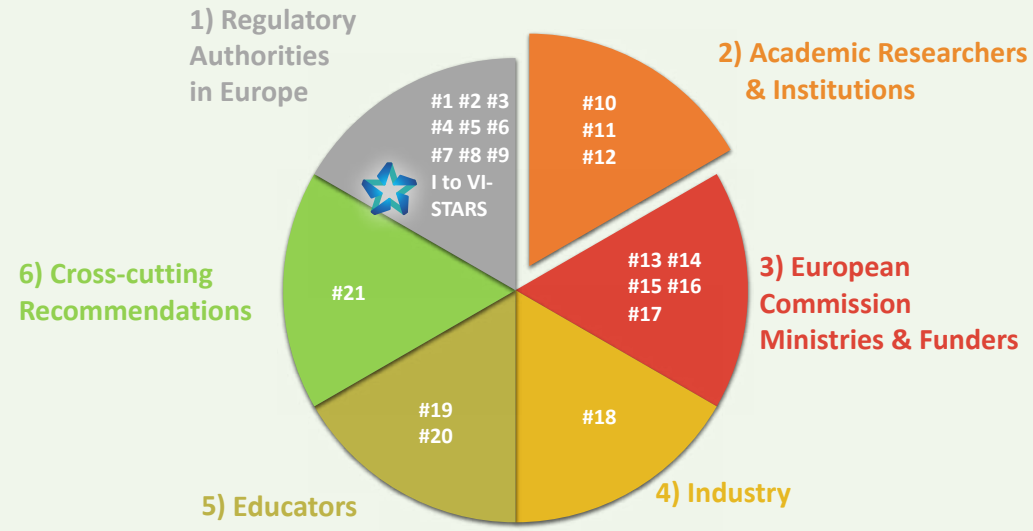


Figure B: Target groups of the STARS recommendations (#1-#21). The Roman numerals refer to the individual STARS activities which have been carried out during the project. For more information on single recommendations, refer to Chapter 5.

Figure C: Implementation Time

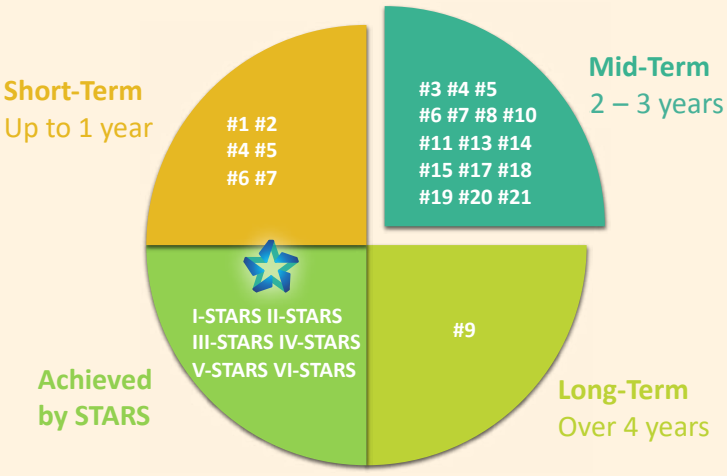


Figure C: Implementation time for the implementation of the individual STARS recommendations.

At a glance: STARS Recommendations

Overview of all STARS recommendations, sorted by key thematic areas (Figure A). The coloured dot indicates the suggested implementation time for the implementation of the individual recommendations (green = up to one year, yellow = up to three years, red = over four years; the STARS logo indicates already performed STARS activities).

General Communication

#1	Update of targeted regulatory information material
#2	Appropriate media channels
#3	Communication and networking events
#4	Low threshold access to regulatory authorities
#5	Increase of awareness and use of regulatory support tools
#7	Low threshold to apply for scientific advice
#12	Early communication with regulators and HTA
#18	Early dialogue between academia and industry
STARS	STARS White Paper
STARS	STARS Survey Paper

Support Tools

#1	Update of targeted regulatory information material
#4	Low threshold access to regulatory authorities
#5	Increase of awareness and use of regulatory support tools
#6	Support in the preparation of scientific advice for academia
#17	Implementation of a pre-grant advice
STARS	STARS Comprehensive Inventory
STARS	STARS Pilots I, II, III

Regulatory Framework and Funding Conditions

#7	Low threshold to apply for scientific advice
#9	Harmonisation of the regulatory processes between the member states
#11	Encouraging compliance with clinical trial results
#13	Introduction and implementation of regulatory aspects for funded biomedical research projects
#14	Monitoring compliance with regulatory affairs during the project
#16	Support of research of regulatory processes by specific funding measures
#17	Implementation of a pre-grant advice

Education and Training

- #1 Update of targeted regulatory information material
- #19 Continuous education and training of regulators
- #20 Continuous regulatory training of the academia
- STARS STARS Core and Comprehensive Curriculum
- STARS STARS Pilots I, II, III

Engagement with Initiatives and Industry

- #8 Expanding and promoting existing structures within NCAs
- #10 Optimize engagement and collaboration of academia
- #15 Sustainability of the STARS achievements and tools
- #18 Early dialogue between academia and industry
- #21 Consideration of lessons learned in regulatory science, procedures and guidelines beyond Europe

Setting the Stage: Overview of the Scientific Interaction between Academia and Regulators

The journey of a medicinal product is complex. It involves many decision points and development steps and it is subject to a complex regulatory framework. In most cases, a transition takes place from academia to global pharmaceutical companies before the initiation of pivotal clinical development studies or an application for regulatory approval of a medicine. Studies have shown that pharmaceutical companies may need to repeat (parts of the) research already carried out by the academic inventors when they decide to move forward towards marketing authorisation (Freedman et al., 2015; Begley et al., 2015).

Such replication of clinical studies and programmes by the pharmaceutical industry, in order to achieve or ensure regulatory compliance, increases time to market access of new medicines and costs. Moreover, this practice also has a direct impact on attrition rates in medicine development, and may be unnecessary and even unethical. This underlines the need to improve regulatory compliance and the quality of academia-driven health research.

Coordination and Support Action on Strengthening Training of Academia in Regulatory Science and Supporting Regulatory Scientific Advice (CSA STARS)

It is considered crucial to improve the regulatory knowledge of academic groups and individual scientists working in the field of health research and regulatory science. This can be done for example by improving professional education and targeted training programmes in regulatory science. Additional support activities, such as scientific advice procedures in clinical development projects, may further enable academic-driven health research to achieve its full impact.

The EC-funded project Strengthening Training of Academia in Regulatory Sciences and Supporting Regulatory Scientific Advice (STARS) was initiated with the aim to improve regulatory education, but also to focus on all other kinds of regulatory support activities that can promote the utilisation and optimal exploitation of regulatory scientific advice procedures.

STARS is a collaboration between 19 European National Competent Authorities (NCAs) from 18 countries, four associate countries, the European Medicines Agency (EMA) and the DLR Project Management Agency, which is a national funding body on behalf of several Federal German ministries, e.g. for Education and Research or Health (Figure 1.1). The project aims to reach out to developers of innovative medicines in academia in order to bridge the regulatory knowledge gap and to enhance the dialogue between academia and regulatory authorities by means of, for example, scientific advice, qualification procedures and bidirectional knowledge exchange. STARS coordinates the efforts between the NCAs and European partners, relevant initiatives and stakeholders, and the academic research community on the national and European level.

Figure 1.1: The major aims of the STARS project, in which 19 European national competent authorities (NCAs), four associate countries and the European Medicines Agency (EMA) are involved (Starokozhko et al., 2021).

Authorisation of Medicines

All medicines must be authorised before they can be marketed and made available to patients. In the EU, there are two main procedures for authorising medicines: the centralised and the decentralised licensing procedure. There is also the possibility of a purely national licensing procedure. Nationally licensed medicinal products can later also be approved in other member states via the so-called mutual-recognition procedure.

The centralised procedure is mandatory for human medicines containing a new active substance to treat human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS), cancer, diabetes, neurodegenerative diseases, autoimmune and other immune dysfunctions, and viral diseases. It is also mandatory for medicinal products derived from biotechnology processes, such as genetic engineering, advanced-therapy medicines (e.g. gene-therapy or tissue-engineered medicines), and orphan medicines.

Centralised procedures are coordinated by the EMA and involve the EMA's Committee for Medicinal products for Human Use (CHMP), which consists of experts from all NCAs. CHMP performs an in depth scientific assessment of the data on pharmaceutical quality, safety and efficacy submitted by the applicant and provides an "Opinion" on the benefit-risk relationship and thus approvability of the respective medicinal product. The marketing authorisation (MA) itself is granted by the European Commission (EC) and valid for the entire European Economic Area (EEA) (Figure 1.2)

The decentralised procedure is mainly used for generic applications but is also possible for innovative products, unless the centralised procedure is mandatory. It can be used to obtain a MA in several member states at the same time, provided there is no pre-existing MA in any member state for the product applied for.

In a national licensing procedure, a medicinal product is to be marketed exclusively in a certain EU member state. Here, each member state has its own national authorisation procedures, based on the national legislation in the member state, which however must be in accordance with EU laws.

In the mutual-recognition procedure, a marketing authorisation for the same medicinal product that has already been granted a MA nationally by a member state can be "recognised" by other EU member states.

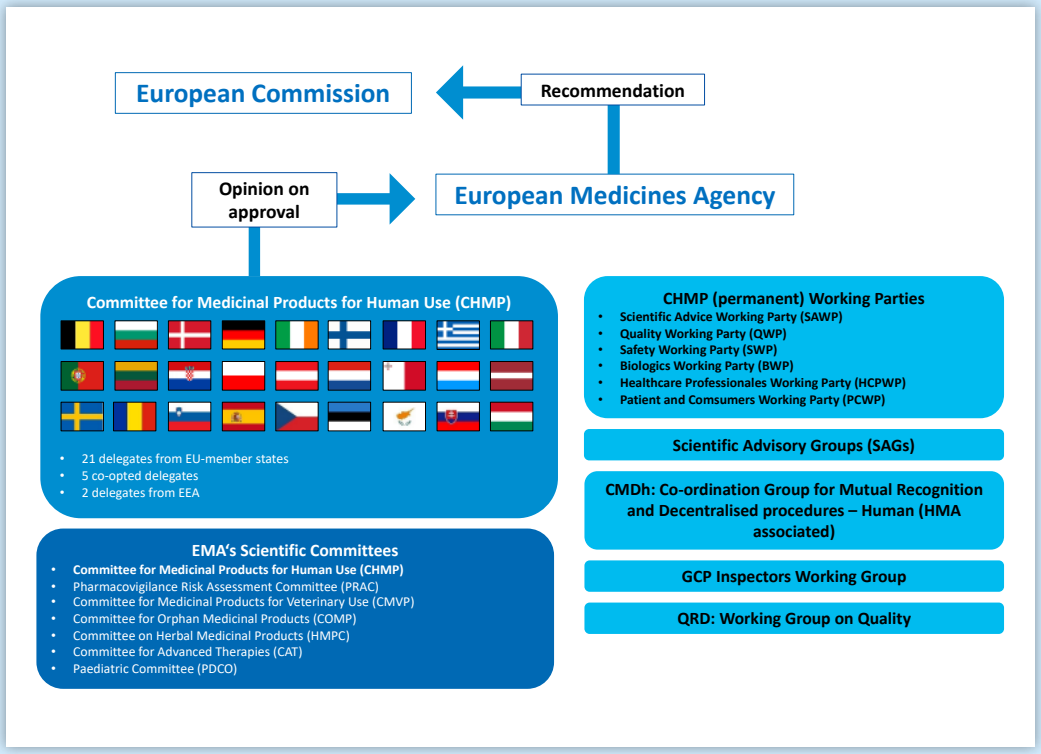


Figure 1.2: The EU regulatory framework: On an organisational level, Europe has a unique system for regulating medicines. The European Union (EU) medicines regulatory network is a partnership of more than 40 national competent authorities (NCAs) within the European Economic Area (EEA) that is coordinated and supported by the EMA. Within this network more than thousand European experts with various scientific backgrounds collaborate in different scientific committees and working parties to provide the best possible expertise in the regulation of medicines in order to ensure that medicines in the EU are safe and effective.

Scientific Advice as a Regulatory Support Tool for Interaction with Regulators

Scientific advice is an important regulatory tool for scientific interaction between developers and regulators. It offers the opportunity to have an early and detailed scientific discussion regarding different aspects and stages of drug development, including the design of clinical trials. In this way, scientific advice provides support and guidance, which improves the communication and interaction between developers and regulators. During a scientific advice procedure, developers can provide information on the development plan of a particular product and ask specific questions relating to the developing plans. The NCA reviews the data and information provided and will potentially have a meeting with the developer to discuss the questions raised and subsequently will provide a written response to the questions incorporating the position of the NCA's position.

Questions in scientific advice could relate to many aspects of product development including non-clinical and/or clinical issues, study trial design, primary and secondary endpoints, statistical analysis plans, or quality issues. Notably, there is evidence that early scientific interaction between developers and regulators throughout the drug developmental process may increase the chance of market access. A study by Hofer and colleagues (Hofer et al., 2015) analysed the impact of scientific advice on the outcome of the subsequent marketing authorisation application and revealed that incorporating the feedback obtained during scientific advice correlates with an increased likelihood of a MA being granted. This finding is in line with an earlier study by Regnstrom and colleagues (Regnstrom et al., 2010) which considered scientific advice as a predictor of a successful marketing authorisation application (MAA) outcome.

Scientific Interaction between Academia and Regulators – Tailored Support on the European and National Level

The academic research environment has an important role in basic biomedical research on drug discovery and development and is a key driver of innovative medicines (Bryans et al., 2019). At the same time, it is recognised that academic researchers often lack relevant regulatory expertise related to specific regulatory requirements. Consequently, there is a delay in the transition from clinical research into clinical practice, resulting in a translational gap between academic innovations and patient treatment (Starokozhko et al., 2021). In this so-called 'valley of death' promising early-stage academic biomedical discoveries remain in the early development phase and do not advance further along the translational chain. There are various reasons for this. One of the most challenging is communication. Communication with regulators often takes place during latter phases of the drug development process, and thus, mostly involves industry stakeholders. Requests for scientific regulatory advice from academia are generally less frequent. Also, there is broad variance across academic and industry initiated research in terms of the level of compliance with regulatory requirements as well as in relation to the quality and effectiveness of the implementation of regulatory sciences in the planning and conduct of research and development projects. It is recognised that academic researchers often lack specific and basic relevant know-how related to regulatory requirements and may have difficulty in identifying key questions to be addressed during regulatory scientific advice procedures. In order to address this knowledge gap and to facilitate better communication, many NCAs have initiated specific and tailored support activities for scientific interaction with academia and have built up innovation offices with close links to local innovators, to initiate early dialogue with universities, research institutes, hospitals, consortia and local small enterprises (see more details in Chapter 2).

