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PART 3/3

COMMISSION STAFF WORKING DOCUMENT

IMPACT ASSESSMENT REPORT

Accompanying the document

Proposal for a Regulation of the European Parliament and of the Council

on standards of quality and safety for substances of human origin intended for human application and repealing Directives 2002/98/EC and 2004/23/EC

{COM(2022) 338 final} - {SEC(2022) 304 final} - {SWD(2022) 189 final} - {SWD(2022) 191 final}

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ANNEX 12: MEASURES PROPOSED TO FACILITATE INNOVATION IN THE BTC SECTOR

New ways to collect, prepare, store and apply BTC to patients can bring significant health benefits, and are usually achieved in an incremental manner [1]. Newly developed methods are mainly driven by the public/non-profit sector, and are rarely patent-protected. Newly developed technologies and practices are usually shared openly through scientific publications and at professional society conferences, allowing for wide access within the public and non-profit sector. A recent example is the broad collaboration between blood services to study whether and how plasma can be used as a possible therapy for COVID patients [2].

Developers (mainly academic/public sector) and authorities have raised two areas to be addressed, to ensure appropriate levels of regulation, avoiding under- or over-regulation while. The issues to be addressed to ensure safety, quality and proof of benefit for BTC processed or used in new ways are:

1. The need for a proportionate authorisation model designed to allow incremental changes in preparations and use of BTC. This model should oblige developers to provide sufficient clinical evidence to ensure safety and efficacy, while not requiring unnecessary efforts that would hamper access to innovation that can bring significant benefit for patients.

2. The need for legal clarity regarding which legal requirements or frameworks will apply to specific BTC and when a particular process or processing step may push that process into another framework. In some cases this will imply a need to understand definitions and requirements in other EU legal frameworks (e.g., 'industrial processing' or 'substantial manipulation' in the pharmaceuticals framework or 'derivative' in the medical device framework) and hence an interaction with the relevant bodies in those frameworks.

The BTC revision proposes two key measures to facilitate such innovation.

12.1 A risk-based proportionate approach for incremental innovation (M4B)

The first measure will extend an existing requirement for preparation process authorisation in the tissue and cell legislation to the blood sector, and create a legal framework for requiring clinical evidence of safety and quality for BTC processed or used in new ways, when the risk or novelty reach certain thresholds. New ways of processing or using BTC comprise a spectrum from very minor changes to entirely new ways to prepare and/or use BTC. The simplest change might involve new information on a label or the validation of storage for a longer period. More significant changes would include improved approaches that aim, for example:

- to achieve preservation (e.g. vitrification of egg cells [3] or adding a storage solution to platelet concentrates [4]);

[1] For a description of the trends of innovation, see Evaluation {SWD (2019) 376 final} , p. 29 and Annex 10

[2] https://www.support-e.eu/

[3] Chian R, Wang Y and Li Y (2013) *Oocyte vitrification: advances, progress and future goals* J Assist Reprod Genet (2014) 31:411–420.

- to inactivate contaminating microbes before BTC storage (e.g. microbial reduction steps added during blood processing [5], or
  to select and concentrate the specific cells that are required for patient treatment (e.g. volume reduction in cord blood [6].

The most innovative changes have involved approaches such as:

- using well-established BTC for a new patient group and indication (e.g. use of plasma from convalescent COVID-19 patients to enhance the immune response of patients fighting the virus);
- the complete removal of living cells from a tissue to enhance re-cellularisation of the tissue in the patient (e.g. de-cellularised heart valves [7] or skin [8]) or
- treatment of the patient's own blood outside their body to inactivate cells that can cause organ rejection in transplanted patients or causing a bone marrow transplant to attack the cells and tissues of the patient (graft-versus-host disease) - a frequent and potentially life-threatening complication of allogeneic bone marrow transplantation (the process is called extra-corporeal photopheresis).

In general, there is also a trend towards increased automation in BTC collection and processing, with computerised systems incorporated during processing to ensure more consistent preparations and improved documentation and traceability.

The EU legal frameworks that aim to ensure safety and quality of these therapies have to reflect this spectrum from minor to significant changes, and the risks they entail.

The measure will build on work that has been carried out by EU authorities and professionals over the last 5 years and that was co-funded by the EU Public Health Programme, incorporating the principles that developed with wide consensus, into EU legislation. Fifteen national competent authorities, in collaboration with learned societies for BTC therapies, have collaborated under an EU-funded joint action that developed a proportionate approach for authorizing changes to BTC processing or use [9]. This approach foresees a series of steps to take before authorising BTC processing changes or the introduction of new BTC processes or uses. [10]

Steps of the GAPP approach to authorize BTC changes

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[4] Platelet Additive Solutions: A Review of the Latest Developments and Their Clinical Implications - FullText - Transfusion Medicine and Hemotherapy 2018, Vol. 45, No. 2 - Karger Publishers

[5] Introducing Pathogen Reduction Technology in Poland: A Cost-Utility Analysis Maria Agapovaa. Transfus Med Hemother 2015;42:158–165

[6] Solves P, Mirabet V, Roig R. Volume reduction in routine cord blood banking. Curr Stem Cell Res Ther. 2010 Dec;5(4):362-6. doi: 10.2174/157488810793351703. PMID: 20528760.

[7] Chapter 19, Guide to the Quality and Safety of Tissues and Cells for Human Application. EDQM, 3rd Edition 2017.

[8] Hogg P[1], Rooney P, Ingham E et al. (2012) Development of a decellularised dermis. Cell Tissue Bank. 2013 Sep; 14(3):465-74.

[9] GAPP Joint Action: Facilitating the Authorisation of Preparation Process for blood, tissues and cells https://www.gapp-ja.eu/

[10] Technical Annex 3 to overall guidance: assessing clinical data as part of Preparation Process Authorisation (PPA) D8.3_Ref.-Ares_2020_4146352_06082020.pdf (gapp-ja.eu)

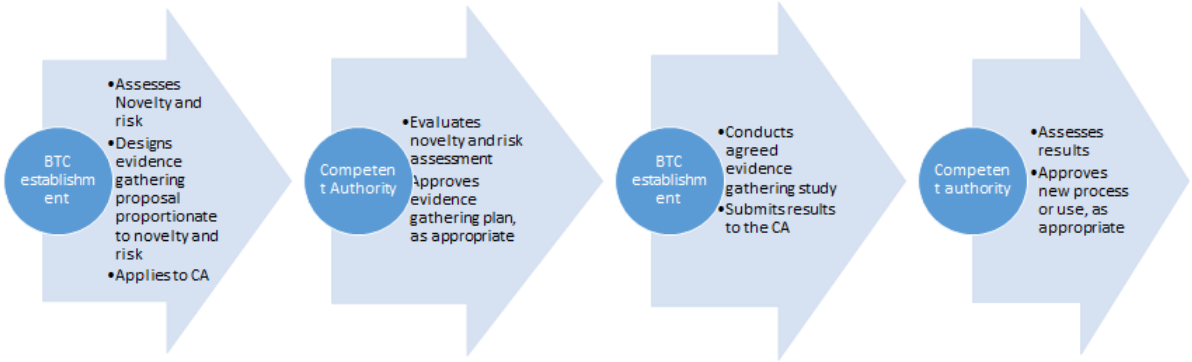


Figure 12.1: steps of the GAPP approach to authorize BTC changes

This starts with an assessment of novelty, by comparing the proposed change to an existing BTC preparation. If the process is not already in use (e.g. in line with a monograph published by EDQM), a risk assessment will be performed. A standard risk-assessment tool has been developed and tested and could be used by BTC establishments for this purpose (EuroGTP II). It takes account of risk factors such as immunogenicity, engraftment failure, disease transmission, toxicity, carcinogenicity, etc. [11,12,13]. The tool leads to four levels of risk: negligible, low, medium and high. The higher the level of risk, the more clinical evidence will be required from the developer for authorisation of the process. This can vary from a description of the process and standard reporting of serious adverse events and reactions (SARE) to full clinical investigation plans with a defined number of patients, in comparison to standard therapies.

[11] Trias E, et al. EuroGTP II Study Group. EuroGTP II: a tool to assess risk, safety and efficacy of substances of human origin. Int J Qual Health Care. 2020 Apr 21;32(1):80-84. doi: 10.1093/intqhc/mzz048. PMID: 31087044

[12] EuroGTPII: An interactive assessment tool for risk assessment of new tissue and cellular therapies and products | EBMT

[13] Assessing the safety risks of new introductions in ART (focusonreproduction.eu) /article/ESHRE-News-EuroGTP-2019

Different risk levels lead to proportionate levels of required clinical evidence (GAPP approach)

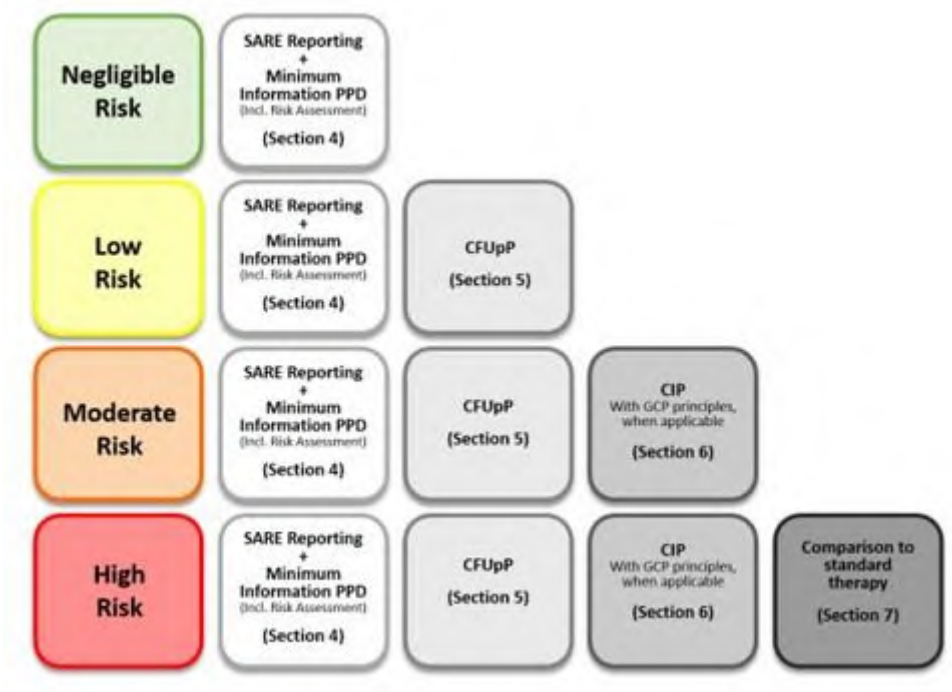


Figure 12.2: GAPP risk levels

Implementing the GAPP approach would mean that developers in BTC establishments would be required to provide this clinical evidence for assessment by the national competent authorities. If satisfactory, the establishment would receive an authorisation for this new preparation process.

All three policy options include the incorporation of this approach in the revised legislation. A common ICT tool is planned to allow national assessors to share data and results of assessments, where appropriate, make common authorisation decisions. Further technical rules can be developed by EU expert bodies, or under either of the two other policy options for the impact assessment. Such guidance might address, in particular, the design of clinical studies or how to enter data in clinical registries.