On the European level, the EMA established a multidisciplinary group, the Innovation Task Force (ITF). This task force aims to foster the research and the uptake of novel methods in the development of safe and effective medicinal products in order to make them available to patients in a timely manner.The EMA's ITF is also a member of the EU-Innovation Network reflecting the collaboration within the European Medicines Regulatory Network as a whole. Please refer to Chapter 2 for more details.

European and National Aspects on Regulatory Science and Support for Academia

Collaboration between regulators and academia is necessary to be prepared for future challenges and opportunities offered by advances in science and technology. It is the task of the EMA and the national regulatory bodies to build and maintain a strong working relationship with European academics and researchers.

A National Competent Authority Supports for Clinical Research and Regulation

NCAs play a central role in managing interaction with academia at national level. They usually have an established bond with the Innovation Hubs and Innovation Offices at local research centres, Technology Transfer Offices (TTO), as well as local funding organisations. These connections make NCAs more approachable for academic developers and facilitate timely interaction.

Various **support tools** are offered by NCAs to guide and interact with academia at different stages of drug development. The aim of these specific support activities is to raise awareness among academia of key regulatory considerations, to offer guidance throughout the regulatory system and to address regulatory challenges from a very early stage of development. These partially informal interactions can clarify very general questions and issues that may arise at the beginning of development. This tailored support activity is intended to take place at an earlier stage than a scientific advice procedure with the aim of preparing and sensitizing applicants to identify the most appropriate and relevant questions to be explored in more detail in a subsequent (formal) scientific advice meeting.

Those support tools include, but are not limited to:

- Informal innovation office meetings, e.g. orientation meeting, kick-off meetings, early regulatory advice
- Formal scientific advice
- Clinical trial application advice
- Pre-submission meetings
- Pipeline portfolio meetings
- Regulatory/procedural advice
- Qualification advice
- Health Technology Assessment advice

Similar to the EMA initiative to support academic developers and small and medium-sized enterprises (SMEs), most of the NCAs offer free or discounted scientific advice services to individual academic researchers, as well as to research consortia. Academic researchers are also often offered support in preparing scientific advice or clinical trial application advice, as part of the non-formal interaction.

In addition, NCAs are offering **training programs,** lectures, workshops and webinars to academic developers, covering various regulatory/legislation topics, aspects on good practices, as well as more specific areas of drug development such as quality, non-clinical and clinical development. One of the examples of such trainings was taken up and implemented in the **STARS Pilot I,** a STARS activity that was specifically designed to transfer one of the best training practices from one member state to another. Pilot I is described in more detail in Chapter 4.

Furthermore, similar to the EMA, NCAs collaborate with academic developers within research projects by means of partnership or as part of advisory boards.

In a number of member states, there is also a close collaboration between the funding agencies and the regulatory bodies. These collaborations foster interaction of academic developers with the relevant agencies as early as possible in the process for relevant grant applications in order to ensure that applicants for funding give appropriate consideration to regulatory aspects in their clinical research proposals.

B European Medicines Regulatory Network and European Medicines Agency Supports for Clinical Research and Regulatory Science

In order to support the development of innovative methodologies, the European medicines regulatory network (EMRN) actively fosters greater collaboration across the regulatory network, and especially collaboration of the regulators with academia. Enabling and leveraging research and innovation in regulatory science is one of the strategic goals published in the European medicines agencies network strategy (HMA& EMA, 2020). The EU-wide network of "innovation offices" **(EU-Innovation Network or EU-IN)** was established in 2015 to strengthen the collaboration between NCAs and EMA on regulatory matters relating to emerging therapies and technologies. It has the objective to support the early development of innovative medicinal products and includes academic groups as a target stakeholder. Up to now, 22 NCAs participate actively in the EU-IN. In a reflection of the EMA regulatory science to 2025 strategy, one of the dedicated goals is enabling and leveraging research and innovation in regulatory science, i.e. leveraging collaborations between the NCAs and academia to address rapidly emerging regulatory science research questions. Here, the EU-IN Network plays an important role by

(1) identifying emerging and challenging topics relevant to innovative therapies and technologies, flagging issues that need regulatory guidance and support;
(2) promoting collaboration between different stakeholders, including academia, by sharing experience and knowledge;
(3) identifying best practices and facilitating the establishment of new contact points across Europe.

EMA plays an important role in supporting the European framework for clinical research and regulation. The EMA has targeted engagement with academia, learned societies and research groups in a range of areas. In line with this, the Regulatory Science Strategy to 2025 (EMA, 2020) captures the objectives that the EMA must pursue in order to achieve an optimal collaboration with academia:

- Develop network-led partnerships with academic research institutions to undertake important research in strategic areas of regulatory science;
- Leverage collaborations between academic and network scientists to address rapidly emerging regulatory science research questions;
- Identify and enable access to the best expertise across Europe and internationally, including collaboration with the European Reference Networks (ERNs);
- Disseminate and exchange knowledge, expertise and innovation across the network and to its stakeholders.

As of September 2020, an EMA-wide collaboration infrastructure – Academia Collaboration Matrix – has been put into place to enhance collaboration between the Agency and its academia stakeholders. In April 2021, the EMA has published the Academic Collaboration Matrix action plan (EMA, 2021).

Communication and engagement with academic stakeholders are built upon the EMA academia stakeholder database, which is composed of more than 75 academia umbrella organisations, learned societies and health care professional databases to ensure a wide coverage of key academia collaborators in regulatory science.

To best support academic drug developers, a series of tools and facilitation channels have been identified throughout key stages of the regulatory process. Amongst others, those include scientific advice, Innovation Task Force (ITF), qualification of novel methodologies for medicine development, orphan designation, PRIority Medicines (PRIME) etc.

Scientific advice and qualification advice is considered as one of the most appropriate ways to reach out to academic developers and support the timely and efficient development of high quality, effective and safe medicinal products for the benefit of patients. Especially, scientific advice is useful for developers of innovative medicinal products where existing scientific guidelines might provide insufficient support.

Early interaction with the regulators is crucial when it comes to developing promising treatments that can benefit patients with rare diseases. To enhance research and development in this area, the EMA has waived fees for developers when they apply for protocol assistance, a special type of scientific advice for orphan medicinal products.

Furthermore, the EMA participates in externally funded research projects with a view to actively support science in relevant areas and optimize regulatory decision-making, as defined in the EU Medicines Agencies Network Strategy, the EMA work programme and the adopted and published Regulatory Science Strategy to 2025. Such collaborative projects improve awareness of developing areas of science and offer opportunities to influence the strategic regulatory science agenda setting.

EMA staff may play the following roles in externally funded research projects:

- Consortium partner
- Advisory board member
- Routine regulatory interactions e.g. ITF

The EMA is currently involved in 20 public funded or private public funded projects. Most projects are EC funded projects (n=17), of which 11 are Innovative Medicines Initiative (IMI). In most cases the EMA contributes as an advisory board member (n=9) or a consortium partner (n=5).

C National Clinical Research Centres

In addition to the international networks mentioned above, national research infrastructure plays a crucial role in supporting and promoting academic research. Regional clinical research centres have the ability to provide timely assistance in all stages of a clinical trial, from protocol development to data analysis and reporting. Additionally, some of the centres are able to provide legal and regulatory assistance and navigate the developers through the complex process of designing and conducting a clinical trial. Some examples of such supportive national research centres are the German Centre of Infection Research (DZIF, Germany), the Netherlands Cancer Institute (The Netherlands), the AIRC Foundation for Cancer Research (Italy), and the Institute of Experimental and Clinical Research (Belgium). Furthermore, in various member states, national clinical trial support centres were established to specifically provide support for the design, conduct, analysis and publication of clinical trials, and support partnerships between academic researchers and industry. Examples include the Spanish Clinical Research Network (Spain) or the Austrian Clinical Research Infrastructures Network (Austria).

Aside from (large) public clinical research centres or organisations, smaller private research organisations that often originate from academia (spin-off clinical research organisations, CROs) are offering support services to academic developers in setting up and implementing clinical trials as well as providing answers for clinical drug development challenges. Examples of such support organisations are listed in the **STARS Comprehensive Inventory** that was established within the STARS project and is addressed in more details in Chapter 4.

D European Research Infrastructures

Research infrastructures are facilities that provide resources and services for research communities to conduct research and foster innovation. These facilities provide valuable support and mentoring especially for academic researchers who often face difficulties in navigating through the complex regulatory system, or have problems in setting up multinational trials, scaling up manufacturing process and lack easy access to therapy development expertise.

Several prominent examples of such research infrastructures are provided in the table below.

Aside the below mentioned programs, the EC provides support and facilitates implementation of various strategies, networks and tools to support sustainable Research Infrastructures in Europe (https://ec.europa.eu/info/research-and-innovation/strategy/european-research-infrastructures_en).

The European Clinical Research Infrastructure Network **(ECRIN)** **https://ecrin.org/**	Not-for-profit intergovernmental organisation that supports the conduct of multinational clinical trials in Europe, providing tailored support to facilitate trial preparation and implementation. Especially, academic trials can profit from the support in broadening the scope of the research and speeding up the development.
European Organisation for Research and Treatment of Cancer **(EORTC)** **https://www.eortc.org/**	Academic, independent, non-profit organisation under Belgian law supporting clinical studies that evaluate new medicinal products for potential registration, conducted in partnership with commercial organisations.
European Infrastructure For Translational Medicine **(EATRIS)** **https://eatris.eu/**	Non-profit European research infrastructure consortium designed to help researchers strengthen the translational potential of their research proposals by providing access to the entire pipeline of academic translational infrastructure and expertise, optimising the route from discovery to proof-of-concept in medicines development. It provides support for advancing biomedical innovations, facilitates academic collaborations with industry, and provides legal and regulatory support and partnering advice.
International Rare Diseases Research Consortium **(IRDiRC)** **https://irdirc.org/**	Consortium that unites national and international governmental and non-profit funding bodies, companies, umbrella patient advocacy organisations, and scientific researchers to promote international collaboration and advance rare diseases research worldwide.
European Strategy Forum on Research Infrastructures **(ESFRI)** **https://www.esfri.eu/**	Non-profit European research infrastructure consortium designed to facilitate the joint establishment and operation of research infrastructures of European interest.
European & Developing Countries Clinical Trials Partnership **(EDCTP)** **https://www.edctp.org/**	Public-public partnership between countries in Europe and sub-Saharan Africa to accelerate the development of new or improved medical interventions for the identification, treatment and prevention of poverty-related infectious diseases through all phases of clinical trials.

E European Funders of Clinical Research

The EU plays a central role in supporting and coordinating innovative research, fostering cooperation and knowledge sharing between different partners. Two of the largest EU funding programmes for research and innovation, Horizon 2020 and Horizon Europe, provide funding for multi-national collaboration projects as well as for individual (academic) researchers or SMEs. Through international collaboration, the EU funding programs aim to make sure that Europe's promising ideas get from the laboratory to the market, solving some of society's biggest challenges.

Another large European funding initiative is the Innovative Medicines Initiative (IMI) that forms a basis for public-private partnership (PPP) in life sciences. Through PPP, academic researchers and SMEs gain access to research funding, and at the same time can benefit from the expertise of pharmaceutical companies and from the opportunity to translate scientific discoveries into useful tools, thereby advancing the development of medicines. Going forward the Innovative Health Initiative is intended to build on the work of IMI.

European (academic) researchers can also profit from various global funding initiatives, such as Wellcome Trust that provides funding and collaborative opportunities for research and innovation in the areas of mental health, infectious disease and climate & health or the Bill & Melinda Gates Foundation that invests in the discovery and translation of innovative solutions to global health and development inequity.

Besides these largest European and global funding organisations, there are various national, private or public charity organisations and funders aiming to help academic researchers, as well as SMEs to turn promising science into benefits for patients. Some of these funding organisations (36 funders in 27 European countries) united into the Science Europe to optimize cross-border collaboration and to improve Europe's research landscape. Furthermore, various (academic) research institutions have put in place funding programs to support local researchers.

Utilization of the offered support tools

Despite the variety of the support tools available on European or national levels for drug developers, their utilization by academia remains limited, as indicative from four survey studies performed by STARS (manuscript submitted in 2022). Please refer to Chapter 3 for further details.

The Need to Strengthen Regulatory Science in Academia

Challenges in Translation – the "Valley of Death"

Innovative ideas and developments often take root in academia (Bryans et al., 2019; Cleary et al., 2020). However, translation of these ideas and findings into therapeutic advances lags behind (Sayhan, 2019). This translation gap, often being referred to as the "valley of death", has been unanimously acknowledged by stakeholders who consistently seek means to address it. Attrition rates have been reported to be as high as 96% in the recent years and are accompanied by inflating costs. Therefore, efforts to reduce attrition rates became a subject of urgency, striving to bringing effective medicines to patients faster, while containing escalating drug development costs and making medicines more affordable (Hammel and Michel, 2019; Schäfer and Kolkhof, 2008).

Reasons for the translation gap in drug discovery are heterogeneous and complex, starting from a poor hypothesis, problems of reproducibility of pre-clinical results, poor external validity of pre-clinical models and lack of representative animal models (Hingorani et al., 2019; Sayhan, 2019).

In the clinical phase of the development, methodological issues, poor patient recruitment and lack of financial and executional resources were identified to be critical factors (Fogel, 2018). Intrinsic factors, such as lack of organisational, technical and regulatory expertise are also identified as barriers for translational science (Parrish et al., 2019).