For the changes that imply the highest level of risk or novelty, the use of the EU clinical trials framework might be appropriate. Already today, assessors of innovations in BTC in several countries (e.g., ANSM in FR and PEI in DE) regularly require the conduct of (adapted) clinical trials. It is estimated that over 50 clinical trials are required for changes in BTC every year by national competent authorities in the EU. In 2020, at least 48 clinical trials were organised to test the preparation and use of COVID-19 convalescent plasma. The use of a common approach across national competent authorities, supported by a common ICT tool, will bring potential for significant efficiencies.

The use of clinical trials in this measure will create a smooth transition from the requirements this framework to the requirements of the medicinal products framework, when the degree of novelty or complexity of processing brings BTC closer to the borderline.

Incorporating this approach in the new legislation will ensure both an appropriate level of protection for patients and facilitated access to safe BTC prepared in new ways and will reduce the risk that unproven BTC therapies with inherent risks are administered to patients.

12.2 A central BTC mechanism to provide legal clarity (M4A)

Continuous developments in the BTC sector raise a high number of questions on how to interpret the BTC legal frameworks and understand whether BTC requirements are applicable and in which situations.

In the absence of a central mechanism to answer these questions they are often brought by the national competent authorities to the meetings of the SoHO Expert Group of competent authorities. This Expert Group is however set-up with a broader scope of activities, is not specifically mandated to advise on scope issues and does not meet with a high frequency. Nonetheless, Annex VIII of the BTC Evaluation report provides a comprehensive overview of questions that have been dealt with by the Expert Group over the course of recent years[14]

The new BTC framework proposes the set-up of a SoHO Coordination Group to include a dedicated working group that will advise on this issue in a more efficient way, providing clarification to requests from competent authorities and professional societies. This working group will facilitate consistent determination and advice on the applicable BTC legal requirements. In cases where a consultation with committees established by other legal acts of the Union on human health / in related fields is necessary to determine whether [and to which extent] the substance, process or preparation falls within the definition of SoHO, the working group shall consult with the equivalent borderlines advisory mechanisms of the appropriate field. Related fields include, but are not limited to, medicinal products, medicinal devices and food.

Such cases can be expected to include situations where:

(a) there is a lack of legal clarity on the classification and applicable legal framework of a therapy,
(b) products combine components falling under different legal frameworks and
(c) BTC become starting material for products that fall under other legal frameworks.

Specific procedures shall be established for requests of such consultations, including the eligibility criteria and mechanisms.

The Committee on Advanced Therapies (CAT) is a well-established equivalent committee working in the pharmaceutical framework. The CAT might not only need to be regularly consulted on scientific aspects relevant to the borderlines between BTC and advanced therapy medicinal products, but could also provide advice on procedural aspects of giving this kind of advice, given their expertise. During preliminary exchanges with the CAT leadership they underlined the need for proportionate and efficient coordination, with email exchanges being sufficient for some cases, while meetings might be required to exchange views on other cases. In an interview for the borderline case studies [15], the CAT members expressed openness for

[14] Evaluation {SWD (2019) 376 final} , Annex VIII, p127-179.
[15] Annex 11, section 11.12.

formal interactions, but underlined the need to avoid contradictions as it is important to provide legal clarity to developers across the EU. CAT interviewees suggested ideas for liaising including clear definitions of roles, responsibilities and consultation mechanisms, the possibility of mutual representations in committees, as well as the idea of a pilot phase.

Other committees to liaise with include the Borderline Classification Group, which is newly established by the Heads of Medicines Agency to have informal expert exchanges on therapies that have been classified differently in different Member States. This group also reflects on mechanisms of interaction to improve EU wide collaboration. The group is closely linked to EMA's Innovation Task Force which provides regulatory/scientific advice to developers on eligibility of EMA procedures, inherently requiring an advice on whether a therapy is to be considered to fall under the EU pharma legislation.

The main liaison to be established with the field of medical devices is the Medical Device Coordination Group. The BDCG includes a Borderline and Classification working group that assists national authorities in classification and determination of regulatory status. The manuals and terms of reference of this group can also provide valuable experiences for the set-up of the equivalent BTC dedicated clarification body. The medical device set-up also includes further elements to explore and build on including:

- A legal provision in the MD Regulation that requires the Commission to ensure that Member States share expertise on medicines, devices, diagnostics, tissues and cells, food, … and consult appropriate agencies;
- Procedures to define lead responsibilities and consultation mechanisms for combination products (both for MD/MP and MD/BTC combinations);
- The so-called Helsinki procedure which allows for rapid collection of national views on specific new devices.

On several occasions, national authorities [16,17] and EMA [18] have proposed to go further by channelling these interactions between sectors through one central multi-disciplinary process or body that could provide advice to developers and help them obtain legal clarity on what is/are the applicable EU legal framework(s) that should apply.

However, this approach would require changes to different frameworks and is beyond the scope of the BTC revision. However, the set-up of a clarification subgroup under the SoHO Coordination Group will be a useful starting point and serve as BTC counterpart to these different bodies in other EU legal frameworks, regardless of the eventual mechanisms for cross-sector consultation.

12.3 Summary

The creation of a dedicated framework to authorize incremental changes in the processing and use of BTC and the creation of a BTC legal clarification mechanism are key measures to significantly facilitate safe and beneficial innovation in the BTC sector. Both mechanisms

[16] Proposals for simplification of EU-legislation – prepared jointly by the Danish Ministry for Business, Industry and Financial Affairs and the Danish Business Forum for Better regulation – March 2019

[17] Position of the French Authorities - April 2021

[18] EMA contribution to the EU pharmaceutical strategy – April 2021

have obtained wide support in the consultations for the BTC impact assessment. They have also been the subject of dedicated exchanges in workshops, including actors and authorities of the pharmaceutical/ATMP and medical device frameworks, who underlined their importance and provided further ideas on their set-up. The costs associated with these measures are relatively low and are assessed as fully justified by the benefits.

The BTC legal clarification mechanism will provide the missing channel of interaction that will allow to provide innovators with legal clarity across the three main EU legal framework for health biotechnologies. This will promote the regulation of innovative BTC and BTC-based products under the best fitting legal requirements for each therapy, supporting safe access to effective therapies for EU citizens.

ANNEX 13: PROBLEM TREE AND INTERVENTION LOGIC

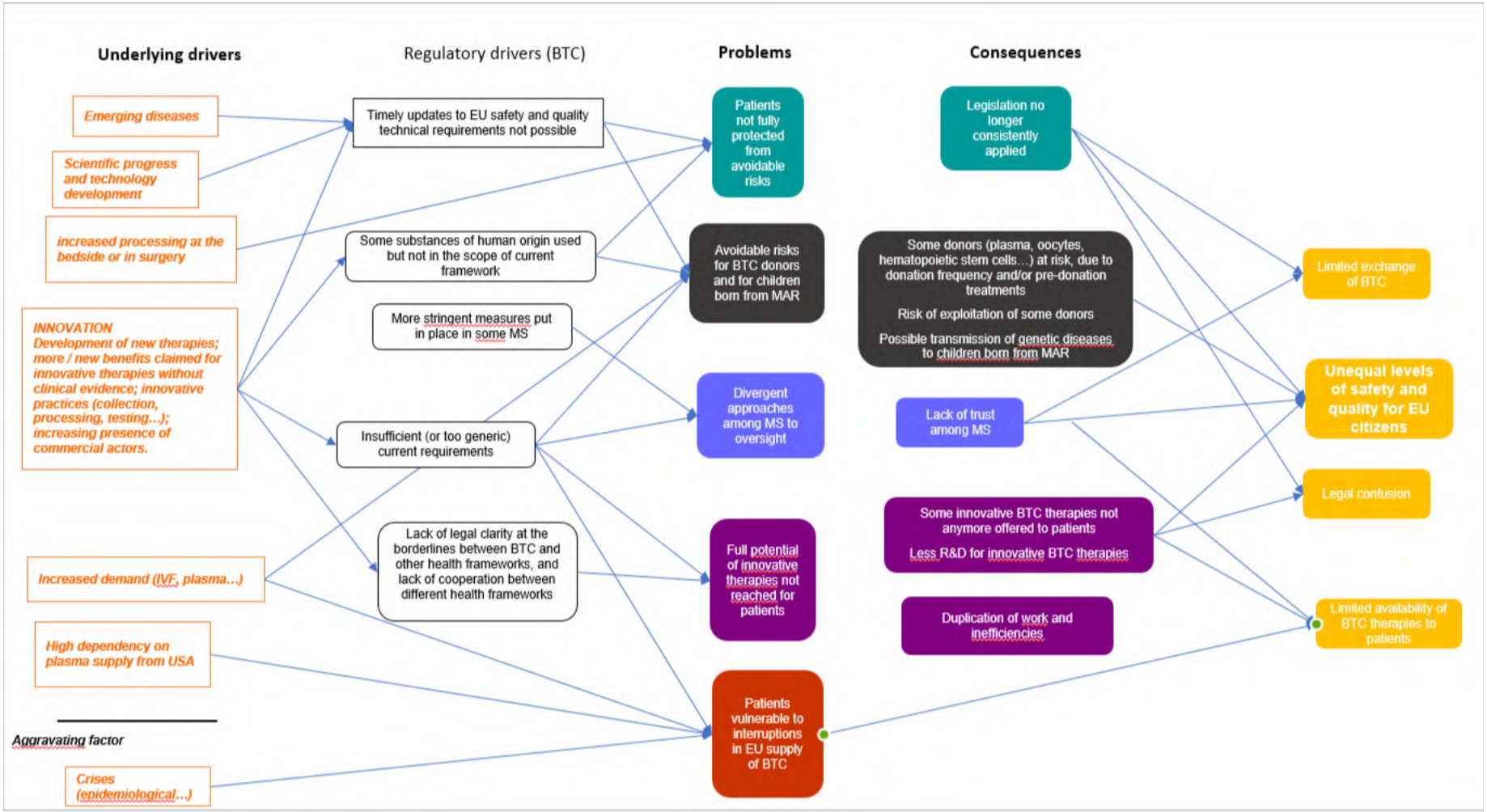


Figure 13.1: problem tree

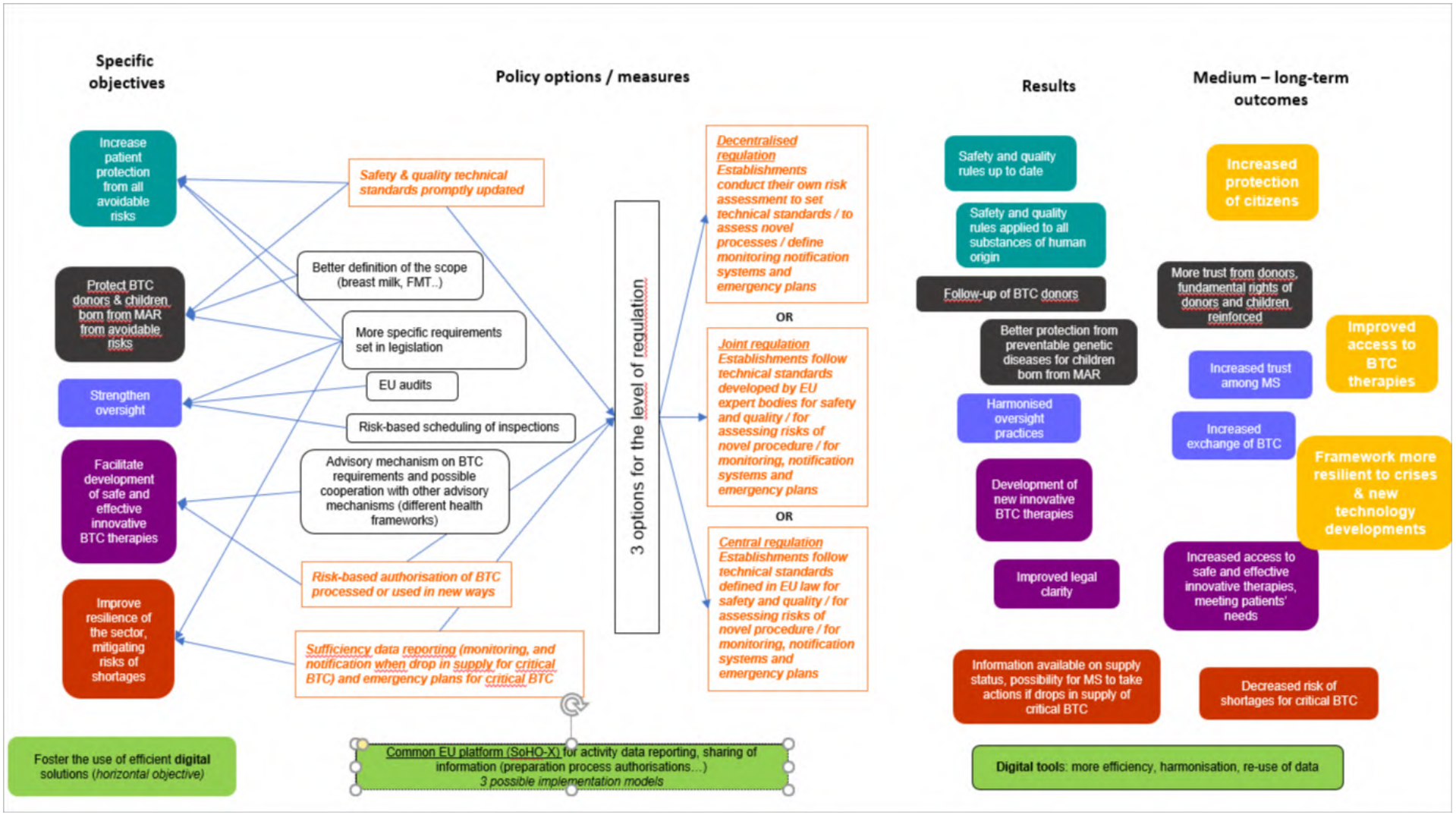


Figure 13.2: intervention logic

ANNEX 14: COLLABORATION WITH COUNCIL OF EUROPE

The work of the Council of Europe in the blood transfusion area started in the 1950s. The relevant Committees are the European Committee on Blood Transfusion (Steering Committee) (CD-P-TS); and the Committee on Quality Assurance in Blood Transfusion Services (Expert Committee) (GTS) that drafts and updates (every 2-3 years) the Guide to the Preparation, use and quality assurance of Blood Components [19], so called " Blood Guide" which is now in its 20th edition. The Department of Biological Standardisation, OMCL Network & HealthCare (DBO) is within the Council of Europe is the European Directorate for Quality Management (EDQM). EDQM focuses on the ethical, legal and organisational aspects of blood transfusion with a view to ensuring quality, increasing availability, avoiding wastage, ensuring optimal use of blood supplies and analysing the possible ethical and organisational impact of new scientific developments.

One section [20] of the 'Blood Guide' is referenced in a blood Directive 2005/62/EC as amended by Directive 2016/1214 and Member States are required to ensure compliance with it. Otherwise, the EDQM guidance is non-binding.

The work of the Council of Europe (EDQM) in the area of organ, tissue and cell transplantation started in 1987. The relevant Committee is the European Committee on Organ Transplantation (Partial Agreement) (CD-P-TO) and its Tissue and Cell Guide Drafting sub-group [21]. The principles guiding the work of the EDQM in this field are ensuring human dignity, maintaining and fulfilling human rights and fundamental freedoms, non-commercialisation of substances of human origin and protecting donors and recipients of organs, tissues and cells.

All EU Member States are represented in the committees responsible for the development and adoption of EDQM guidelines and the guidelines are considered to represent best practice, with many EU inspectors using them as a point of reference during establishment inspections.

Collaboration between DG SANTE and EDQM has a long history, with a formal first grant agreement in 2010, which was presented and celebrated in a dedicated 2020 conference [22].

The European Commission and EDQM concluded a third grant agreement (2019-2021) under which EDQM committed to collaborate on the following topics:

- Development and regular updating of technical SoHO guidance
- A proficiency testing scheme for blood establishments

[19] EDQM Guide for Blood: EDQM Guide for https://www.edqm.eu/en/blood-guide.

[20] This section defines Good Practice Guidelines for blood establishments. It provides a framework for the establishment of quality management in those establishments.

[21] EDQM Guide for Tissues and Cells: EDQM Guide for https://www.edqm.eu/en/organs-tissues -and -cells-technical-guides.

[22] 10 years of collaboration between the European Commission and the EDQM in the field of blood | EDQM - European Directorate for the Quality of Medicines

- Quality management, auditing and training for blood establishments
- Analysis of EU SARE data for blood, tissues and cells, annually
- Standardisation of tissue and cell activity data reporting
- Development of strategies for increasing plasma collection in Europe
- Training of EU vigilance officers to improve SARE reporting
- Support for assessment of BTC standards and practices in EU applicant and neighbouring countries.

Well-developed deliverables have been provided to DG SANTE from this work. These have included published guidance documents, results of infectious disease proficiency testing schemes, training courses held on SARE reporting and on quality management, SARE reports published, data sets for activity data developed and published a major symposium organised on plasma supply.

The preparation for the next grant agreement, covering the period 2022 to 2024, is ongoing.

ANNEX 15: CURRENT AND FUTURE SOHO TASKS OF ECDC

15.1 Current support for Substances of Human Origin Sector

The European Centre for Disease Prevention and Control (ECDC) is an EU agency aimed at strengthening Europe's defences against infectious diseases. ECDC works in three key strategic areas: it provides evidence for effective and efficient decision-making, it strengthens public health systems, and it supports the response to public health threats. In 2012, ECDC appointed its first Senior Expert dedicated to vigilance of infectious safety of substances of human origin (SoHO), based today within the Epidemic Intelligence and Response unit. The work of ECDC on this topic underlines the important role of transfusion, transplantation and medically assisted reproduction in the secondary spread of infectious diseases. Since the appointment, there is continuous communication between DG SANTE and ECDC.

Between 2014 and 2018, ECDC conducted 57 rapid risk assessments, on the request of the European Commission, regarding a range of communicable disease transmission risks of relevance to SoHO. These risk assessments detailed optional public health measures that Member States or operators could implement to reduce certain risks. In addition, ECDC provided scientific advice for the sector on hepatitis B and C, on Ebola and SoHO, on a screening algorithm for sperm donors, on syphilis testing and on the transmission of tick-borne encephalitis by SoHO. In some cases, these risk assessments led to amendments to EU implementing Acts for BTC.

As new communicable diseases took hold in the EU, ECDC published guides for SoHO preparedness plans for West Nile Virus and Zika. The centre is routinely represented at meetings of Member State SoHO competent authorities, where updates are provided by them on global issues of relevance to the safety of SoHO from a communicable disease threat perspective.

15.2 The COVID-19 pandemic and the proposal for an extended role for ECDC

Support to the SoHO sector was heightened during the COVID-19 pandemic with guidance for the sector published first in March of 2020 and updated twice during the subsequent year (see Annex 9). In addition, ECDC supported the Member State competent authorities and DG SANTE in the development of a common approach to the collection and use of plasma from convalescent donors for the potential treatment of COVID-19 patients.

In a broader sense, the role of ECDC during the pandemic was essential to the EU response. Building on lessons learnt from the COVID-19 pandemic, and as part of the European Health Union, in November 2020 the Commission proposed a set of proposals to reinforce EU preparedness, surveillance, risk assessment and early warning and response, giving the EU and Member States stronger tools to take quick, decisive and coordinated action together [23].

[23] Communication From The Commission To The European Parliament, The Council, The European Economic And Social Committee And The Committee Of The Regions Building a European Health Union: Reinforcing the EU's resilience for cross-border health threats. COM/2020/724 final.

This was associated with a Proposal for a Regulation that would strengthen the mandate of ECDC [24].

That proposal defined new or reinforced tasks, in particular:

- epidemiological surveillance via integrated systems enabling real-time surveillance
- preparedness and response planning, reporting and auditing
- provision of non-binding recommendations and options for risk management, and
- building a network for substances of human origin.

The Proposal provides for the role of the network mentioned above. Article 5 (subject to final approval in the trilogue discussions between Commission, EP and Council) describes that ECDC, through the operation of the network for SoHO, will:

- detect, monitor and report on serious cross-border communicable disease threats to health including a threat to substances of human origin (paragraph 4(b))
- allow for continuous and rapid access to sero-epidemiological data [25] via sero-epidemiological surveys within the population, including assessment of donor population exposure and immunity and support the Centre by monitoring disease outbreaks that are relevant to substances of human origin and their supply to patients, and with the development of guidelines for blood, tissues and cells safety and quality. (Paragraph 8).

The network will include nominated experts from national blood and transplant services and their authorities and will be established in line with similar networks already in place to support the work of ECDC.

These additional SoHO tasks, and the proposed network will require increased resources to support the SoHO sector. ECDC is proceeding with plans to put this network, and a supporting internal structure to support it, in place. At a BTC Impact Assessment Hearing, hosted by DG SANTE [26], ECDC presented the plan for the network and its future coordination as shown in Figure 15.1 below.

[24] Proposal for a Regulation Of The European Parliament And Of The Council amending Regulation (EC) No 851/2004 establishing a European Centre for disease prevention and control. COM/2020/726 final.

[25] Aggregated anonymised data indicating the rates of infection of a particular infectious disease marker in the blood donor population. Such data can be a valuable indicator of community infection rates in general.