While industry usually possesses the needed regulatory and translational knowledge, academic researchers struggle with the complex regulatory framework and steps required to advance a promising discovery to the clinic (Gilliland et al., 2016; McGowran and Harris, 2020; Rath et al., 2020). Especially, development of innovative advanced medicines and technologies is particularly challenging and is characterized by extremely low success rates (de Wilde et al., 2016; Salvatore, 2020). Here, insufficient institutional and organizational support for translational science in academia and poor incentives for academics to start the journey to product commercialization have been mentioned as one of the limiting factors (Higham, 2019; Sayhan, 2019).

Furthermore, aside from all the scientific hurdles and considerations, legal issues, such as intellectual property rights which are especially relevant in the field of drug repurposing, may sometimes play a detrimental role for the drug candidate's success (Pushpakom et al., 2019; Breckenridge and Jacob, 2019; Asker-Hagelberg et al., 2022).

Altogether, translation of discoveries into approved medicinal products is a challenging process with numerous requirements and aspects that need to be considered to move forward (Mohs and Greig, 2017). Here, the regulatory framework is an important element, playing a role of a gatekeeper by setting efficacy and safety requirements that need to be met for medicinal product to enter the market. Knowledge and understanding of regulatory aspects can help to increase the efficiency and success of the development program. **Therefore, strengthening regulatory knowledge among developers, especially in academia, is considered essential to foster innovation and successful translation of new products and technologies to the market** (Harris and O'Reilly, 2020, Starokozhko et al., 2021).

Best Practice and Gaps Identified by STARS

In order to strengthen the regulatory knowledge of academic scientists involved in drug development and clinical research, the STARS consortium delved into gaps that affect the process or limit the chance of promising academic innovations reaching patients.

Recognizing the achievements and the key role of academia in fundamental research, the intention of the STARS consortium is, among others, to map best practices and facilitate their implementation Europe-wide, in order to harmonise and strengthen the system for the benefit of patients. The aim was to make the European environment for the development of medicines more attractive and competitive.

Considering that academia, funding bodies and regulators all have key roles in academic clinical research related to the development of medicinal products, the consortium performed a set of surveys to analyse activities, gaps and best practices

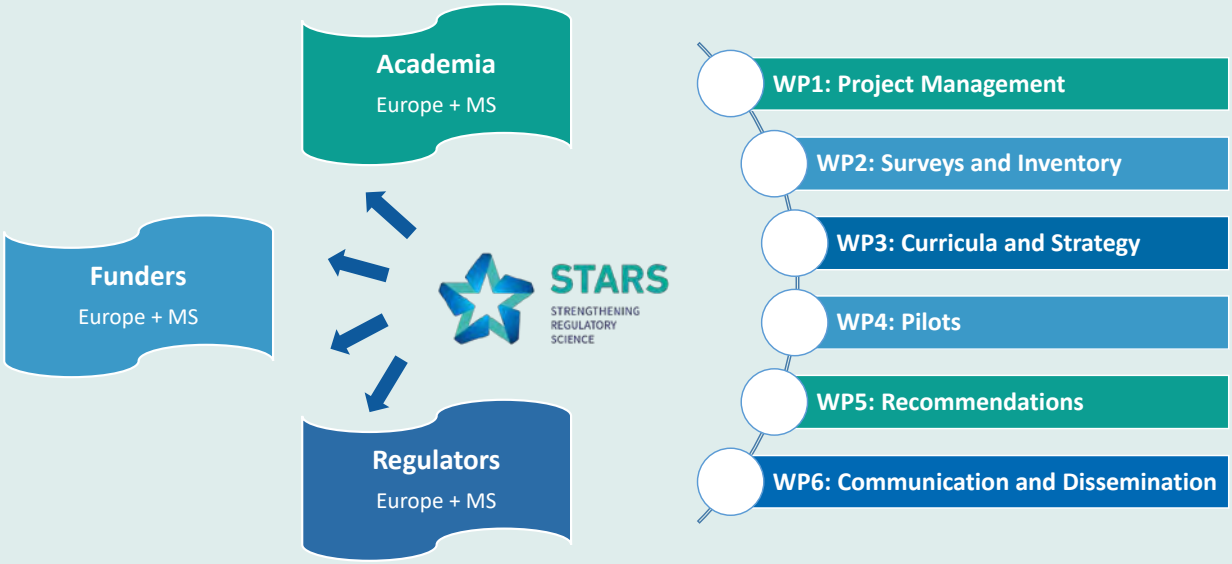


Figure 3.1: Overview of the major stakeholder's interaction and the working program of STARS (MS = member state, WP = work package).

in the current regulatory network. These analyses were the basis for all STARS activities within the work packages defined (Figure 3.1).

Academia

In order to investigate the level of regulatory awareness, knowledge, attitude and approaches of the stakeholders in relation to academic clinical research and regulatory science, STARS launched a survey among European academia in 2019. In total, 449 academic health research groups and 88 health research centres participated in the survey.

The analysis indicated that the surveys sent out to the academic health research centres, reached mostly senior level target audiences working at academic health research units focused on interventional clinical studies, non-interventional studies and basic biomedical research in 2014-2018.

Interestingly, the awareness among academia of regulatory supports offered by NCAs is moderate. In total, 59% and 71% of the respondent research centres were aware of EMA's and NCAs' regulatory supports, respectively. Among research groups, a lower level of awareness was found: 34% are aware of the regulatory supports offered by EMA and 47% are familiar with the NCAs' support services. Responders indicated that the best known service formats were the web-based offerings such as document templates, Q&A pages and guidelines. **STARS identified the necessity to increase awareness of regulatory support activities among academic researchers and research centres.**

Secondly, an inadequate level of regulatory knowledge was identified in both the research groups and research centres. This finding relates closely to other results of the STARS survey indicating that designing clinical trials and preparing regulatory applications as well as reporting procedures during studies are the biggest challenges for academia in regulatory affairs. **More targeted and effective support for regulatory requirements for clinical trial design, the application process, and reporting requirements could facilitate academic research towards the later phases of product development and ultimately an authorised medicine.**

The results also showed that communication between the authorities and academia could be improved in terms of quantity and quality, which would lead to a better understanding between both sides in complex matters. The consortium pointed out that lack of common terminology and the regulatory terms and abbreviations used in the communication by the authorities represent a source for misunderstanding among regulators and academia. **A glossary on NCA webpages that explains the regulatory vocabulary and abbreviations in a simple manner would support communication with stakeholders. The dissemination of such a glossary could be via academic research centres. Furthermore, regulators should – wherever possible – avoid using regulatory jargon and abbreviations when communicating with academic researcher.**

Funding Bodies

Academic research is generally funded by programmes sustained by funding bodies that could be a pivotal stakeholder in strengthening regulatory science. Based on this premise, STARS surveyed 40 funding bodies with the aim of collecting information in relation to the dialogue between funding bodies and regulatory experts/NCAs. Moreover, the consortium was interested to ascertain the extent to which regulatory aspects are considered in the grant application processes and funding decisions.

The analysis highlighted that funding bodies mainly fund pre-clinical research, basic biomedical research and first-in-human/phase I studies. In the category of clinical studies, the highest priority for funding bodies are the interventional studies. Notably, funding bodies rarely require regulatory

documents in support of the grant application. Nonetheless, more than half of the funding bodies usually accept the inclusion of regulatory service fees in the project budget. The level of interaction between funding bodies and regulatory authorities is limited and where it takes place it is mainly for issues related to general regulatory topics, regulatory documents and feasibility of study design.

Finally, the analysis indicated that only half of the funding body respondents envisaged the necessity to consider regulatory matters as part of the grant approval procedure. **The STARS consortium identified a need for regulators to increase interactions with funding bodies and grant evaluators, by providing the option for public funding agencies to get advice directly from regulatory authorities via the innovation offices.**

NCAs and EMA: Support Activities for Academia

In order to complete the analysis about activities, gaps and best practices, STARS launched a survey to 21 European NCAs and EMA in 2019.

Early interaction with regulators would support academia to understand the regulatory requirements to generate robust evidence needed to establish a benefit-risk-analysis of a new or adapted medicinal product.

In this regard, the STARS survey collected information about (i) available regulatory support for academia, (ii) the current regulatory knowledge of academic sponsors, (iii) and regulators' experiences during support activities directed to academia.

The survey analysis highlighted a consensus in relation to the need to support academia in order to boost research and accelerate drug discovery. Indeed, several support activities, such as scientific advice, qualification procedures and innovation meetings have been implemented by the majority of European NCAs and the EMA. Despite the range of support options offered, the STARS consortium revealed that academia uses these less frequently when compared with industry and SMEs.

Among the offered support activities, scientific advice represents a valuable tool in providing information on quality, non-clinical and clinical development, thus providing a road map for research and development. Interestingly, the survey indicated an increasing number of requests for scientific advice submitted by academic institutions in the time period between 2014 and 2018. However, the level of such requests remained suboptimal despite reduced fees or in some cases free of charge access. As an example, in 2018 nearly 50% of the scientific advice procedures issued by all the NCAs were given to multinational pharmaceutical enterprises whereas only 5% were given to universities, 2.5% to research institutes and 4.4% to university hospitals. NCAs identified a lack of common terminology, lack of awareness of regulatory requirements and a hesitancy to seek support as the main obstacles faced by academia when considering scientific advice. The regulatory preparedness of academic research was evaluated as deficient, indicating **the need to reinforce regulatory training programmes tailored for academia.**

It has been highlighted that academia is highly interested in receiving support for topics related to their routine activity (i.e., good clinical practice and clinical study statistics). Conversely, limited interest was observed towards developing a general understanding of the entire regulatory landscape. A more general understanding of regulatory requirements and hurdles would help academia to understand how the findings of their clinical research could be translated into a product eligible for authorisation. As mentioned earlier, a wide range of support activities other than scientific advice are also offered by regulators, especially relating to clinical studies, pharmacovigilance and regulatory procedures. Moreover, the STARS consortium has noticed that regulators wish to overcome this limitation and ensure that advice is available to academia on topics related to the entire medicinal lifecycle.

Notably, innovation meetings represent a widespread and valuable tool for NCAs to support the academia in the earlier stages of development as attested by the number of innovation offices established in recent years in the regulatory agencies. Hence, STARS highlights **a need to more closely align the training needs of academia with the supports offered by regulators, and for regulators to develop more comprehensive services to inform about all regulatory requirements.** In order to facilitate academia in overcoming barriers that limit translational research and to navigate academia through the regulatory framework, these issues need to be urgently addressed.

It has been noted that NCAs have been already supported by external representatives of EMA's working parties and committees, industry, scientific associations and patients' organisations in delivering existing support activities. Their role in the development of new support activities and/or the optimisation of existing supports could be carefully discussed. A plethora of regulatory forums/stakeholders might play a more comprehensive role in supporting academia through the medicinal product development. Representatives of EMA's working parties and committees, and scientific associations could be involved in training activities offered to academia. Patient representatives' involvement for instance could be encouraged to help and ensure that clinical research also considers the needs of patients. STARS envisages a **multidisciplinary approach and an exchange of competences and experiences for an advanced dialogue with academia.**

Overall, the identified gaps and barriers can be summarised as follows:

- lack of awareness and use of NCA supports by academia;
- lack of common terminology in communication leading to differences in understanding;
- insufficient regulatory knowledge and a sub-optimal alignment of regulatory supports with the needs of academia.

To overcome the identified barriers and on the basis of the performed analysis, STARS has identified five pillars that need to be urgently implemented:

1. Promoting **pro-active engagement** between regulators and academia. More time and resources should be dedicated to creation and provision of methods and channels that allow regulators to actively reach out to academia, in order **to present and advertise the authority's regulatory support.**

2. Defining the new concept of **"train the trainers".** Regulators should aim at providing a **cascade training** to local representatives of clinical trial centres and/or innovation hubs. A cascade training could be encouraged and promoted within academic settings since academic researchers identified that support available from local organisations such as research centres or innovation hubs are the most important and practical source of information. Such a training could be more easily sustained by NCAs considering their resource constraints and the diverse nature of the target audience.

3. Here, the dialogue between academia and regulators has been analysed only in terms of role and activities of more advanced health researchers. However, graduate and post-graduate students represent not only important actors in the academic landscape, but are also the next generation personnel for the health systems. For this reason, STARS also aims at strengthening the **education of students on regulatory affairs.** The survey analysis has revealed that almost half of the European regulators already offer training activities to graduate and post-graduate students, mainly in the form of lectures and internships. Surveyed NCAs stated a necessity to cover a broader variety of themes than currently provided. To this end, the STARS consortium **provides a curricula on regulatory training for academic students, researches and healthcare professionals** (see Chapter 4).

4. NCAs consider their websites as a primary source for updated information material, guidelines and legislation. According to regulators, such materials help to meet the information needs of academia. In turn, also academia has indicated that NCA websites are one of their primary sources of information and are extensively consulted. Therefore, NCAs should look for **further optimization of the web-based support,** e.g. implement a **one stop shop** to assist academia during the whole product lifecycle including development, quality, non-clinical, clinical and finally HTA aspects, when appropriate and if in the NCA's remit.

5. To provide very early support in drug development to academia, **STARS envisages a new format for regulatory advice: Pre-grant scientific regulatory advice** (PGRSA) is proposed to evaluate project specific regulatory requirements and possible regulatory challenges before/during the grant application preparation. The aim is that NCAs provide to both the applicants and the funding institutions an assessment of the possibilities to develop a safe and effective approach from "bench to bedside" based on regulatory standards (see Chapter 4).

Opportunities for Strengthening Regulatory Science: Activities of CSA STARS

Aims and Activities of the CSA STARS

The purpose of STARS is to systematically develop and implement regulatory support tailored for academia, reaching from new advice concepts to training programs in a coordinated European approach. The aim is to improve regulatory knowledge about the complete product life cycle as a substantial part of the training of academic researchers as well as an integrated part of scientific research in daily work. The concept focusses on bridging academia research and regulatory considerations and includes all relevant stakeholders. The main idea is to provide regulatory support to academia for innovative pharmaceutical developments as early as possible and pave the way for these developments from bench to bedside. The transfer into practice is based on comprehensive survey data as well as two stakeholder workshops, which have been conducted to gain more information about the availability of and demand for regulatory support activities, as well as on pilots that aim to transfer and implement best practice approaches of the concepts developed as shown subsequently.