[26] BTC Impact Assessment Hearing on Keeping Technical Rules Up-to-date

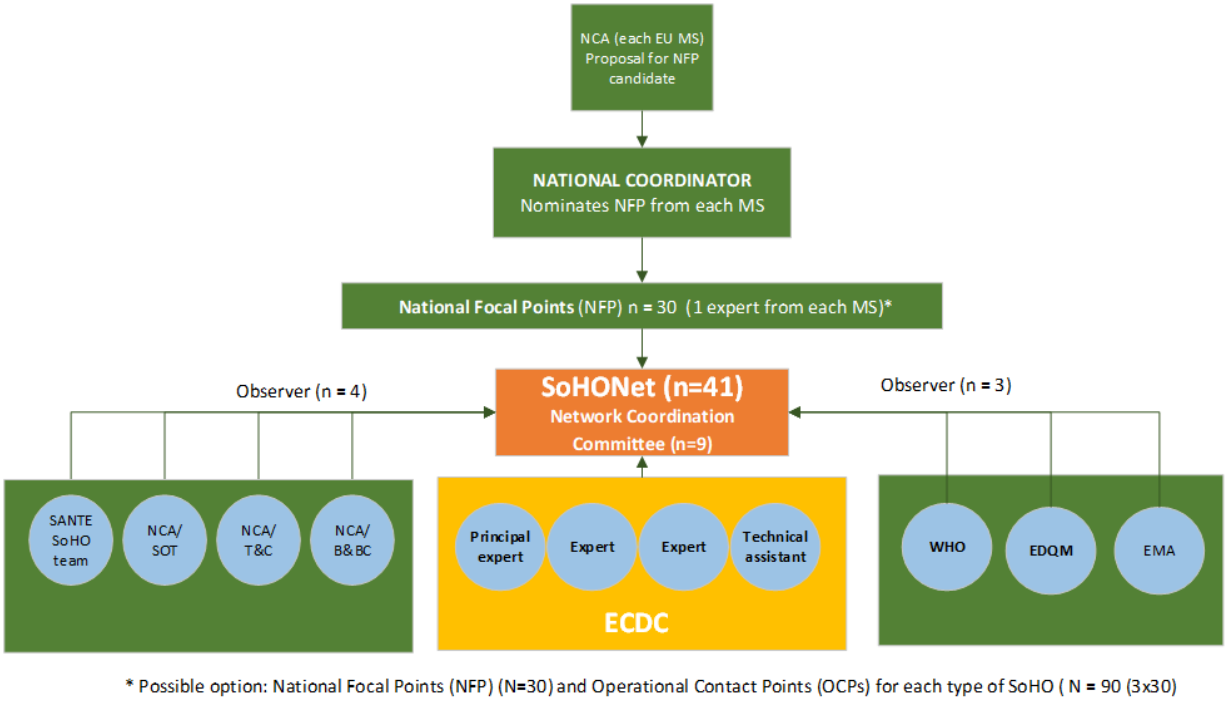


Figure 15.1: European Network for Substances of Human Origin – SoHONet

15.3 The ECDC role in the revised BTC framework

The policy options proposed for the revision of the BTC legislation have built on these developments. Under policy Option 2, technical rules on donor eligibility and testing would be removed from EU legislation and replaced by references to Technical Standards published by expert bodies. For risks associated with communicable disease transmission by SoHO, the expert body concerned would be ECDC.

Policy option 2 proposals were strongly supported by Member State authorities and professionals in the BTC field, both in the public consultations and in workshops on relevant topics, in particular the Hearing hosted by the Commission to discuss keeping technical rules up-to-date. At that Hearing, ECDC confirmed that the following topics are relevant to communicable diseases and could be defined by ECDC, in line with the centre's mandate:

- Rules for donor deferral/exclusion to prevent transmission of communicable diseases
- Requirements for donor selection questionnaires in relation to communicable disease transmission risk
- Communicable diseases to be screened in donors routinely and in specific circumstances
- Communicable disease testing methods to be applied (e.g. serology, NAT etc.)
- Rules on reporting of positive donor testing results to competent authorities or ECDC, if required by legislation
- Rules on combining measures (donor questionnaires, testing, microbial inactivation) to achieve required safety levels of BTC.

ANNEX 16: DETAILS OF THE MEASURES AND POLICY OPTIONS

	Option 1	Option 2	Option 3
	Decentralised regulation	**Joint regulation**	**Central Regulation**
Objectives 1 & 2	Common measures (M1A, M2A): o Define strong principles for protecting citizens and remove outdated specific technical provisions; o Clarify the scope to include all SoHO applied to human persons for therapeutic or any other purpose with specific exceptions; o Implement improved reporting on serious adverse reactions and events (including self-reporting by BTC donors).		
	Provides **blood and tissue establishments** with the freedom to make reference to a variety of national and international guidance when conducting risk assessments of their own activities with a view to setting their internal technical standards to protect citizens (M1B, M2B).	Requires blood and tissue establishments to follow the technical standards for safety and quality, developed and maintained by nominated **expert bodies** as referred to in EU legislation. Member States are required to publish more stringent national rules in an accessible format (M1B, M2B).	Requires blood and tissue establishments to follow the technical standards for safety and quality defined in **EU law.** Member States are required to publish more stringent national rules in an accessible format (M1B, M2B).
Objective 3	Common measures (M3A&B): o Define stronger principles (e.g. independence of inspectors); o Implement a graded approach to oversight, proportionate to the risk level of the establishments/activities carried out; o Provide a legal basis for EU audits; o Provide a legal basis for joint inspections; o Implement a scheme for voluntary mutual peer audits among the NCAs; provide training and guidance (by the Commission). Regardless of the policy option, establishments are always inspected and authorised by their competent authority for BTC; SoHO entities are registered.		
Objective 4	Common measures (M4A): o A BTC advisory mechanism to provide advice and legal clarity to Member States on when and what BTC requirements are applicable to BTC innovations processed or used in new ways; o A risk-based authorisation by competent authorities for BTC processed or used in new ways, with proportionate requirements for clinical data on the efficacy (benefits) provided by establishments; *the three PO apply for conducting risk assessments of novel processes by establishments:*		
	Establishments have to design their risk assessments on novel processes, which are	Establishments conduct risk assessments on novel processes in compliance with technical guidance from	Establishments conduct risk assessments on novel processes in compliance with technical

	evaluated by the competent authority inspectors (M4B).	expert bodies as referred to in EU legislation (M4B)	rules set in EU legislation (M4B)
Objective 5	Common measures (M5A): o Implement measures for crisis preparedness: strengthened supply monitoring (reporting of activity data); *the three PO apply* Implement measures for crisis management (emergency plans, notification in case of drop in supply) for critical BTC; *the three PO apply* o Provisions in EU legislation to strengthen Member States ability to intervene to control and adjust supply, as necessary, under their national competence, and allow evidence-based support action at EU level.		
	Establishments have to develop monitoring and notification systems and emergency plans. These will be reviewed for adequacy by the authority during inspection (M5B).	Establishments follow the guidance from expert bodies, as referred to in EU legislation, for rules on sufficiency data reporting (including monitoring and notifications) and on emergency preparedness (M5B).	Establishments follow the rules set in EU legislation on sufficiency data reporting (including monitoring and notifications) and on emergency preparedness (M5B).

Table 16.1: description of the policy options and common measures

* BTC advisory mechanism: to be an efficient and timely advisory mechanism, when questions can relate to other legal frameworks (borderlines, starting materials, combination products), such BTC advisory mechanism will allow to build an interface that articulates with equivalent advisory bodies in other EU legal frameworks (including Committee for Advanced Therapies (EMA), Innovation Task Force (EMA), Borderline Classification Group (HMA), Medical Device Coordination Group (and its relevant sub-groups e.g. Borderline & Classification Working Group). Eventually, this will allow to come to more common EU-level advice and legal clarity for innovators of new BTC-based therapies, across legal sectors. This is further explained in Annex 12.

Simplification can be brought by an EU-wide data system in the SoHO sector to support the use of best available evidence and data for the professionals, health providers, innovators, public authorities and other stakeholders through federated interoperable systems. The development of such network of resilient, secure and trustworthy infrastructures and technologies provides the frame for a fit-for purpose, coherent interoperable and technology-driven regulatory reporting.

In the context of **oversight**, the extended scope (to include breast milk, FMT, processing at the bedside etc.) will bring additional responsibilities and regulatory obligations for competent authorities. The burden will be simplified by the introduction of a **graded approach** to define the extent of regulatory intervention.

Safety & Quality	Examples	Regulatory Intervention

Impact		All entities to be registered
High	Blood and Tissue Establishments	High: Establishment AUTHORISATION (risk-based inspections, full requirements for quality management, facilities, personnel etc.) +Preparation process authorisation for every process carried out
Medium	Entities that process SoHO with immediate use – autologous bedside, in surgery, Intrauterine insemination (IUI) clinics	Medium: REGISTRATION with limited reporting obligations (annual activity data and adverse outcome reports) + preparation process authorisation
Low	Other entities active in the SoHO field (but that do not process or store BTC donations, e.g. donor registries, clinical users of SoHO, distributors)	Low: REGISTRATION (with limited reporting obligations where relevant)

Table 16.2: Graded approach for efficient oversight

For improved readability and simplification, the measures were grouped according to their intended effect in achieving the five objectives. This grouping is used to report on costs and expected impacts. When measures differ by option, the wording of option 2 is presented.

Objective	***Group***	***Measure – DG SANTE***	***Measure - ICF***
Patient protection	**M1A** – Fill regulatory gaps (e.g. FMT, breast milk) *(common to all policy options)*	M1.2: EU law incorporates definitions ensuring that safety and quality provisions apply to all SOHO/BTC for which the Treaty give competence to the EU.	M1.2: EU law is changed so that all SOHO/BTC for which the EU has legal competence are covered by EU safety and quality rules (bringing breast milk, faecal microbial transplants, etc. under EU law)
		M1.9: "Same surgical procedure" exclusion for point of care preparations is refined/removed – hospitals, healthcare providers are required to register their activities and report.	M4.1: The "same surgical procedure" exclusion for point of care preparations is refined/removed.
	M1B - Up-to-date technical rules *(differs by policy option)*	M1.3: EU law requires MS to publish more stringent rules in an accessible format.	M1.3: EU law requires MS to publish more stringent rules in an accessible format.
		M1.4: EU development components of IT platform for quality and safety requirements.	M1.4: The European Commission builds an IT platform that provides information on quality and safety requirements
		M1.5+M1.6: EU law requires NCA inspectors to evaluate the BTC establishments' risk assessments ensure that they have been conducted effectively and that the rules adequately managed the identified risks AND EU law requires BTC establishments to assess risks associated with their donor selection etc. procedures and to set technical rules for safety and quality compliant with the "high level principles" in EU legislation. They must base the rules on risk assessment and scientific evidence, and update whenever the need arises. BE/TEs can follow inter/national	M1.5+M1.6: National competent authority inspectors have to evaluate blood and tissue establishments' risk assessments to ensure that they have been conducted effectively and that the rules set adequately manage the identified risks. AND Blood and tissue establishments are required to assess the risks associated with their procedures, and to set technical rules for safety and quality, compliant with the

		guidance or standards from other bodies in setting their rules. OR M1.7: EU law requires establishments to take into account ECDC/EDQM rules on quality & safety requirements. EU law require BE/TE to 'take into account' the rules issued by the expert bodies. Or M1.8: EU law incorporates quality & safety requirements and contains a mechanism for regular updates to respond to changing risks and technologies under Comitology rules.	principles defined in EU law. They must base the rules on risk assessment and scientific evidence, and update whenever the need arises. They can follow inter/national guidance or standards from other bodies in setting their rules. OR M1.7: Blood and tissue establishments are required to follow ECDC/EDQM technical rules on quality & safety requirements. EDQM/ECDC update their guidance as required; MS expert group participates in the EDQM drafting and review process.) OR M1.8: Blood and tissue establishments are required to take into account quality and safety requirements that are defined in EU law. There is a mechanism to provide regular updates in response to changing risks and technologies (using Comitology rules).
Donor & offspring protection	**M2A** – Set donor and offspring protection principles in law *(common to all policy options)*	M2.1: EU law on donor and offspring safety amended to ensure (a) reporting of SARE for donors and offspring and (b) monitoring of those donors and offspring with specific concerns.	M3.1: EU law incorporates high level principles to protect BTC donors, including reporting measures (SARE/monitoring outcome), also self-reporting of adverse events by donors
		M2.2: EU law incorporate high level principles to protect donors and offspring born from donated gametes/embryos. That includes donor eligibility, data protection, that children do not have genetic conditions reasonably avoidable through selection and testing; that	M3.2: EU law incorporates high level principles to protect offspring born from donated gametes/embryos, including reporting measures (SARE/monitoring outcome).