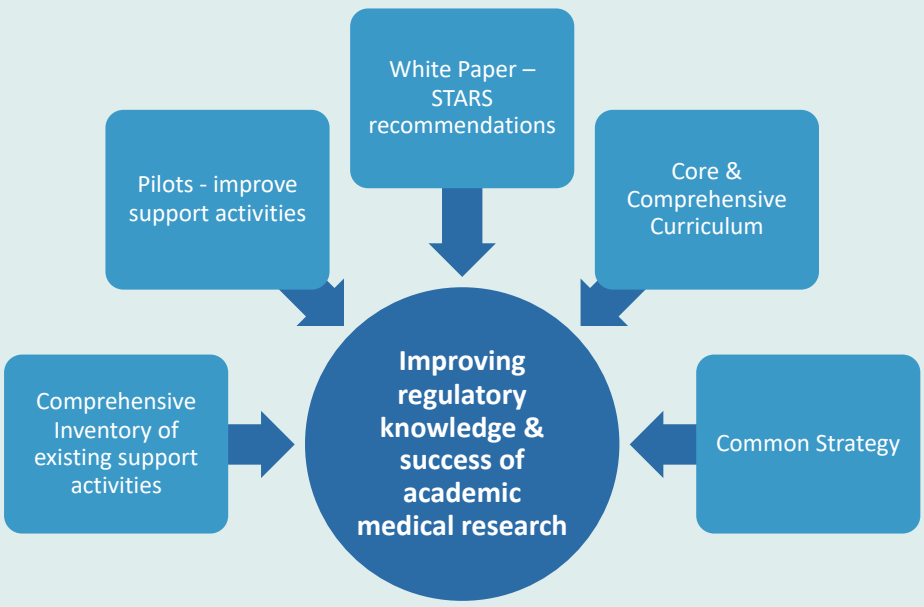
The following sections describe the activities which have been conducted during 2019 and 2022. The concept of the

activities are based on comprehensive surveys (see Chapter 3) which were carried out in the beginning of the STARS project.

Comprehensive Inventory

One aim of STARS is to collect and disseminate information about available regulatory supports for academic drug developers in Europe. To this end, STARS has established a Comprehensive Inventory in which various regulatory support services provided by NCAs, public actors and private

Figure 4.1: Working program of STARS with five major outcomes, which have a direct impact on the improvement of regulatory knowledge and success of academic medical research.



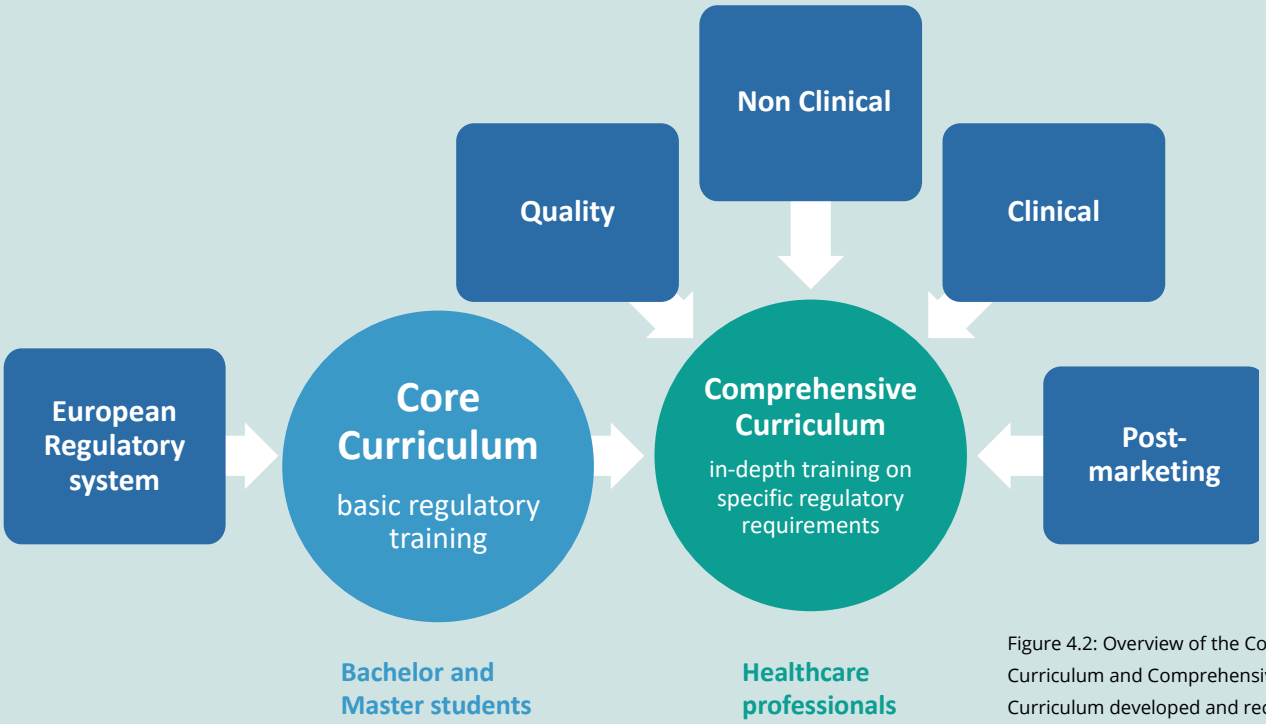


Figure 4.2: Overview of the Core Curriculum and Comprehensive Curriculum developed and recommended by the STARS consortium.

entities are listed. The inventory is published on the STARS website and it can be filtered by country, expertise area and support scope via an easy-to-use search function. The content of the inventory is based on the data collected via the STARS surveys. However, all stakeholders are encouraged to contact the STARS consortium if they have information about existing regulatory support services which are not yet in the inventory. Prior to the end of the STARS project, the consortium aims to identify a host organisation for sustaining the regular updating and the web presence of the comprehensive inventory.

STARS Curricula

To overcome the regulatory knowledge gaps, the STARS consortium developed a curriculum to strengthen the awareness of regulatory science in academia, on the basis of the previously mentioned activities and survey data within the STARS project. The focus was on the development of a **Core Curriculum (CoC)** dedicated to basic regulatory training, and a **Comprehensive Curriculum (CpC)** focused on a more in-depth training on specific regulatory requirements. The curricula concept has been conceived as guidance to achieve a harmonised and common level of regulatory knowledge in academia in the near future. The STARS consortium is not teaching the curricula. The curricula are considered as a superordinate recommendation for an EU-harmonized concept. It is addressed to universities or post-graduate courses in the EU member states. The STARS curricula do not aim to substitute or replace any existing European curricula, and the curricula can be adapted to the different needs and requirements of the respective national education systems of the European member states.

The implementation of the curricula will improve the translation of the research outcomes increasing knowledge and the likelihood of successful development and approval of a new medicinal product/technology and ultimately facilitate their use in clinical practice.

In general, the two curricula share fundamental perspectives in accordance with the STARS principles:

- **Science driven:** topics, gaps, and challenges should be discussed considering the scientific rationale of a research project.
- **Multidisciplinary/multistakeholder:** regulatory science needs open dialogue, communication and collaboration between regulators and medicinal products/technologies developers to identify regulatory challenges, possible gaps, and critical issues in the product development as early as possible. The successful outcome of an improved regulatory dialogue among academia and regulators is especially needed when it comes to the development of a novel medicinal product/technology to facilitate translation of a research finding into clinical practice.
- **Exchange of experience and competences:** the curricula are a chance and an occasion for continuous and bidirectional learning, as well as for improving the knowledge of new regulations. Established knowledge exchange, where academia receive training on regulatory aspects and regulators learn about the most recent methodologies, tools and technologies from academia can be mutually beneficial for both parties.
- **Open discussion:** open discussions between regulators and health researchers in academia about case studies, projects and regulatory challenges emerging from scientific development allow the developement of greater knowledge in regulatory sciences.

The STARS consortium has published an accompanying document with more background on the development of the curricula as well as detailed information on learning outcomes. The document is published on the STARS website.

The developed curricula offers recommendations for the contents and learning outcomes (LOs) to be considered in implementing training activities in academia. The STARS consortium envisages that individual universities could develop their own course based on the curricula contents and LOs. STARS endorses partnerships between universities and national and/or European academic networks focussing on academic research in (bio)medical science in order to deliver and organise the courses.

In relation to the NCA role, STARS encourages the European regulatory agencies in taking an active role in supporting national academia to develop and implement a curriculum in regulatory science. Several actions could be taken by NCAs to promote training of academia in regulatory science balancing the level of involvement in accordance to their own capacity (i.e. human capability, policy). STARS envisages a network of NCAs that could actively offer training activities and/or mutual support in training. Through the network, NCAs could facilitate the exchange of training experts and materials among the participants and establish collaborations. Harmonisation of activities and networking across NCAs seems to be a key element for sharing and continuously updating tools and resources thus allowing academia training capacity and sustainability in the future.

STARS recommends to consider the "train the trainers" concept in order to reach a wider target, especially where an expertise centre for consultations at universities is established.

The Core Curriculum

The Core Curriculum is mainly targeted at graduate students (bachelor and master's degree) interested in regulatory science and in gaining **basic knowledge/training** of European regulations on medicinal products and borderline between medicines and medical devices. This Core Curriculum aims to provide attendees an overview of regulatory science and the regulatory system in Europe, giving an overview of development pathways, the EU legislation and the use of guidelines, with an introduction on the core parts of a clinical trial application and marketing authorization application (quality, non-clinical and clinical) and on the post-marketing processes.

Universities will provide graduates with key regulatory knowledge to enrich their professional education for a future position in different areas, such as drug research and development, regulatory authorities for medicinal products, as well as the pharmaceutical industry.

The Comprehensive Curriculum

With the rapid expansion of pharmaceutical and biomedical products and increasing complexity of innovative technologies and products, more highly skilled professionals who have the expertise to conduct research in compliance with complex regulatory policies and challenging procedures are needed. The Comprehensive Curriculum is designed for an **advanced training level** to acquire more in-depth knowledge in regulatory science and to gain more information on different and especially innovative regulatory areas with the overarching goal to successfully develop novel medicinal products and technologies for patients. The target audiences are researchers and healthcare professionals involved in medicinal development.

This course will provide an overview of legislation, tools, approaches, standards and latest guidelines that are essential to develop innovative medicinal products with the required level of quality, safety, and efficacy to be marketed within the EU. This specialised education is crucial for professionals to develop a comprehensive understanding of the appropriate regulatory requirements related to their specific field of interest and of the timely use of the NCA support activities during the product development. Hence, professionals will be

STARS Core Curriculum in Regulatory Science

European regulatory system

- EU regulatory bodies and their roles/activities
- Pharmaceutical legal framework
- Pharmacovigilance in EU
- Regulatory activities of EMA and NCAs in support of innovation, research and product development
- Phases of clinical trials and the level of quality/non-clinical/clinical evidence required
- EU marketing authorization procedures
- Early access tools
- Post-marketing phase
- Medicines and medical devices

STARS Comprehensive Curriculum in Regulatory Science

Module – Quality

- Principles and guidelines applying to the pharmaceutical development
- The specific regulatory framework to address quality requirements in the relevant field of study, considering those which are particular to the specific product of interest
- Quality requirements for investigational medicinal products
- CTD modules 1, 2 and 3
- EU legal framework and national implementation of GMP, role and scope of GMP inspections
- European pharmacopeia structure and relevant monographs
- From assessment to product information

Module – Non-Clinical

- Principles and guidelines applied to the non-clinical development
- CTD modules 1, 2 and 4
- Proof of principle: in vitro and in vivo studies addressing PD activity
- Pre-clinical studies to support first in human (FIH) study
- Establishing the clinical dose
- Non-clinical studies to support MAA
- Importance of animal species selection
- Alternative approaches to animal model
- Basic principles of GLP
- Basic principles of environmental risk assessment
- Studies in juvenile animals to support paediatric use
- Regulatory and scientific requirements for non-clinical development
- Integration of non-clinical results with quality and clinical data
- From assessment to product information

Module – Clinical

- Clinical trial legislation in the EU, GCP, declaration of Helsinki and ethical principles, relevant guidelines
- CTA
- EU clinical trials information system
- Pharmacovigilance in clinical trials
- Overview of scientific guidelines
- CTD modules 1, 2 and 5
- Structure and content of clinical study report
- Real word data and patient registries
- Paediatric medicines
- Orphan medicines
- ATMPs
- Vaccines
- Biosimilars, generics and hybrid applications
- From assessment to product information

Module – Post-marketing surveillance

- Pharmacovigilance legislation, GVP, relevant guidelines
- Collection and management of suspected adverse reactions
- Risk Management Plan
- PASS, PAES and other post-authorisation activities
- Risk Minimisation Measures
- Pharmacovigilance systems
- Signal management
- Overview and assessment of PSURs
- Referrals for safety reasons
- Renewals and annual re-assessment
- Safety communication

Figure 4.3: STARS Comprehensive Curriculum in Regulatory Science. Abbreviations: ATMP – Advanced therapy medicinal products, CTA – Clinical trial application, CTD – Common technical document, GCP – Good clinical practice, GLP – Good laboratory practice, GMP – Good manufacturing practice, GVP – Good pharmacovigilance practice, MAA – Marketing authorisation applications, PAES – Post-authorisation efficacy study, PASS – Post-authorisation safety study, PD – Pharmacodynamics, PSUR – Periodic safety update reports.

trained to identify and interpret the regulatory framework as well as specific guidelines that will be crucial in driving forward their research to develop a medicinal product.

The Comprehensive Curriculum focuses on the five main areas/milestones in the medicinal product lifecycle: 1) European Regulatory system; 2) Quality; 3) Non-clinical; 4) Clinical; (5) Post-Marketing Surveillance. More details on contents and learning outcomes of the curricula are available on the STARS website in an accompanying document.

STARS Pilots

In order to provide a proof-of-concept and to demonstrate that selected support activities and elements work efficiently, the STARS consortium has performed three pilots.