		genetic conditions are reported and appropriate follow-up actions taken.	
		M2.3: EU law incorporates new definitions.	M3.3: EU law incorporates new definitions (e.g. to include genetic disease transmission by medically assisted reproduction using donor gametes or embryos as an 'adverse reaction')
	M2B – Up-to-date technical standards for donor and offspring protection *(differs by policy option)*	M2.4: EU law require BE/TEs to define detailed quality & safety requirements to protect donors and protect children born from donated gametes or embryos. OR M2.5: EU law requires establishments to take into account ECDC/EDQM rules on quality & safety requirement for donors and offspring from MAR. OR M2.6: EU law incorporates quality & safety requirements for donors and MAR offspring, and a mechanism incorporated to update these as needed.	M3.5: EU law requires establishments to define detailed quality & safety requirements to protect donors and protect children born from donated gametes or embryos. OR M3.6: EU law requires expert bodies to define detailed quality & safety requirements for donors and offspring of medically assisted reproduction, and requires establishments to follow the rules issued by the expert bodies. OR M3.7: EU law incorporates quality and safety requirements for donors and offspring of medically assisted reproduction, and a mechanism to update these as needed.
Oversight	**M3A** - Set principles for oversight in legislation (e.g. independence of authority, risk-based inspections) *(common to all policy options)*	M3.1: EU law incorporates oversight principles for the organisation and for staff	M2.1: EU law incorporates oversight principles for the NCA and for staff
		M3.2: EU law obligates NCAs to base their inspection regimes on a risk-based approach.	M2.2: EU law requires competent authorities to base their inspection regimes on a risk-based approach
		M3.3 Commission develops and maintains common	M2.3: The European Commission will develop and

		guidance on oversight	maintain common guidance on oversight
		M3.5: EU law provides legal framework for Joint Member State inspections of blood and tissue establishments	M2.5: EU law is amended to implement a legal framework for Joint Member State inspections of blood and tissue establishments
	M3B - Provide EU support *(common to all policy options)*	M3.4: Commission audits of national control systems, accompanied by MS experts	M2.4: Commission audits of national control systems, accompanied by MS experts
		M3.6: EU Support for training & IT	M2.6: The European Commission will develop the relevant component of the IT platform for oversight
Innovation	**M4A** - Create BTC mechanism to advise on applicability of BTC legislation and liaise with equivalent MD and (AT)MP mechanisms *(common to all policy options)*	M4.1: Establishment of EU level advisory mechanism to recommend/advise MS on when/what BTC requirements should be applied in part or in full.	M4.2: An EU level advisory mechanism is established to recommend/advise MS on when/what BTC requirements should be applied in part or in full
		M4.2: Interplay SoHO/pharma/MD: A mechanism is introduced to prompt regulators of 'adjacent' legal frameworks (SOHO/Pharma/Medical Devices) to better coordinate their rules, especially in respect of substances that are regulated under more than one legal framework.	M4.3: A mechanism is introduced to prompt regulators of 'adjacent' legal frameworks (SOHO/Pharma/Medical Devices) to better coordinate their rules, especially in respect of substances that are regulated under more than one legal framework.
		M4.3: Classification advice: advice related to other legal frameworks. EU level advisory mechanism will advise where other frameworks (in particular medical devices and medicinal products) might be applied for particular novel BTC. Implementation might involve exchange/mutual consultation with advisory bodies for MP (EMA innovation task force, EMA CAT) and MD frameworks (Borderlines and Classification Working Party).	M4.4: An EU level advisory mechanism will advise where other frameworks (in particular medical devices and medicinal products) might be applied for particular novel BTC. Implementation might involve exchange/mutual consultation with advisory bodies for MP (EMA innovation task force, EMA CAT) and MD frameworks (Borderlines and Classification Working Party).

	M4B - Risk-based authorisation BTC processed or used in new ways, including clinical data when justified, with guidance *(differs by policy option)*	M4.4: The EU legislation will set principles for authorisation procedure (good practice for authorisation procedures including validation of facilities, equipment and processing and clinical data requirement according to level of risk and novelty) to demonstrate safety and efficacy in patients.	M4.5: EU law sets principles for authorisation procedure (good practice for authorisation procedures including validation of facilities, equipment and processing and clinical data requirement according to level of risk and novelty) to demonstrate safety and efficacy in patients.
		M4.5: Strengthened Preparation Process Authorisation: EU law modified so that, for major changes in the steps of collection, processing and use of BTC, competent authorities will have to grant prior authorisation based on data demonstrating safety and benefit for patients that justifies any risks associated with treatment with BTC prepared in innovative ways.	M4.6: EU law requires that, for major changes in the steps of collection, processing and use of BTC, competent authorities have to grant prior authorisation based on data demonstrating safety and benefit for patients that justifies any risks associated with treatment with BTC prepared in innovative ways.
		M4.6: The EU legislation will set rules for implementing a clinical trial for BTC (if high level of risks)	M4.7: EU law sets rules for implementing a clinical trial for BTC (if high level of risks).
		M4.7: EU will develop an exchange (IT) platform for NCAs to exchange info regarding (novel) process authorisations (the platform would be used for (voluntary) acceptance of	M4.8: The European Commission will develop an exchange (IT) platform for competent authorities to exchange info regarding (novel)

		authorisations among MS). This includes clinical evidence collected by clinicians with the support of learned societies.	process authorisations (the platform would be used for (voluntary) acceptance of authorisations among MS). This includes clinical evidence collected by clinicians with the support of learned societies.
		M4.8: EU law obligates BE/TEs to conduct risk assessments on novel processes. These are evaluated by the competent authority inspectors.	M4.9: EU law requires establishments to conduct risk assessments on novel processes. These are evaluated by the competent authority inspectors.
		M4.9: EU law obligates BE/TEs to design the risk assessments on novel processes following inter/national or standards from other bodies. OR M4.10: EU law obligates BE/TEs to conduct risk assessments on novel processes in compliance with technical guidance from expert bodies as referred to in EU legislation OR M4.11: EU law obligates BE/TEs to conduct risk assessments on novel processes in compliance with technical rules set in EU legislation	M4.10: EU law requires establishments to design the risk assessments on novel processes. Establishments could follow inter/national or standards from other bodies. OR M4.11: EU law requires establishments to conduct risk assessments on novel processes in compliance with technical guidance from expert bodies as referred to in EU legislation. OR M4.12: EU law requires establishments to conduct risk assessments on novel processes in compliance with technical rules set in EU legislation.
Supply monitoring	**M5A** – introduce supply monitoring and notification rules *(common to all policy options)*	M5.1: EU law is amended to impose mandatory monitoring obligations on blood and tissue establishment, including activity report, export, imports and supplies, linked to existing reports, such as SARE, as well as notifications.	M5.1: EU law is amended to impose mandatory monitoring obligations (activity data reporting) on blood and tissue establishments.

		M5.2: EU law is amended to require mandatory notification of sufficiency data for certain critical BTC in case of shortage/drop in supply (rapid notifications)	M5.2: EU law is amended to require mandatory notification of sufficiency data for critical BTC in case of shortage/drop in supply (rapid notifications) by blood and tissue establishments to their national competent authorities (and from those to the Commission).
		M5.3: EU law is amended to require mandatory emergency plans, for critical BTC, at the level of the blood and tissue establishments, and national competent authorities.	M5.3: EU law is amended to require mandatory emergency plans, for critical BTC, at the level of the blood and tissue establishments, and national competent authorities.
		M5.4: The European Commission will develop the relevant component of the (IT) platform for exchange of information on supply and activity.	M5.4: The European Commission will develop the relevant component of the IT platform for exchange of information on supply and activity.
		M5.5: Provisions in EU legislation to strengthen Member States ability to intervene to control and adjust supply, as necessary, under their national competence, and allow evidence-based support action at EU level.	M5.5: EU law is amended to strengthen MS ability to intervene to control and adjust supply, as necessary, under their national competence, and allow evidence-based support action at EU level.
	M5B – Require emergency preparedness plans with guidance *(differs by policy option)*	M5.6: EU law is amended to obligate BE/TEs to develop monitoring and notification systems and contingency plans. These will be reviewed for adequacy by the authority during inspection. OR M5.7: EU law is amended with references to guidance from expert bodies for rules on sufficiency data reporting (including monitoring and notifications) and on emergency	M5.6: EU law is amended to obligate BE/TEs to develop monitoring and notification systems and contingency plans. These will be reviewed for adequacy by the authority during inspection. OR M5.7: EU law is amended with references to guidance from expert bodies for rules on sufficiency data reporting (including monitoring

		preparedness/contingency. OR M5.8: EU law is amended to include rules on sufficiency data reporting (including monitoring and notifications) and on emergency preparedness	and notifications) and on emergency preparedness/contingency. OR M5.8: EU law is amended to include rules on sufficiency data reporting (incl. monitoring and notifications) and on emergency preparedness

Table 16.3: grouping of measures

Objective 1: Ensure safety and quality for patients treated with BTC therapies and fully protect them from risks linked to BTC.				
The measures proposed under Objective 1 aim to increase patient protection from avoidable risks, by keeping technical rules for safety and quality up to date. The options share many of the same components but differ in where the rules (which blood and tissue establishments need to follow when preparing their risk assessments) are defined. The scope of European law on BTC is changed to fill in gaps and cover other substances of human origin Quality and safety principles are set into the new law. Depending on the option, blood and tissue establishments have freedom to use available guidance from a much wider range of sources when conduction risk assessments of their own activities with a view to setting their internal technical standards (option 1), or they have to follow guidance provided by EU expert bodies (Option 2), or they have to follow rules set in EU law. Under all Options, the Commission will build an IT platform to share safety/quality information. Under Options 2 and 3, Member States are required to publish more stringent national rules in an accessible format.				
Measures		**1. Decentralised regulation**	**2. Joint regulation**	**3. Central Regulation**
M1.1	Principles for safety and quality principles in EU law	☐	☐	☐
M1.2	EU law is changed so that all SOHO/BTC for which the EU has legal competence are covered by EU safety and quality rules (bringing breast milk, faecal microbial transplants, etc. under EU law)	☐	☐	☐
M1.3	Member States are required to publish more stringent BTC rules in an accessible format		☐	☐
M1.4	The European Commission builds an IT platform that provides information on quality and safety requirements	☐	☐	☐
M1.5	National competent authority inspectors have to evaluate blood and tissue establishments' risk assessments to ensure that they have been conducted effectively and that the rules set adequately manage the identified risks	☐		
M1.6	Blood and tissue establishments are required to assess the risks associated with their procedures, and to set technical rules for safety and quality, compliant with the principles defined in EU law. They must base the rules on risk assessment and scientific evidence, and update whenever the need arises. They can follow inter/national guidance or standards from other bodies in setting their rules.	☐		
M1.7	Blood and tissue establishments are required to follow ECDC/EDQM technical rules on quality & safety requirements. EDQM/ECDC update their guidance as required; MS expert group participates in the EDQM drafting and review process.)		☐	
M1.8	Blood and tissue establishments are required to take into account quality and safety requirements			☐

	that are defined in EU law. There is a mechanism to provide regular updates in response to changing risks and technologies (using Comitology rules).			
M1.9	The "same surgical procedure" exclusion for point of care preparations is refined/removed.	☐	☐	☐

Objective 2: Ensure safety and quality for BTC donors and for children born from donated eggs, sperm or embryos

The measures proposed under Objective 2 are intended to reduce the avoidable risks for BTC donors and for children born from donated eggs, sperm or embryos. The intended outcome is they are protected from the risks that are specific to those groups, including exposure to hormonal treatment for egg and stem cell donation and the risks of genetic disease transmission to children born from assisted reproduction.