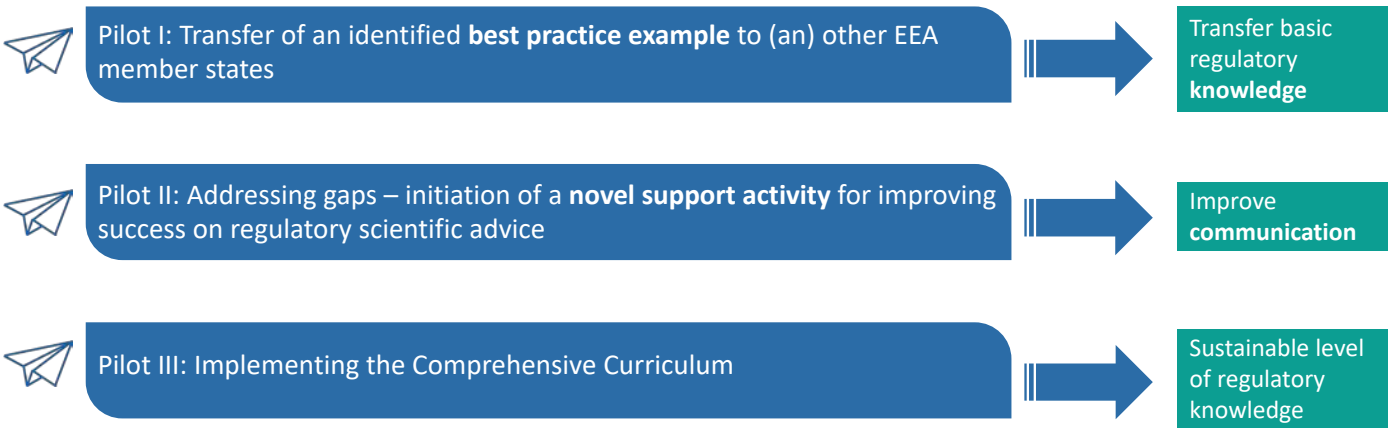


Figure 4.4: The three STARS pilots.

Pilot I: Transfer of a Best Practice Example

The aim of Pilot I was to transfer a best practice example for regulatory support and guidance to academia to (an)other EEA member state. The identification of the best practice example was based on the analysis of a surveys to academic researchers and NCAs.

The analysis of the academic survey data revealed that many the researchers seek to increase their regulatory knowledge in relation to clinical trial design as well as general regulatory matters. Therefore, it was decided to address this unmet need by incorporating a **short term, basic training on essential regulatory knowledge** as part of Pilot I. The figure below shows the concept of the pilot (Chapter 3).

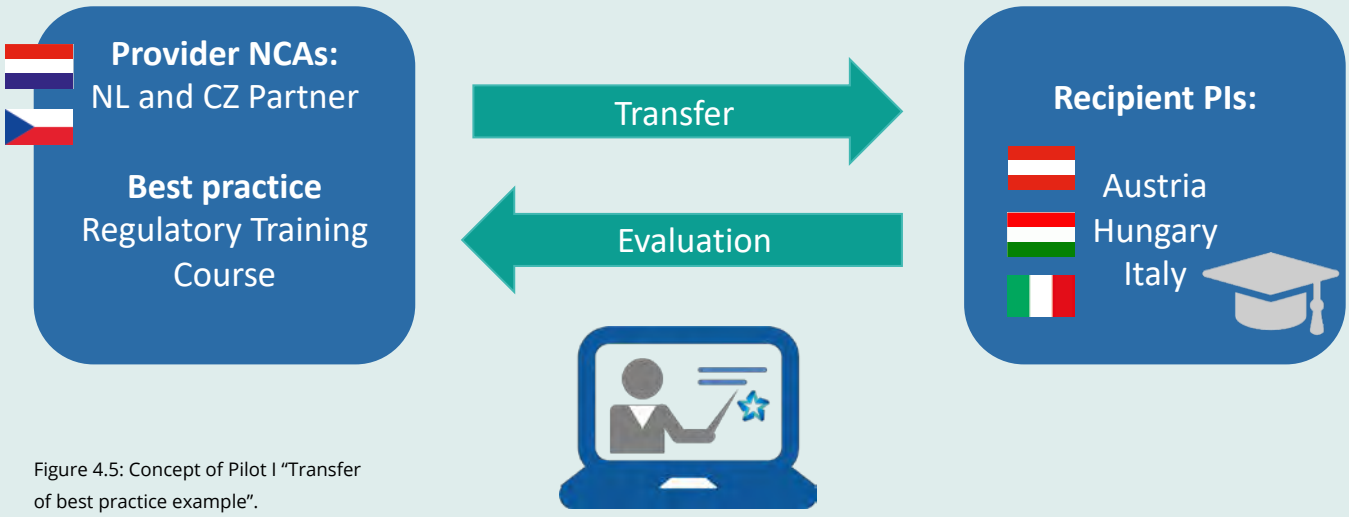


Figure 4.5: Concept of Pilot I "Transfer of best practice example".

The objectives of the training were defined as follows:

- to cover clinical, non-clinical and quality aspects relating to all important steps in drug development – from laboratory practice to clinical applications
- to introduce national and European regulatory frameworks and give an overview of regulatory support tools for academia
- to give the opportunity to interact with regulators and ask questions.

Based on the survey data, a number of NCAs (FAMHP in Belgium, HALMED in Croatia, HPRA in Ireland, INFARMED in Portugal, MEB in the Netherlands, and SUKL in the Czech Republic) were requested to provide information on existing support activities related to the identified objectives. As a result of the review of the responses and engagement with the NCAs, SUKL and MEB were selected to provide the training as part of Pilot I. Prior to the course, the STARS consortium validated the scripts of the lectures. Due to the Covid-19 pandemic situation it was decided to offer the training via webinar (4 hours per day on 4 consecutive days).

The recipient countries were selected in an elaborated process based on the survey results which showed limited awareness of regulatory support tools and difficulties in reaching a sufficient level of regulatory knowledge in scientific research. As a result, Austria, Hungary and Italy agreed to participate in the Pilot I. Subsequently, Austrian, Italian and Hungarian researchers were invited to the training, including, but not limited to the principal investigators (PIs) who participated in the STARS surveys. Registration for the course was subject to completion of a feedback questionnaire for evaluation of the pilot.

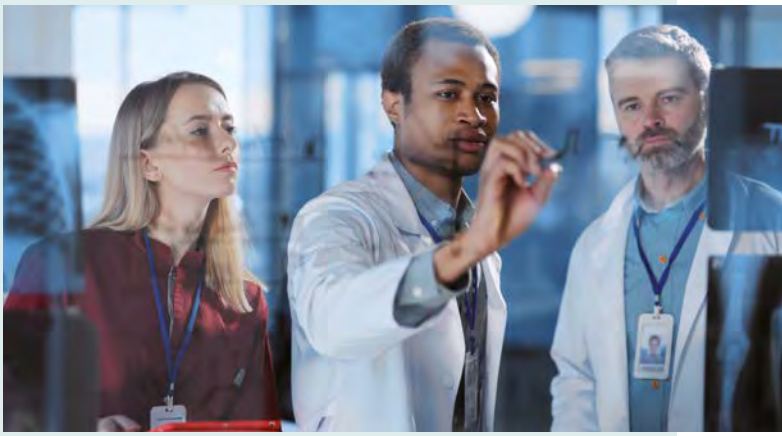
Results of Pilot I

The registration was filled by 174 researchers in total (69 from Italy, 50 from Hungary, 39 from Austria, and 21 from the Czech Republic). The institutional background was balanced between academic researcher centres (27%), university hospitals (25%), and non-profit organizations (20%). Almost a half (45%) were involved in applied research, 14% in fundamental research and 26% percent in both. More than half of the registered PIs have less than 15 years research experience, 46% have already filled in a clinical trial application (CTA) form, and 36% have defined their level of regulatory knowledge as average. More than half of the participants (61%) have never contacted the NCA or EMA. Half of them have heard about ATMPs, 44% of them are familiar only with GCP, 10% only with GLP, 5% only with GMP and 41% with more than 1 of these.

The number of training attendees ranged between 80 and 120 per day. The post-training evaluation questionnaire was filled in by 52 participants. The majority of the participants who rated the course gave a rating of 8 or 9 out of 10 points. The course was rated useful for almost all participants (n=51). The length, the language and online platform of the presentation was mostly satisfactory. E.g., 42 participants rated the length of the course very appropriate and 10 participants rated the course as too short. **Almost all of the participants (94%) would recommend the course for other colleagues.**

Pilot I Conclusions

According to the evaluation of the survey based on the results of the all responses, it can be concluded that the audience was satisfied with the Pilot I in all respects (content, length and format). Based on the high number of Pilot I participants, the importance and relevance of this course is well supported. According to the feedback its content and format was also well established, although it could be fine-tuned, by having it as a regular training, going into more details, with more interactive elements and having it in the native language.



Pilot II: Initiation of a Novel Support Activity

The objective of the Pilot II was to identify a gap which required the establishment of a new support activity with a substantial impact on academic driven health research and a potential to provide benefit for patients.

Analogous to the above described Pilot I, the selection for the topic of the second Pilot II was based on the results of the surveys (Chapter 3).

In total, data from 449 academic health research groups, 88 health research centres, 40 funding bodies and 21 NCAs were analysed with a view to best practices and gaps in the level of regulatory awareness, knowledge, attitude, and approaches of the stakeholders in relation to academic clinical research and regulatory science.

The comprehensive data analysis revealed that there is a need in the academic community for tools to **improve the communication** between regulators and academia, and that timely response is probably the most significant need.

The novel support activity regarding communication tools was designed as **a one-stop-shop** for academic and clinical researchers in Spain. The one-stop-shop provided a collection of general contents, documents and guidelines but also a platform to submit queries to the Spanish NCA, to be forwarded to the best available expert resource within the EU-IN Network, if needed. The overall objective of the one-stop-shop was to provide a low-threshold contact point, to facilitate informal exchange of information and regulatory guidance in the development process, and by this to complement and reinforce established formal regulatory advice procedures (like national scientific advice and innovation office meetings), in order to improve the direct regulatory impact of results obtained in academic medical research.

The pilot took place in September 2021. The one-stop-shop platform was set up as a subsite of the STARS webpage.

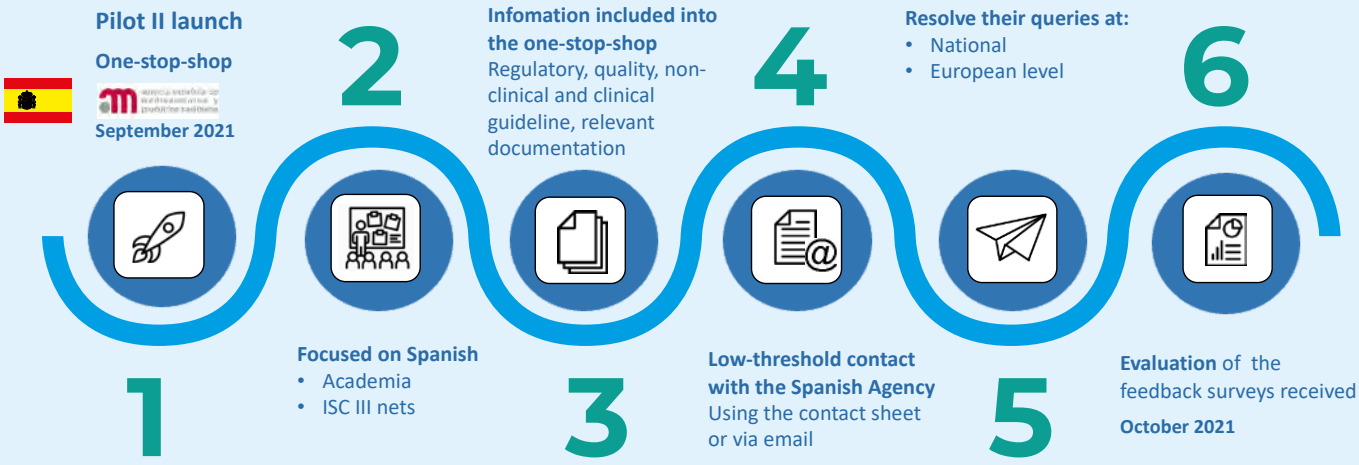


Figure 4.6: Workflow of Pilot II – Initiation of a one-stop-shop as novel support activity.

Structure of the one-stop-shop:

- **Explanation Board:** The explanation board included general background information about the STARS project and about the pilot project. It also included the official invitation letter for the researchers in English and Spanish.

- **Information Board:** The information board included multiple regulatory documents and requirements for the regulatory approval in Spain and in Europe. Thus, researchers were able to get all regulatory relevant information in just "one stop". Researchers were able to download these documents and to solve open questions. If questions were not solved by reviewing the information shared, researchers were invited to use the Communication Board to directly contact AEMPS via contact sheet or email.

The regulations, directives, guidelines, etc. included were as follows:

- Regulatory guidelines and legislation
- Quality Guidelines (Chemistry)
- Quality Guidelines (Biologics)
- Planning of Clinical Trials
- Non-Clinical Guidelines
- Clinical Guidelines

- **Communication Board:** The communication board included an interactive PDF contact form. Spanish academia were invited to fill out the form and to send it to the Spanish Agency to ask questions about regulatory, technical and scientific issues arising from innovative medicinal product development, new technologies, and borderline products. The queries were coordinated by the innovation office at AEMPS and if needed, they were forwarded to regulatory experts at national or European level.

- **Feedback Board:** The researcher's feedback was very important for evaluation and success of Pilot II. Here, we asked the participants to fill a short questionnaire about their experience with the platform.

Pilot II Conclusions

The one-stop-shop was a novel and unique support activity. It acted as a low-threshold and easy-to-enter first contact point between researchers and regulators.

The evaluation revealed that 11 queries were sent via the contact form. In total, 10 people participated in the feedback survey. None of the queries required the involvement of experts from the EU-IN network. For one query, input from an expert outside the innovation office was needed.

According to the evaluation of the feedback survey, it can be concluded that the majority of the researchers considered the one-stop-shop as very useful and helpful. The platform was considered as user-friendly. One limitation in the implementation of Pilot II was that the overall user rate was quite low. One explanation might be the time of implementation (September 2021) was too short and too close to the summer break.