Measures		1. Decentralised regulation	2. Joint regulation	3. Central Regulation
M2.1	EU law incorporates high level principles to protect BTC donors, including reporting measures (SARE/monitoring outcome), also self-reporting of adverse events by donors	☐	☐	☐
M2.2	EU law incorporates high level principles to protect offspring born from donated gametes/embryos, including reporting measures (SARE/monitoring outcome).	☐	☐	☐
M2.3	EU law incorporates new definitions (e.g. to include genetic disease transmission by medically assisted reproduction using donor gametes or embryos as an 'adverse reaction')	☐	☐	☐
M2.4	The European Commission will develop the relevant component of an IT platform for quality and safety requirements	☐	☐	☐
M2.5	EU law requires establishments to define detailed quality & safety requirements to protect donors and protect children born from donated gametes or embryos	☐		
M2.6	EU law requires expert bodies to define detailed quality & safety requirements for donors and offspring of medically assisted reproduction, and requires establishments to follow the rules issued by the expert bodies.		☐	
M2.7	EU law incorporates quality and safety requirements for donors and offspring of medically assisted reproduction, and a mechanism to update these as needed			☐

Objective 3: Strengthen and allow for harmonisation of oversight practices among Member States	
There is a single package, built up from six distinct measures that are together intended to tackle the problem of divergent approaches to oversight**.** These measures are expected to lead to the strengthening and harmonisation of oversight among Member States and ensure trusted, effective and independent oversight of BTC activities. They should help to secure equal protection of citizens, and facilitation of exchange of BTC among MS.	

Measures		Options 1-2-3
M3.1	EU law incorporates oversight principles for the NCA and for staff	☐
M3.2	EU law requires competent authorities to base their inspection regimes on a risk-based approach	☐
M3.3	The European Commission will develop and maintain common guidance on oversight	☐
M3.4	Commission audits of national control systems, accompanied by MS experts	☐
M3.5	EU law is amended to implement a legal framework for Joint Member State inspections of blood and tissue establishments	☐
M3.6	The European Commission will develop the relevant component of the IT platform for oversight	☐

Objective 4: Ensure the framework is future-proof and facilitates the development of safe and effective innovative BTC therapies
The measures proposed under Objective 4 intend to tackle the problem that the scale and pace of innovation in the BTC sector is reduced by features of the existing framework, including insufficient provision for authorisation of novel BTC, insufficient provisions for proof of clinical value of BTC and unclear borderlines between the BTC framework and those for medicinal products, medical devices, etc.. There is no forum that can classify BTC-based therapies and technologies at the interface of other EU legal frameworks. The aim is to facilitate innovation of safe BTC therapies. Most of the Objective 4 measures appear in all options. The options differ in what rules the establishments are required to use when conducting their risk assessments.

Measures		1. Decentralised regulation	2. Joint regulation	3. Central Regulation
M4.1	An EU level advisory mechanism is established to recommend/advise MS on when/what BTC requirements should be applied in part or in full	☐	☐	☐
M4.2	A mechanism is introduced to prompt regulators of 'adjacent' legal frameworks	☐	☐	☐

	(SOHO/Pharma/Medical Devices) to better coordinate their rules, especially in respect of substances that are regulated under more than one legal framework.			
M4.3	An EU level advisory mechanism will advise where other frameworks (in particular medical devices and medicinal products) might be applied for particular novel BTC. Implementation might involve exchange/mutual consultation with advisory bodies for MP (EMA innovation task force, EMA CAT) and MD frameworks (Borderlines and Classification Working Party).	☐	☐	☐
M4.4	EU law sets principles for authorisation procedure (good practice for authorisation procedures including validation of facilities, equipment and processing and clinical data requirement according to level of risk and novelty) to demonstrate safety and efficacy in patients.	☐	☐	☐
M4.5	EU law requires that, for major changes in the steps of collection, processing and use of BTC, competent authorities have to grant prior authorisation based on data demonstrating safety and benefit for patients that justifies any risks associated with treatment with BTC prepared in innovative ways.	☐	☐	☐
M4.6	EU law sets rules for implementing a clinical trial for BTC (if high level of risks).	☐	☐	☐
M4.7	The European Commission will develop an exchange (IT) platform for competent authorities to exchange info regarding (novel) process authorisations (the platform would be used for (voluntary) acceptance of authorisations among MS). This includes clinical evidence collected by clinicians with the support of learned societies.	☐	☐	☐
M4.8	EU law requires establishments to conduct risk assessments on novel processes. These are evaluated by the competent authority inspectors.	☐	☐	☐
M4.9	EU law requires establishments to design the risk assessments on novel processes. Establishments could follow inter/national or standards from other bodies.	☐		
M4.10	EU law requires establishments to conduct risk assessments on novel processes in compliance with technical guidance from expert bodies as referred to in EU legislation.		☐	
M4.11	EU law requires establishments to conduct risk assessments on novel processes in compliance with technical rules set in EU legislation.			☐

Objective 5: Improve the resilience of the sector, mitigating risk of shortages.				
These measures are intended to reduce the risk of shortages due to insufficient or unreliable BTC supply by establishing system to monitor donations and supply and to support pre-emptive and/or corrective action in case of disruptive epidemiological outbreaks, or similar events. There are eight measures, most are common to all options.				
Measures		**1. Decentralised regulation**	**2. Joint regulation**	**3. Central Regulation**
M5.1	EU law is amended to impose mandatory monitoring obligations (activity data reporting) on blood and tissue establishments.	☐	☐	☐
M5.2	EU law is amended to require mandatory notification of sufficiency data for critical BTC in case of shortage/drop in supply (rapid notifications) by blood and tissue establishments to their national competent authorities (and from those to the Commission).	☐	☐	☐
M5.3	EU law is amended to require mandatory emergency plans, for critical BTC, at the level of the blood and tissue establishments, and national competent authorities.	☐	☐	☐
M5.4	The European Commission will develop the relevant component of the IT platform for exchange of information on supply and activity	☐	☐	☐
M5.5	EU law is amended to strengthen MS ability to intervene to control and adjust supply, as necessary, under their national competence, and allow evidence-based support action at EU level.	☐	☐	☐
M5.6	EU law is amended to obligate BE/TEs to develop monitoring and notification systems and contingency plans. These will be reviewed for adequacy by the authority during inspection.	☐		
M5.7	EU law is amended with references to guidance from expert bodies for rules on sufficiency data reporting (incl monitoring and notifications) and on emergency preparedness/contingency.		☐	
M5.8	EU law is amended to include rules on sufficiency data reporting (incl. monitoring and notifications) and on emergency preparedness			☐

Table 16.4: Details of measures for each objective.

ANNEX 17: EU MEASURES THAT CAN OFFSET THE COSTS FOR PUBLIC AUTHORITIES AND ESTABLISHMENTS

For Member States, technical assistance is foreseen to adjust to the new regulatory requirements (e.g. reporting on more stringent national measures; implementation of authorisation processes) using an established technical assistance instrument. In the EU budget, EUR 9.6 m is foreseen to offset for such one-off costs – this is mainly relevant for MS which do not yet implement some of the proposed measures – typically the smaller ones or Central and Eastern European countries. A continued administrative support of EUR 2.7 m is foreseen for continued support annually (as from 2026).

For professionals, financial and technical support is foreseen to facilitate adjustment to the new regulatory requirements, in particular for digitalisation to connect local data systems to the central network to allow automated reporting on SARE, activity data, clinical data on efficacy and supply sufficiency. This adjustment support is foreseen for establishments (BE/TE – EUR 10 m), for clinical societies (EUR 4.4 m) and for registered entities in hospitals (EUR 2 m). A continued administrative support is also foreseen for clinical societies who are expected to play an important role in the digital aspects (EUR 1.5 m) and for hospital/entities for whom some light new reporting requirements are created (EUR 2 m).

Different EU budgets can be explored for this additional technical and financial support to offset the costs of adjustment on the local/national level (including EU4Health, European Health Data Space, or support for structural reforms).

	2022	**2023**	**2024**	**2025**	**2026 +**	
Costs of offsetting measures, expressed in EUR 1000	**negotiation/ adoption**		**phased in implementation**		**running costs**	NPV
technical assistance to sector	**3 500**	**4 900**	**12 700**	**4.900**	**6.200**	5 797
technical assistance to **MS** to support adjustment	1 500	2 700	2 700	2 700	2 700	2 303
technical assistance to **BE/TE** to support adjustment			10 000			971
technical assistance to **clinical societie**s to support adjustment incl. support to BE/TE and hospitals		2 200		2 200	1 500	1 236
technical assistance to **hospitals/registering entities** to support registering and clinical data reporting	2 000				2 000	1 404

Table 17.1: summary of measures to off-set costs for BTC establishments and national authorities

ANNEX 18: SUMMARY OF THE ONLINE CONSULTATIONS

18.1 Introduction

This document presents a summary of the results of the Public and Targeted Consultations carried out between 21 January 2021 and 15 April 2021 in the context of the revision of the EU legal frameworks on blood, tissues and cells. As such, it expands the Summary Report of the Public Consultation [27] by adding the conclusions of the Targeted Consultation. It supplements the Stakeholder Consultation, which is part of the Impact Assessment.

The aim of the Consultation was to collect stakeholders' views on the validity of the findings of the evaluation of the BTC legislation, in particular in light of the COVID-19 crisis, and their opinions on the policy options, and measures, proposed in the Inception Impact Assessment [28] to address the shortcomings identified in the evaluation. Both questionnaires, that for the Public and for the Targeted Consultation, were structured according to the 5 key problems identified in relation to the current legislation:

1) Patients are not fully protected from avoidable risks;
2) There are avoidable risks for BTC donors and for children born from donated gametes;
3) Divergent approaches to oversight cause unequal levels of safety and quality and barriers to exchange of BTC across the EU;
4) BTC legislation lags behind innovation;
5) The EU is vulnerable to interruptions in supply of some BTC.

Specific issues explored included the level at which technical rules for the protection of BTC donors and recipients should be defined, especially considering the comparative cost-effectiveness of different approaches, secondly the effectiveness of proposed measures to improve oversight of BTC activities, thirdly the impact of measures proposed to support BTC innovation for patient benefit and finally the effectiveness of measures proposed to support a sustainable supply of BTC. Where this was considered necessary, the consultations also gathered data and experiences to further consolidate the understanding of the presented problems.

This report provides an overview of the responses received from both consultations, grouping them by stakeholder category, where relevant. A summary of stakeholder opinions on the options proposed to address the problems are presented under the headings of the five problems. Stakeholders' responses are published together with this report and in line with the Commission's applicable rules.

18.2 Respondents

Two online questionnaires were used: One directed at the general public (Public Consultation) and one directed at stakeholders directly impacted by the legal revision

[27] https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12734-Blood-tissues-and-cells-for-medical-treatments-&-therapies-revised-EU-rules/public-consultation_en

[28] https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12734-Blood-tissues-and-cells-for-medical-treatments-&-therapies-revised-EU-rules_en

(Targeted Consultation). To respond to the Targeted Consultation, participants had to be affiliated with an organisation active in the BTC field. Those eligible to respond to the Targeted consultation were encouraged to also reply to the Public Consultation, and to keep their responses to the Targeted Consultation to the fields in which they had experience. Of the respondents to both questionnaires, 32% stated that their organisation is registered in the Transparency Register.

The Public Consultation gathered a total of 214 replies, including 19 from individuals/citizens (9%) and 195 from non-individual respondents (91%). This group was largely made up of company/business stakeholders (61; 29%) and non-governmental organisations (44; 21%). It also included 35 public authorities (16%) as well as 24 academic/research institutions (11%), 17 business associations (8%), 1 consumer organisation and 13 other non-individual respondents.

The responses of the Public Consultation were screened for duplicates and 'coordinated/campaign responses' (same content/free text submitted by more than 10 respondents) using PowerBI. This analysis detected 15 coordinated responses, representing views of the cord blood bank sector.

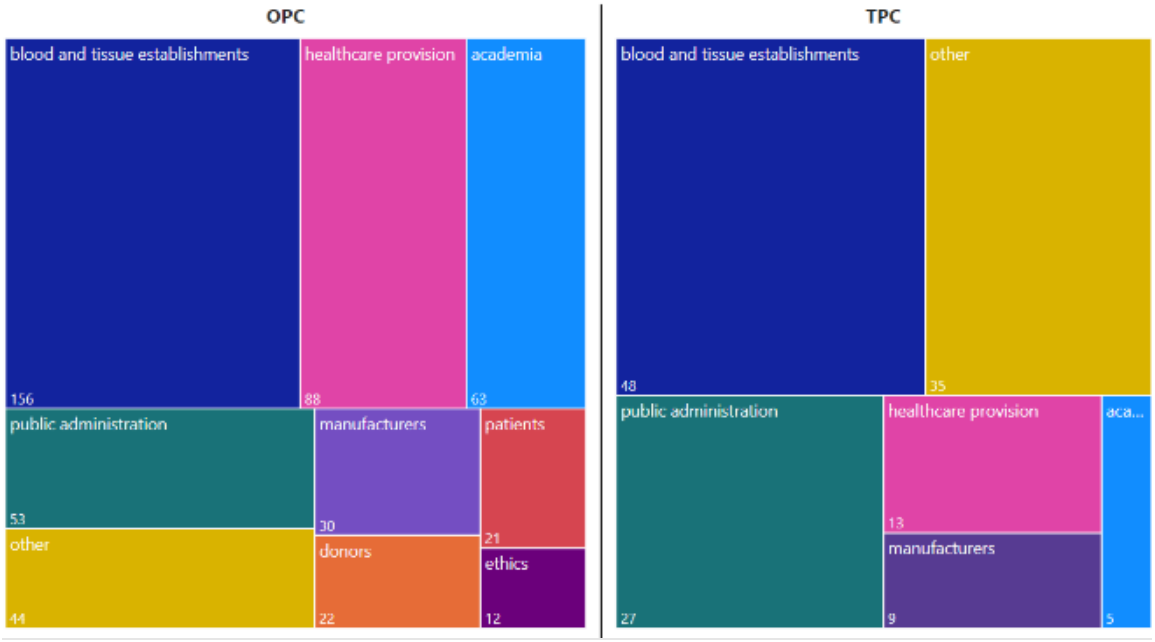
A total of 159 responses were received for the Targeted Consultation. Here, respondents were asked on a more granular level to select the description best suited to their role in the sector, the responses to which were then categorized. The group of respondents included blood and tissue establishments (48; 35%), public administration (27; 20%), healthcare providers (13; 9%) manufacturers (9; 7%) and academia (5; 4%) as well as 35 other non-individual respondents (Figure 18.1)[29].

Across both surveys, the breakdown of the respondents by activities indicates that the different groups of targeted stakeholders were satisfactorily addressed[30], reflecting especially the key role of BTC establishments in the sector, as well as the role of healthcare providers and academia. Member State competent authorities, ministries and other public administration bodies were also well represented among the respondents. Non-governmental organisations representing donors and patients and ethics bodies also responded, as well as private industry (manufacturers of products based on blood, tissues or cells as well as manufacturers of the devices needed in the processing of BTC).

Figure 18.1. Activities of respondents to both Consultations. For Public Consultation: non-individual respondents only; multiple answers possible. For Targeted Consultation: all respondents; one answer possible. (Public Consultation, n= 214; Targeted Consultation, n= 159)

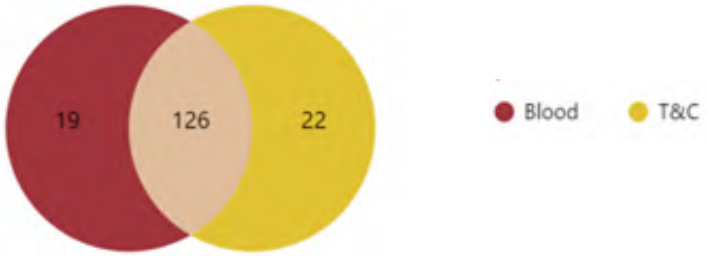
[29] Stakeholders describing themselves as "others" were prompted to give a free-text explanation. This group included mainly respondents that considered themselves belonging to multiple of the suggested categories, as for example some professional representations, innovators, regulators and authorities.

[30] The list of stakeholders to be consulted can be seen in the consultation strategy published in the Inception Impact Assessment in 2020: https://ec.europa.eu/info/law/better-regulation/



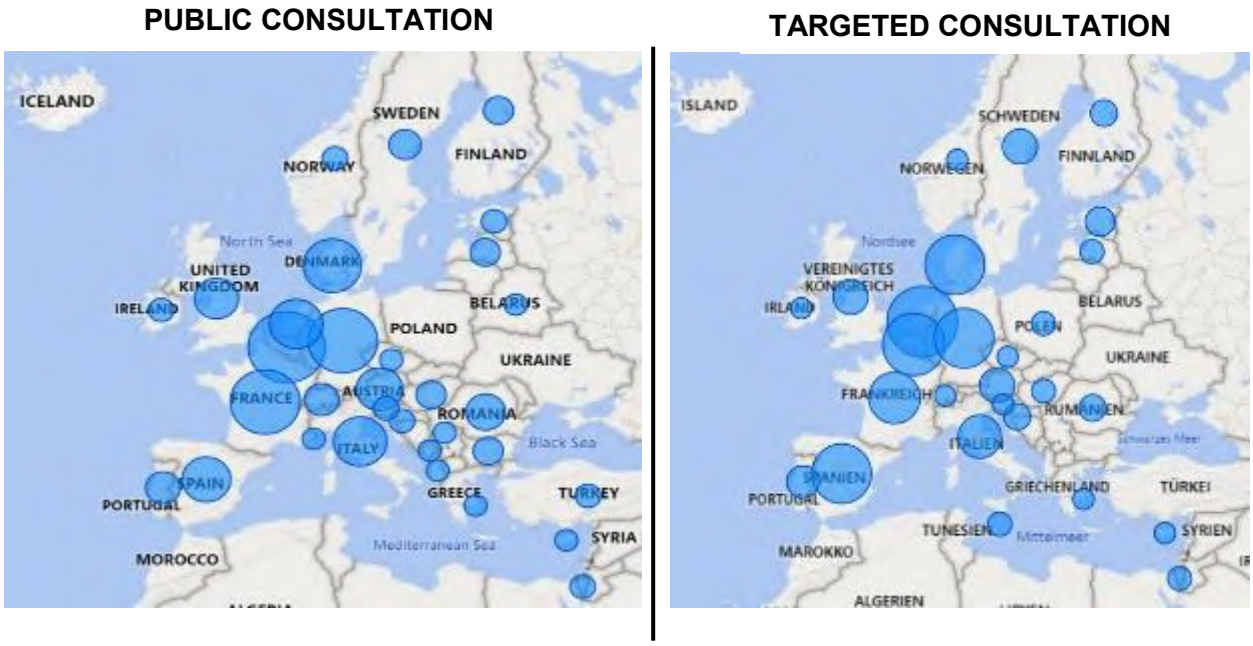
The majority of the organisations responding to either survey work both in the blood and the tissues & cells sector (126), while 19 indicated to be active exclusively in the blood sector and 22 exclusively in the tissues & cells sector (Figure 18.2).

Figure 18.2: Stakeholders active in the Blood Sector and the Tissues and Cells Sector.



As regards the geographical distribution of respondents (Figure 18.3), the highest number of replies came from Belgium, including from several EU advocacy/umbrella organisations, followed by Germany, France, and the Netherlands. In the Targeted Consultation, there were respondents from almost every EU Member State, and from several non-EU countries.