Overall, the participants were satisfied with the support provided by the innovation office and with the responses obtained. It was stated that the advice would probably help to reach or to succeed in the next step in their project. The participants of Pilot II were also satisfied with the timelines and they would recommend this service to others. The success of the pilot was also reflected in comments made by the researchers suggesting that the platform should be maintained on a permanent basis.

Pilot III: Implementing the STARS Comprehensive Curriculum

Pilot III represents the first approach towards implementing a Comprehensive Curriculum (for further information about the Comprehensive Curriculum, please refer to page 26) for strengthening regulatory knowledge in academia. As outlined in Chapter 3, the accelerated development of innovative medicinal products and therapies together with the increasing complexity of new technologies and approaches tend to start in academic and non-commercial research institutions. As a key element for successful research it is necessary to bridge the translational gap and train highly skilled professionals in regulatory knowledge to conduct research in compliance with complex regulatory policies and align challenging procedures to regulatory requirements.

For the third pilot, AEMPS as STARS project partner collaborated with relevant Spanish academic post-graduate networks from Carlos III Institute (ISCIII), hospitals and institutions (such as the Spanish Association Against Cancer or the Andalusian Network) in order to implement the Comprehensive Curriculum (see Figure 4.3). Pilot III provided a concise overview of essential regulatory information and knowledge to develop (innovative) medicinal products to bring high quality, safe and efficacious products to the European market.

The format was conceived as an online training programme to provide key entrance for clinical researchers and scientists at different levels of education and regulatory knowledge. They were introduced into the legal framework and scientific guidance and also could learn about the timely use of the NCA support activities during the development of their products.

The online training programme called "Regulatory Support to Spanish Academia from STARS Core to Comprehensive Curriculum" consisted of the Core Curriculum with some information from the other four modules included in the Comprehensive Curriculum (quality module, non-clinical module, clinical module and post-marketing surveillance module) as it is shown in Figure 4.7.

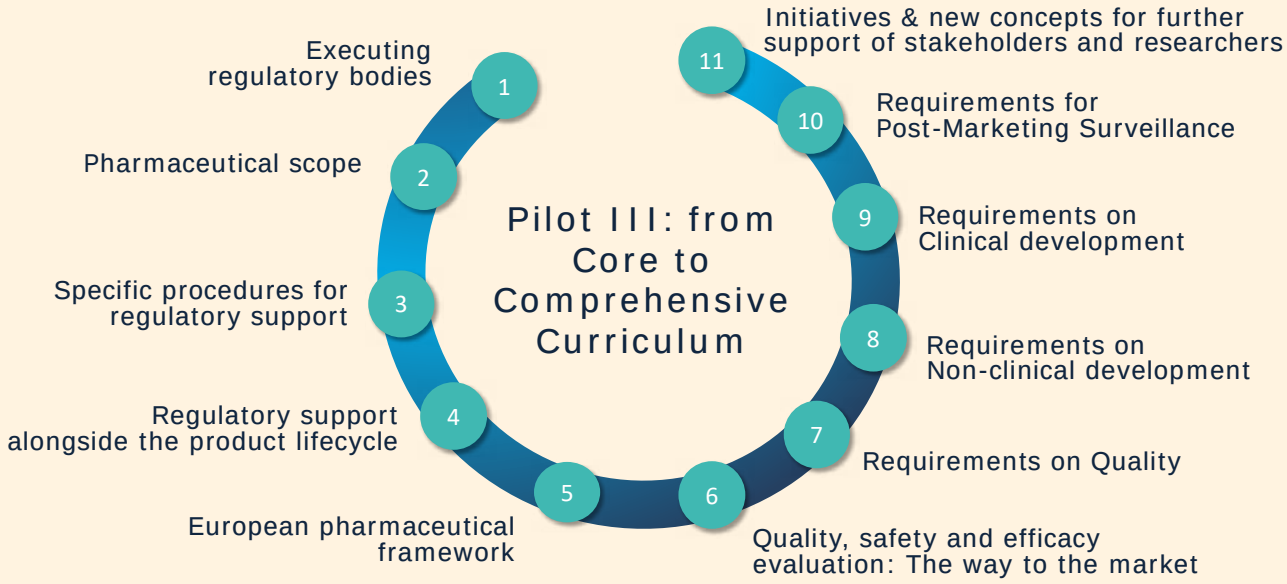


Figure 4.7: Contents of the Pilot III online training programme implemented during the STARS project.

Figure 4.8: Workflow of Pilot III – Implementation of the STARS Comprehensive Curriculum.

Figure 4.8 shows the workflow of Pilot III from the launch until the evaluation of the feedback surveys received in order to evaluate the Pilot. The Innovation Office at the Spanish Agency AEMPS was in charge of it. The overarching goal for the participating researchers and scientists is the successful translation of their research from "bench to bedside" to improve patient care especially with innovative approaches and technologies.

Pilot III was available from 16 February until 16 March 2022 and was free of charge. More information about the Core and the Comprehensive Curriculum is given on page 27.

Results and Conclusions of Pilot III

In total, Pilot III had 1,112 website visits, around 2,000 page views and 689 downloads of different documents. The webpage received numerous visits from different countries, especially from Spain (48.7 %), being the primary target member state. 112 contact forms and 61 feedback surveys from Spanish clinical and academia researchers were received. The important aspect is that this result is closely related to the high number of applicants working in applied research (mostly clinical research, 73 %). Most participants were qualified researchers (77 %), the largest part of them with many years of experience (40 % > 15 years, 37 % > 6 years). This result further provides evidence that disseminating regulatory knowledge is a key driver to improve research and especially translational science.

A special demand existed among researchers to improve their regulatory knowledge in innovative areas, such as ATMPs (38 %). ATMPs is a disruptive area to be taken into account for the future development of the Comprehensive Curriculum.

According to the evaluation of the survey, it clearly confirmed that the information included into the training course enabled the majority of the participants not only to better understand the role of the EU regulatory bodies, but also to identify the current European regulatory system supporting the marketing authorisation and the early access tools. The information provided on regulatory activities of NCAs and EMA in support of innovation, research and product development, was considered essential for the researchers at any time of their developments. The most important aspect was that this regulatory support was seen as crucial not only to save them time, effort and financial resources, but also to accelerate development of safe and efficient new medicines for patient supply in a timely manner. As overall conclusion, the majority of the applicants consider that the regulatory support provided met their needs, even though they have stated that more detailed and precise information on the product development, non-clinical and clinical parts would be welcome as well as receiving the online training programme as a lecture to be able to interact with the speaker.

Pre-Grant Regulatory Scientific Advice

The situation of many patients waiting for effective treatments and the latest pandemic situation show the need for an accelerated and more efficient development of innovative complex therapies and technologies. To meet this need, public clinical trial funding opportunities have increased at national as well as at the EU-level. Academia and other non-commercial innovative research organisations are the main beneficiaries of these programmes. Such innovative projects are often challenging and likely to require additional (early) regulatory support to bridge the gap in pharmaceutical development from basic to clinical research and to bring new medicinal products and therapies to the patients.

In order to improve support for innovative academic research projects, it is recommended to communicate with academia already at the stage of grant application. It is considered crucial to raise awareness for regulatory aspects that are pre-requisite for successful (clinical) research early on. To achieve this, STARS aims to develop a **pre-grant regulatory scientific advice (PGRSA)** as part of the STARS Common Strategy. The basic idea of the PGRSA concept is to provide early and easily accessible regulatory scientific advice for grant applications to encourage support for successful outcomes of research projects. The concept focuses on providing recommendations for the implementation of this support activity at the NCAs, based on key factors for (potential) success in the specific academic environment. In some member states early advice formats already exist which have been used to develop a first concept. This concept has been discussed within the STARS consortium and subsequently presented to relevant stakeholders such as academia, funding bodies, NCAs, EMA and Clinical Research Centres for further discussion.

The PGRSA intends to amend and further optimize existing structures of all principal players involved. Experience with early advice formats, such as innovation or pre-submission meetings, is already available in different member states (see Chapter 2, National Competent Authority Supports for Clinical Research and Regulation). So far, a concrete scheme for a PGRSA has not yet been introduced in any of the member states. This concept can be used as a precursor to develop a best practice model, which could in a first approach be introduced at national level. If such a concepts proofs viable, it subsequently can be offered and introduced in a joint and harmonized approach to all member states deciding to join. However, the decision of the NCAs to join ultimately depends on the available resources they can provide for this

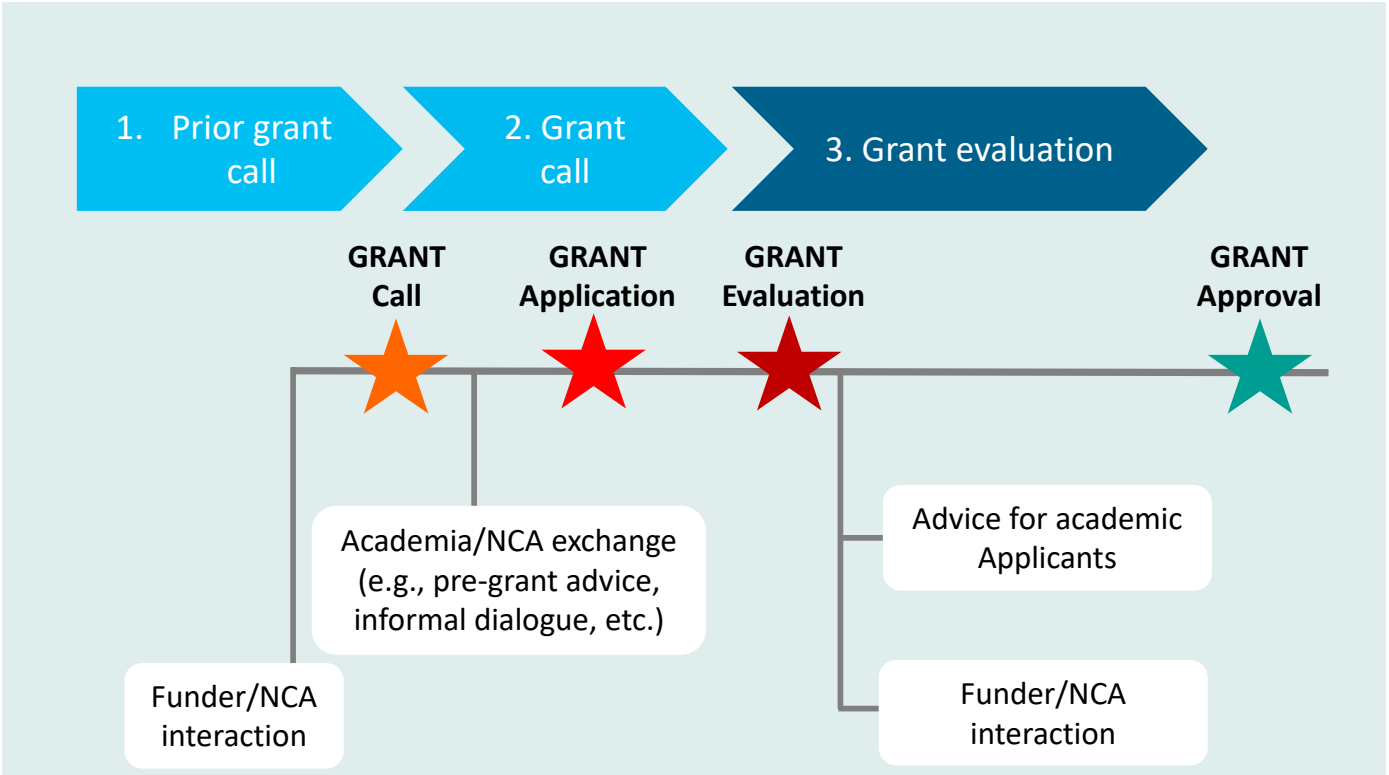


Figure 4.9: Pre-grant regulatory scientific advice concept.

early advice format. Funding bodies play already with view to NCAs an important role in this concept as they could support NCAs in increasing their resources. Nonetheless, the most important role for the funding bodies is to provide financial support to academia. Addressing compliance to regulatory requirements in the grant calls will encourage researchers to seek regulatory advice and ask for the regulatory point of view on the feasibility on the project proposed before finalizing the research proposal. This will help to ensure that provision is made as part of project funding for regulatory aspects and support in those member states where this support is not free of charge. Funding bodies usually do not directly involve NCAs or EMA in the grant application process to discuss regulatory topics (see chapter 3 – surveys to the funding bodies).

A possible conflict of interest could be dealt with in the same way as other national scientific advice. The recommended PGRSA concept will stimulate the following interactions between funders, academia and regulators at different stages of a grant call (see Figure 4.9):

1. Prior grant call:
Regulators/funders interaction could aim at discussing the regulatory requirements needed to adequately inform the grant call;

2. Grant call:
Regulators/academic interaction could aim at discussing the evidence of regulatory compliance to be provided in the grant application;

3. Grant evaluation:
Regulators/funders interaction could aim at discussing proposals pre-selected by the funding body from the regulatory point of view or could establish their own pre-selection process or, as a third option, the pre-selection could be a joint approach of both; checking of the regulatory pathway of the project remains in the decision of each NCA. The same possibilities could be introduced for establishing a structured method for a review process.

Regulatory advice to academic applicants could be provided by regulators in relation to regulatory matters between the two evaluation stages when foreseen by the call.

The PGRSA concept opens certain flexibility to choose or focus on a stage of interaction to develop a PGRSA in a first approach. However, there have been identified the following key success factors, which need to be considered for an efficient implementation of the PGRSA:

Key success factors for efficient implementation of the PGRSA:

1.) Offer a low-threshold entry point for academia at informal level to directly interact with the NCAs to foster an early dialogue on regulatory aspects and guide funded projects early into regulatory channels.

2.) Provide early support for innovative academia-driven (clinical) research applying to funding programs at national level of the EU member states as well as at European level.

3.) Encourage applicants to ask for early regulatory support, e.g. at the stage of grant applications to address regulatory aspects very early in the funding process.

4.) Offer the pre-grant advice as an additional advice format to the already existing early advice formats (e.g. pre-advice, kick-off meeting, innovation meetings) to increase emphasis on regulatory aspects as part of the funding process.

5.) Establish an active interplay between funders, developers and regulators as an early mechanism to ensure that appropriate considerations are given to regulatory aspects to further improve regulatory science:

a. Provide links to relevant regulatory tools in the call text.
b. Integrate the pre-grant advice format into funding programs as a standardized offer.
c. Include consultation of regulatory bodies as a strong recommendation in grant proposals.

6.) Include an early reimbursement instrument for applicants to guarantee the usage of such an early advice tool by academia and ensure incorporation of costs for regulatory advice as part of the grant approval process.

7.) Establish closer interaction and coordinated approach between the funding bodies and the NCAs before calls for grant applications to ensure the inclusion of such activities into the project planning and the financial resources.

8.) More detailed exchange between funding bodies and NCAs to adapt mechanisms for identification of research projects warranting advice from regulatory bodies.

To summarize, the results of the STARS surveys and the feedback received by academic stakeholders during two stakeholder workshops strongly suggest that (academic) research would benefit significantly from the implementation of a PGRSA concept at NCAs to support grant applications. Therefore, the STARS consortium encourages funding bodies and academia to engage with regulatory authorities and increase the use of available regulatory supports and advice formats in order to:

- considerably improve the likelihood of a successful outcome of projects by early planning and early implementation of regulatory requirements;
- further optimise effective and sustainable use of the financial funding resources, including providing financial means for PGRSA before granting an application;
- maximise the impact of the funding provided and the potential for the research to have a significant clinical impact by direct early dialogue with NCAs.

The ultimate goal of the above introduced PGRSA scheme is to stimulate and improve a close interaction with all involved stakeholders, namely funders, NCAs, academia, and aggregation points (APs) at universities, such as clinical research units or clinical trial centres.

The PGRSA concept is based a strong interplay between these three main stakeholders (see Figure 4.10) to allow a successful translation from basic research into clinical practice by integrating the regulatory requirements very early in the drug developmental process.

In order to encourage academia to seek regulatory support early in grant applications there is a need for financial support for the PGRSA. This will allow academia to build up a comprehensive and feasible development plan for their research and achieve the ultimate goal of bringing innovative treatment concepts to the patients. The concept foresees mutual exchange between the three main players which is based on the need to identify and address upcoming challenges or crucial regulatory aspects to be considered during clinical research and future development.

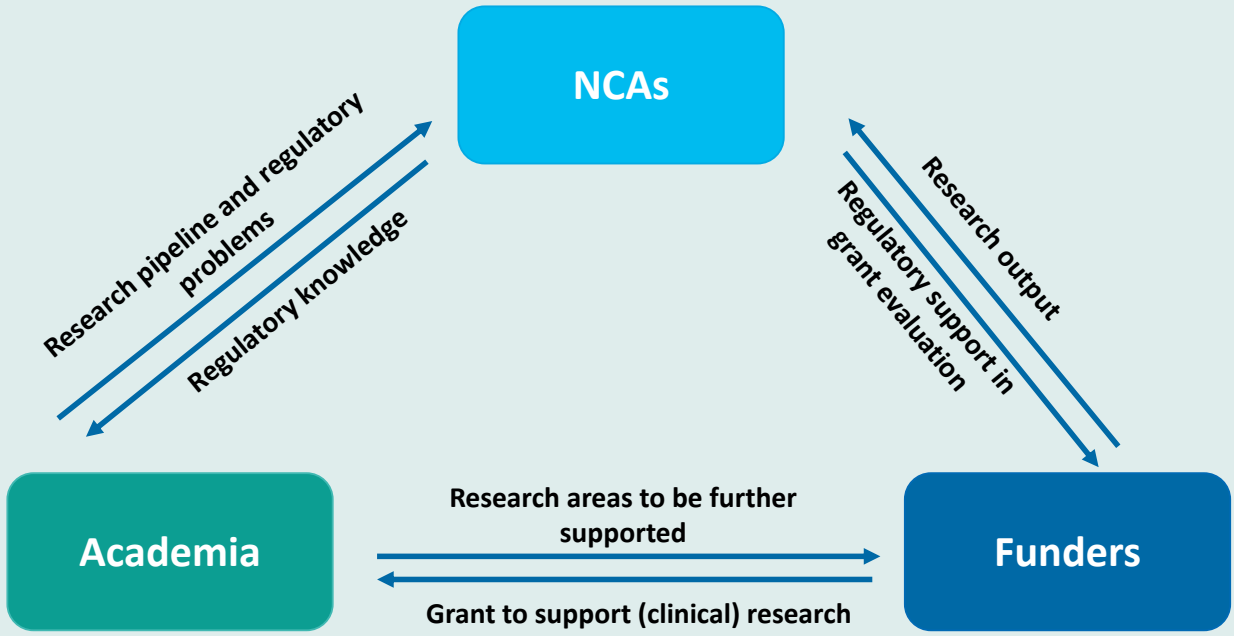


Figure 4.10: Stakeholders close interaction in the PGRSA scheme.

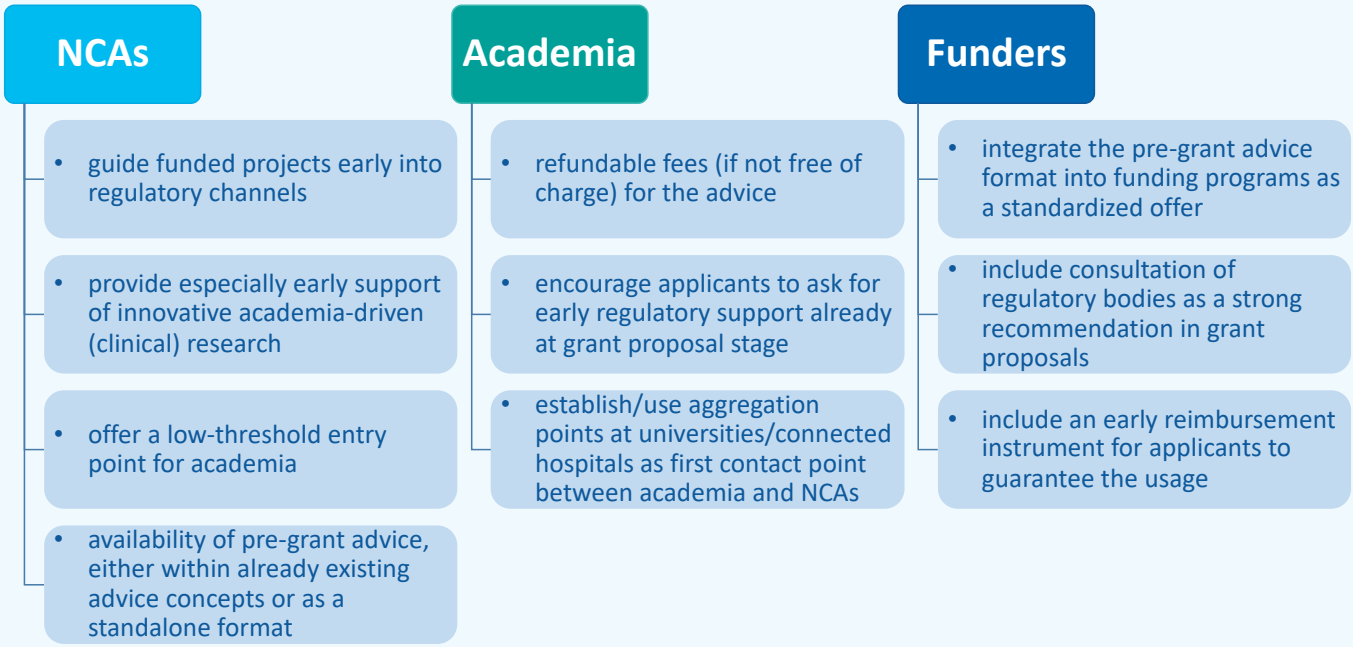


Figure 4.11: Active Interplay between NCAs, Academia, and Funders

STARS Recommendations to Improve the Regulatory Knowledge, Awareness and Skills of Academia across Europe

The previous chapters gave an overview of the current regulatory European framework as well as the national landscape in general. It was described, how the different STARS activities and achievements are designed and how these are aiming to tackle some of the recognised needs and challenges.

In this chapter, STARS provides a set of recommendations to further improve the awareness, knowledge and competence of academia and how to adapt and optimise the regulatory system in the future. STARS has identified several central strategic areas and respective stakeholders or target groups to whom these recommendations are addressed. For some recommendations, there are additional decision-makers listed, who need to support the mentioned activities.

(1) Regulatory authorities in Europe (EMA & NCAs)

#1 Provision and regular update of targeted information material and user guides about the regulatory framework and legal approval procedures in place

- A basic knowledge of regulatory frameworks is a prerequisite for the successful translation of biomedical research. A good general level of expertise within the research community enables a better understanding of complex regulatory requirements that apply to the development of medicinal products and medical devices for licensing purposes.
- Provision of simple user guides specifically targeted at non-commercial researchers incorporating an overview of the main aspects of medicinal product legislation would be a useful starting point for academic researchers to develop an understanding of regulatory requirements and support 'regulatory readiness'. Information materials should be up-to-date and adequate, user friendly and appealing, e.g. short explanatory video clips, interactive web-tools, podcasts or information leaflets. Dissemination of practical guideline videos or checklists, e.g. easy and clear support for clinical trial application forms, would be useful information material.
- The language should be wherever possible generally understandable, thus technical terms should either be avoided or if used, be explained, for example by providing a glossary with regulatory vocabulary and abbreviations.
- The STARS Comprehensive Inventory, which provides a systematic overview of provider and contact points for regulatory support services for academia should be disseminated and further developed. It is important to provide a navigation through the regulatory landscape with information about whom to approach at different stages of development and where to find relevant material.

#2 Use of appropriate media channels to reach out to academia

- Academic research groups use the websites of the EMA and the national authorities in the first place to obtain relevant information. Therefore, all related websites should be clearly designed with the aim that academic groups can quickly and easily navigate the website to find relevant documents and information.
- Animated videos, decisions trees, information boards with chat boxes (as used by Pilot II) or Q&A pages with a very good search function might be tools to use.
- Cross-linking NCAs and EMA website can be helpful
- All outdated information needs to be regularly updated with valid, up-to-date information, search-engine optimisation and interlinking design should be established. High quality and reliability of the presented data must be ensured.
- Tailor-made subpages for academia could provide key information in easily accessible formats, e.g. short video clips, an overview of contact points, specific training material, FAQs and checklists. It is recommended to involve academic stakeholders ("customer") in the development of such communication tools, in order to meet the specific requirements for academic researchers and to learn directly about their needs and challenges (targeted crowd-sourcing).

#3 Communication and networking events

- Interactive events, like local open house days, roadshows or innovation days organized by regulatory authorities will encourage academia, NCAs and funding bodies to exchange about relevant topics, needs and developments. Interactive sessions can contribute and stimulate collaboration between academia, NCAs, funding bodies and where suitable industry and other stakeholders. At such events, academia gets more insight into regulatory procedures, and can present and discuss their projects and ask scientific questions. Regulatory authorities would surely benefit from this multi-directional communication by learning about innovative developments and methodologies. This would foster constructive communication and where possible cooperation between the regulatory authorities, academia and other important players.
- NCAs and funding bodies should advertise as much as possible their support services and training courses given by them and by others. National and European societies might act as aggregation points.

#4 Low threshold access to regulatory authorities

- The aim should be an informal early communication between academia and regulatory authorities. In order to ensure early communication, a low threshold access and specific contact points at NCAs for academia is recommended.
- Existing networks, such as national innovation offices or the EU-IN network could support this purpose.
- Specific online communication platforms, like chat-based platforms with Q&A functions could further support such offers and developments.
- It is key to remove the misconception that there is a high hurdle for engaging with regulators.

#5 Increase of awareness and use of regulatory support tools

- The STARS surveys revealed that established regulatory support tools, like (informal) orientation meetings or scientific advice meetings are used with varying frequency across Europe. However, some academic groups are still not even aware of these tools. Therefore, it is important to increase awareness by advertising and communicating such offers, e.g. at conferences, scientific events, via innovation offices, funding bodies etc.
- In parallel, a closer contact between regulators, research community and university technology transfer offices can be facilitated. A 'train the trainer' approach could be applied whereby regulatory authorities could target individuals within research centres who interact with researchers on a daily basis and provide them with key information that they can use and share on site. Existing research networks could also be used to disseminate knowledge and information.
- Collection and provision of existing regulatory support tools on European and/or national level. A 'one stop shop' approach similar to that employed in Pilot II could be helpful. The use of case studies highlighting previous scientific advices with academia could help to overcome any hesitancy to engage with competent authorities.

#6 Support in the preparation of scientific advice for academia

- In contrast to pharmaceutical companies with in-house expertise in regulatory affairs, academic researchers often are not aware of how to prepare and ask the right questions in the most efficient manner. Low-threshold services at regulatory bodies like informal meetings that provide information about the advice procedure, the preparation of data presentation, question and forms can be a helpful source for academia to make the most out of a formal scientific advice meeting.
- Consider sharing the information about the advice procedure, the preparation of scientific advice briefing books and presentations to local TTO/Innovation Offices to lower the threshold and increase efficiency.

#7 Low threshold to apply for regulatory advice

- Next to a low threshold communication and contact point, academia has to consider financial aspects. Reduction of costs or fee waivers need to be considered (e.g., the EMA has introduced a fee waiver for academia for scientific advice for orphan medicines).
- Concept of pre-grant advice (see also Chapter 4)

#8 Expanding and promoting existing structures within NCAs

- Ensure that available structures such as innovation offices or the EU-IN innovation network are easily accessible and are tailored also to the needs of academia.
- Consider whether existing support at EU and national level are suitable for academic researcher who often require a more individual support and a certain flexibility.
- Establishment of new and/or expansion of already existing structures for early support of academia by regulators, ensuring that these are easily accessible and are specifically tailored to the needs of academia.
- Maintenance and expansion of the STARS Comprehensive Inventory, which gives an overview and contact points of regulatory support services for academia across Europe.

#9 Harmonisation of the regulatory processes between the member states is expected to be beneficial for all stakeholders, including the academics.

- Strengthen the European environment for clinical trials via ACT EU initiative (Accelerating Clinical Trials in the EU), which is co-led by the EC, HMA, and the EMA. EU ACT has identified ten priority actions for 2022/2023, including enabling innovative trial methods, establishing a multi-stakeholder platform, and supporting the modernisation of good clinical practice (Accelerating Clinical Trials in the EU (ACT EU), HMA, EC, EMA, 2022; Szepessy et al., 2022).
- While academic researchers may tend to engage initially with their national regulatory authority, harmonisation of regulatory processes will assist them to seek input from other regulatory authorities. The harmonisation should include adapted and standardised forms and processes as well as mutual online service platforms.
- Procedures such as simultaneous national scientific advice (SNSA) can facilitate such engagement and facilitate multinational research.

(2) Academic Researchers and Institutions (e.g. Universities & Research Institutes)

#10 Optimize engagement and collaboration of academia

- Foster closer interaction between research groups.
- Incentives for academia for data sharing and networking: highlight the advantages of open communication (e.g. avoidance of same hurdles by different researchers/research groups).
- Incentives for academia in form of certifications and diplomas, scholarships to motivate scientists to complete on-line regulatory courses (= career building).
- Implementation of a new regulatory science extensive/comprehensive network: academia (+ ethic committees) + funding bodies + regulatory agencies + European research networks (i.e. ECRIN). Highlight the advantages of such networks (e.g. timely regulatory support).
- Establish and maintain more specific research networks/data sharing platforms on national and if possible on European level (e.g. platforms for development of cell and gene-therapy, real-world evidence etc.).

#11 Encouraging compliance with clinical trial results reporting requirements on EudraCT

- It should be an obligation to publish clinical trial results on European Union Drug Regulating Authorities Clinical Trials Database (EudraCT).
- In this connection the agreement and implementation of minimum standards for promoting academic sponsors to report in EudraCT should be developed.

#12 Early communication with regulators and HTA before starting research project

- Foster common scientific publications between regulatory and academic people and create awareness for the challenges performing regulatory conform clinical research.
- Involve patients as early as possible in the process.
- It needs an agreement on innovative funding schemes for academia to approach regulators in proposal application procedures.

(3) European Commission, Ministries and Funders (e.g. RTD & Research and Health Ministries as well as other funders)

#13 Introduction and implementation of regulatory needs and aspects for funded biomedical research projects

- Funders, researchers and regulators should develop settings and agreements for translational research and clinical trial approaches to increase the attention paid and weight given to regulatory aspects when evaluating research proposals / funding applications.
- Enhanced cooperation between funding bodies and regulatory authorities could enable key regulatory considerations to be described in funding calls to signpost these to academic researchers and to ensure that they are considered and addressed in funding submissions.
- It is suggested that where appropriate, regulatory experts should join the reviewing processes for funding applications in order to assess the regulatory readiness of a research proposal.
- The awareness of funders and researchers of the significance of regulatory considerations, especially in late clinical research and/or clinical trials, should be increased in order to ensure early and appropriate consideration of regulatory aspects in the development of research calls or in grant application processes. This will help to maximise the potential impact of the funding by ensuring that appropriate regulatory standards are implemented. This will increase the likelihood of regulatory approval and ultimately the application of the outcomes of research in clinical practice.
- Funders should consider to reimburse fees for regulatory support and related tools as well as for regulatory training of researchers.

#14 Monitoring compliance with regulatory affairs during the project

- Not only regulatory bodies, but also funding bodies should consider the integration of a monitoring of fulfilment of the regulatory requirements in the project reporting.
- Reporting of clinical trial protocols and results into the EU databases provided for this purpose (EudraCT) in order to ensure transparency in clinical trials should be strongly encouraged.

#15 Sustainability of the STARS achievements and tools

- Sustainability of the work done by STARS and the implementation of the recommendations should be carried on. They should be picked up by initiatives and European programmes like the European Partnerships in Horizon Europe. These initiatives will have an important role in the support of translational project towards innovative therapies.
- Sustain the STARS comprehensive inventory.
- Consideration of the STARS pilots and STARS curricula for future developments.

#16 Support research of regulatory processes by specific funding measures or modules

- To ensure up-to-date regulatory decision, e.g. usage of real world data.
- Proactively engage with funders to explore new funding mechanisms

#17 Implementation of a pre-grant advice

- Pre-grant advice should be implemented as part of translational research calls as a mechanism to ensure that appropriate consideration is given to regulatory aspects in funding submissions / grant applications.
- Consideration should be given in advance of issuing a call as to whether pre-grant advice would be applicable / desirable given the nature of the call and the proposed research and the need to make the most effective use of available resources.
- Such advice could be complementary to informal advice given at an earlier stage via supports such as innovation offices.
- See page 34 in Chapter 4 for a comprehensive details on the pre-grant advice concept.

(4) Industry (e.g. Pharmaceutical & Biomedical)

#18 The early contact and dialogue between academic researchers/institutions and start-ups, small medium enterprises and industry should be fostered reciprocal

- Such a communication might support later steps, like the regulatory approval or in translating the research results successfully into health systems.
- Suitable formats or platforms should be developed and established for public-private partnerships like the Innovative Medicines Initiative (IMI) could be used for lesson learned of such a platform or process.

(5) Education (e.g. Universities & Regulatory Authorities)

#19 Continuous education and training of regulators

- Education of regulators, such as visiting conferences, doing courses and training such as in the EU Network Training Centre (EU NTC) in order to ensure up-to-date decision making standards.

#20 Continuous regulatory training of the academia

- Education and training of academia with consideration of all career levels, beginning early during graduate studies of medical and life science students up to advanced career levels.
- Provision of a superordinate curriculum with recommendations on harmonised training and education approach across Europe in order to achieve a common level of regulatory knowledge in academia.
- Implementation of the "train-the-trainer concept" and knowledge exchange on local level.
- Support the harmonization of the curricula for academia in Europe.
- Researchers should be encouraged to take part in regulatory courses. Funders might ask researcher to complete courses as part of a funding.
- Influence the public and policy-makers to support this recommendation taking high-level impact angels on economy, employment and public health.
- See page 26 in Chapter 4 for details and specifications on the STARS curricula.

(6) Cross-cutting Recommendations

#21 Consideration of lessons learned in regulatory science, procedures and guidelines beyond Europe, e.g. along with the STARS global conference in 2022

Conclusion and Outlook

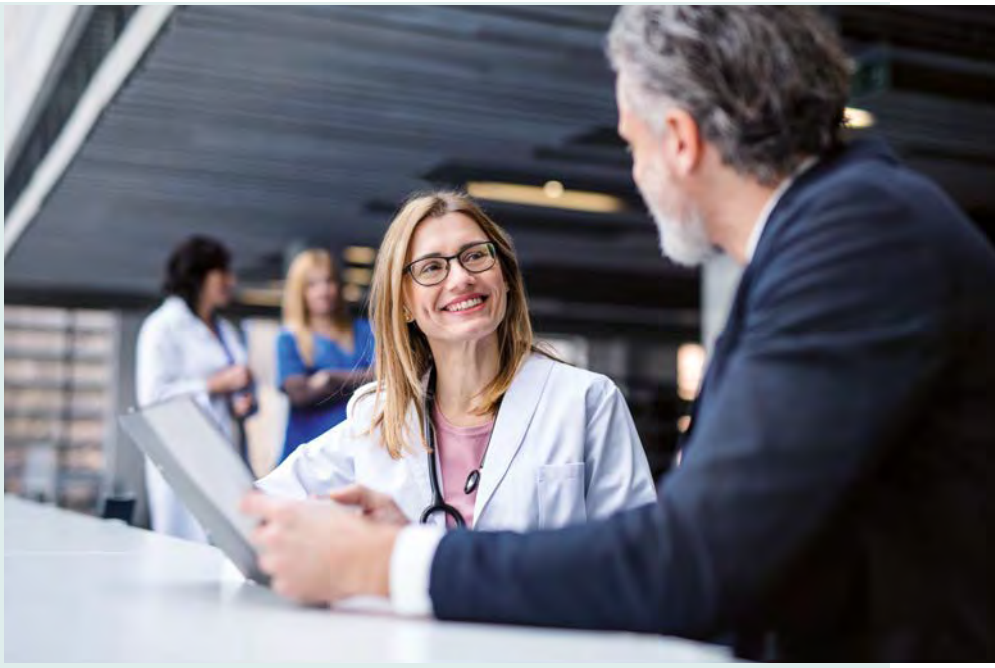
The majority of biomedical clinical research aims novel active substances or the optimisation of pharmacological treatments. However, most researchers focus more on their general research and related scientific publications and thereby often neglect the timely consideration of regulatory prospects and requirements. Thus, innovations do not reach patients, society, and economy in a timely and efficient manner. Consequently, the STARS project contributed to bridge this translational gap by various activities in order to analyse and to support the regulatory knowledge of academia in Europe, including specific training offers.

In an EC-funded consortium including the majority of European NCAs, the EMA, and a German funding agency (DLR), we have analysed the regulatory landscape in Europe and the effectiveness of regulatory support tools available for academia, funders and NCAs. STARS examined and addressed the underlying factors causing the above-mentioned downsides which limit the impact and overall efficacy of publically funded academic health research. STARS identified in close cooperation and exchange with relevant stakeholders (academic research community, funders, payers, industry association, and networks) best practice examples and certain gaps, and performed three pilot projects to test and transfer an identified best practice, but also to initiate a new support activity. In addition, STARS addressed training needs and developed curricula recommendations for regulatory training in the academic career.

This strategy paper summarises the major achievements of STARS and derived recommendations based on comprehensive survey data, evaluation of the pilots, and input from stakeholders and experts via two STARS workshops.

The crucial step is the implementation of these recommendations by all required stakeholders. STARS is convinced that most recommendations can be implemented over the next three years (short and mid-term range, see page 8 – 9). However, various stakeholders have to agree and actively participate in this process as it will be a cooperative effort (see also Chapter 5).

It is important to recognize that this Common Strategy and its recommendations will need to be further developed and adapted. First calls and projects in Horizon Europe already consider the idea of an early regulator-academia dialogue. This is crucial as improving communication and finding a common language were identified as the most relevant needs to improve the success of academic research (see Figure A in page 7). Another important step forward is the development of specifically tailored educational programs. STARS provides a draft of Core and Comprehensive Curricula, aiming to achieve a harmonized and common level of regulatory knowledge across Europe. With this, the sustainable implementation of regulatory science and support in Europe will have a great chance to improve the benefits for patients and healthcare systems arising from academic driven research.



Appendices

I. Authors
II. References
III. Glossary/Abbreviations

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AIFA Italian Medicines Agency (Italy)
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BfArM Federal Institute for Drugs and Medical Devices (Germany)
DLR-PT DLR Project Management Agency (Germany)
EMA European Medicines Agency (Europe)
FAMHP Federal Agency for Medicines and Health Products (Belgium)
Fimea Finnish Medicines Agency (Finland)
HPRA Health Products Regulatory Authority (Ireland)
INFARMED National Authority of Medicines and Health Products (Portugal)
MEB Medicines Evaluation Board (The Netherlands)
MHRA Medicines And Healthcare Products Regulatory Agency (United Kingdom)
MA Medicines Authority (Malta)
MPA Medical Products Agency (Sweden)
OGYÉI National Institute of Pharmacy and Nutrition (Hungaria)
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Appendix II: References

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Appendix IV: Glossary/ Abbreviations

ACT EU	**Accelerating Clinical Trials in the EU (ACT EU):** Initiative to transform how clinical trials are initiated, designed and runlaunched by the EC, HMA, and EMA
ATMP	**Advanced Therapy Medicinal Products:** Medicinal products for the use in humans based on genes, tissues or cells.
CHMP	**Committee for Medicinal products for Human Use:** Committee responsible for human medicines at the EMA
CRO	**Clinical research organisation:** A service organization that offers its clinical trial management services to pharmaceutical, biotechnology, and medical device companies as well as governments, academic institutions, and other research entities.
CSA	**Coordination and support action:** Funding instrument of the European Commission.
DLR-PT	**DLR Projektträger**
EATRIS	**European Infrastructure For Translational Medicine**
EC	**European Commission**
ECRIN	**The European Clinical Research Infrastructure Network**
EDCTP	**European & Developing Countries Clinical Trials Partnership**
EEA	**European Economic Area**
EMA	**European Medicines Agency:** Decentralised agency of the European Union (EU) responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU.
EMRN	**European medicines regulatory network**
EORTC	**European Organisation for Research and Treatment of Cancer**
ERN	**European Reference Network:** Virtual networks of Reference Centres involving health care providers across Europe with the aim to tackle complex or rare diseases and health conditions that require highly specialised treatments and focussed expertise and resources.
ESFRI	European Strategy Forum on Research Infrastructures
EU	**European Union**
GCP	**Good clinical practice**
GLP	**Good laboratory practice**
GMP	**Good manufacturing practice**
IMI	**Innovative Medicines Initiative:** a public-private partnership aiming to speed up the development of better and safer medicines for patients.
ITF	**Innovation Task Force:** Multidisciplinary group at the EMA that includes scientific, regulatory and legal competences. It was established to ensure coordination across the EMA and to provide a forum for early dialogue with applicants on innovative aspects in medicines development.
IRDiRC	**International Rare Diseases Research Consortium**
LO	**Learning outcomes**
MA	**Marketing authorisation**
MAA	**Marketing authorisation application:** Application for the approval to market a medicine in one, several or all European Union Member States.
MS	**European Union Member State.**
NCA	**National competent authority:** A medicines regulatory authority in a European Union Member State.
PGRSA	**Pre-grant regulatory scientific advice**
PPP	**Public-private partnership**
PRIME	**Priority medicines:** A scheme launched by EMA to enhance support for the development of medicines that target an unmet medical need.
SA	**Scientific advice:** A procedure in which the NCA or the EMA provides advice on appropriate test instruments, endpoint, and studies required in the development of a medicine or on the quality of a medicine.
SME	**Small and medium-sized enterprises**
STARS	**Strengthening Training of Academia in Regulatory Science**

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