Figure 18.3. Geographic coverage of respondents to both Public Consultations (Size of blue circles proportional to number of respondents based in this country). (Public Consultation, n= 214; Targeted Consultation, n= 159)



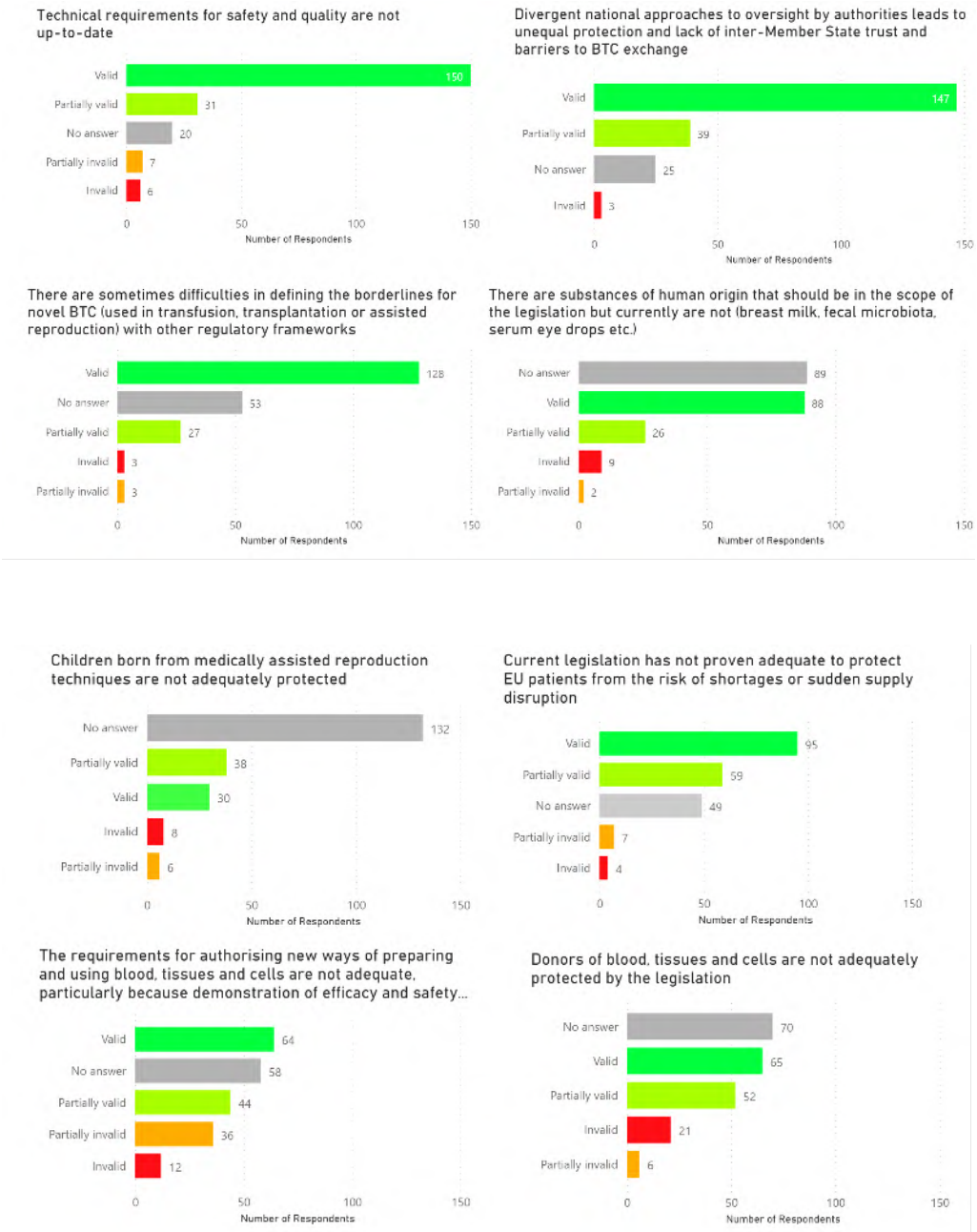
In addition to the answers given to both questionnaires, 39 different additional documents were annexed by respondents, including a number of position statements of relevance to future policy.

18.3 Summary of Responses

18.3.1 Validity of the Evaluation Findings

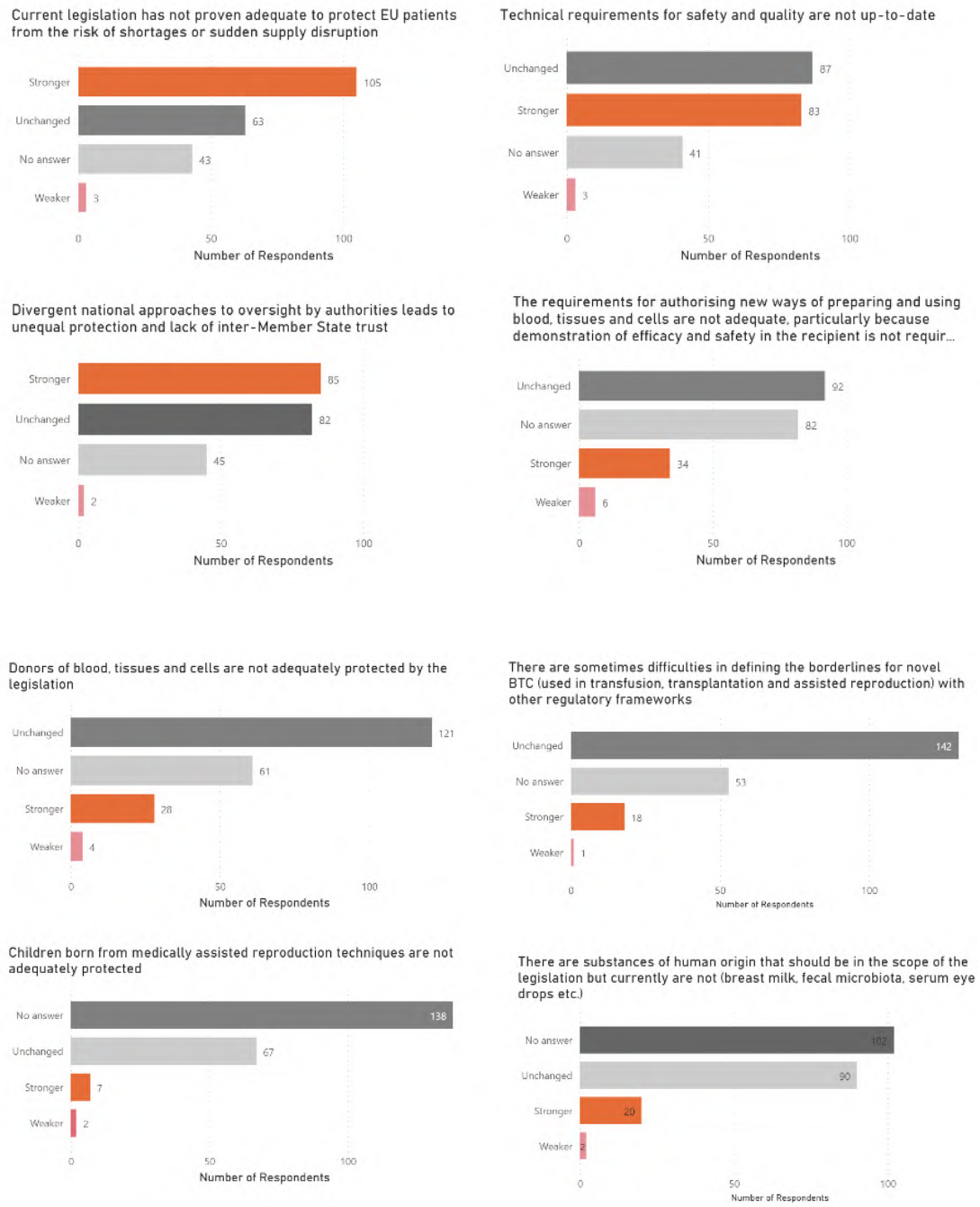
The findings of the 2019 evaluation were largely confirmed by the respondents to the Public Consultation as still valid in 2021 (Figure 18.4) and in the light of the COVID-19 crisis (Figure 18.5). Throughout, issues relevant to a limited sub-set of stakeholder groups tended to receive a higher number of 'no answer' responses and thus lower rates of complete agreement (this applied in particular to questions related to specific disciplines such as medically assisted reproduction).

Figure 18.4. To what extent are the findings of the evaluation still valid one year since the publication of the evaluation? (Public Consultation, n = 214).



When asked about the impact of the ongoing COVID-19 crisis specifically, participants in the Public Consultation agreed that the shortcomings identified in the evaluation retained their validity and were not weakened (Figure 18.5). Especially in regards to shortages and sudden supply disruption, and to a slightly weaker extent in regards to technical requirements and lacking harmonization in oversight, large groups of respondents agreed that the pandemic had even exacerbated the problem. In the other categories, most respondents indicated that the findings of the evaluation were unchanged.

Figure 18.5. How did the COVID-19 pandemic influence the evaluation conclusions? (Public Consultation, n = 214)



In the Public Consultation, respondents were also asked to share, in free text form, any lessons learnt from the COVID-19 pandemic that could be of relevance to the revision process. A total of 111 responses were received, many of which highlighted the increased importance of measures already under consideration in the revision process. In particular, the need to maintain transport and supply chains in the BTC sector (22 mentions), the added value of preparedness or contingency plans (17 mentions) as well as a strengthened role for ECDC (15 mentions), and the benefits of harmonization (14 mentions) were agreed upon by many respondents. References were also made to rule setting in the EU, highlighting the need for more speed and regulatory flexibility, for example as regards the Plasma Master File (8 mentions each). Notably, public authorities were more likely to reference a strengthened role of ECDC while answers on harmonization or flexibility were more likely to come from blood/tissue establishments, healthcare providers or professional representations. The need to maintain transport and supply chains was mainly underlined by blood and tissue establishments, while comments highlighting the importance of preparedness/contingency plans were relatively widely distributed.

18.3.2 Objective 1: Patient protection

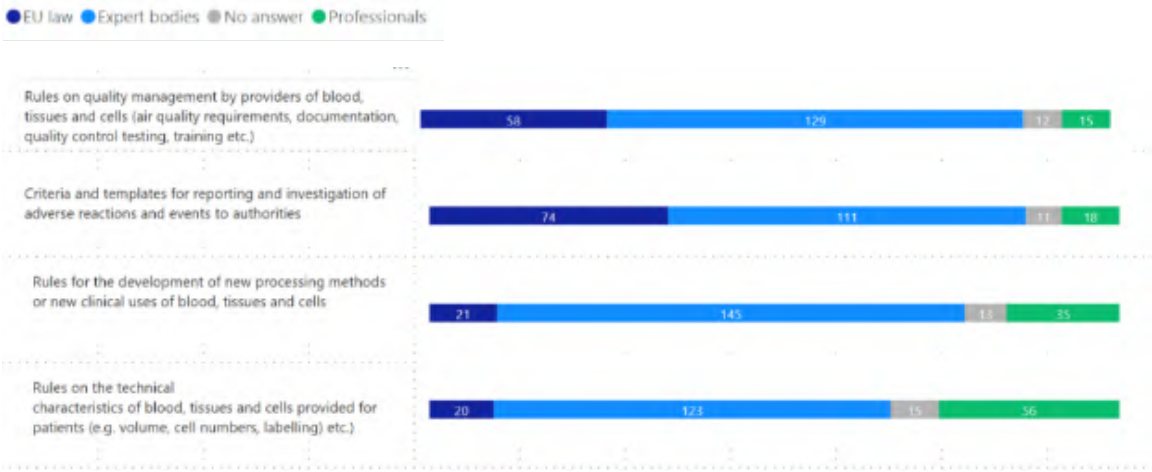
To ensure optimal patient protection, technical rules for the collection, processing, storage and distribution of BTC need to be kept up to date with scientific evidence. Three key options have been proposed to address this need in the revised legal framework:

1) technical rules are set by professionals themselves;
2) technical rules are set by expert bodies such as the ECDC and EDQM (Council of Europe);
3) technical rules are set in EU law.

Stakeholders were presented with all three of these options and asked to express their preference, considering particular areas of technical rule setting (Figure 18.6).

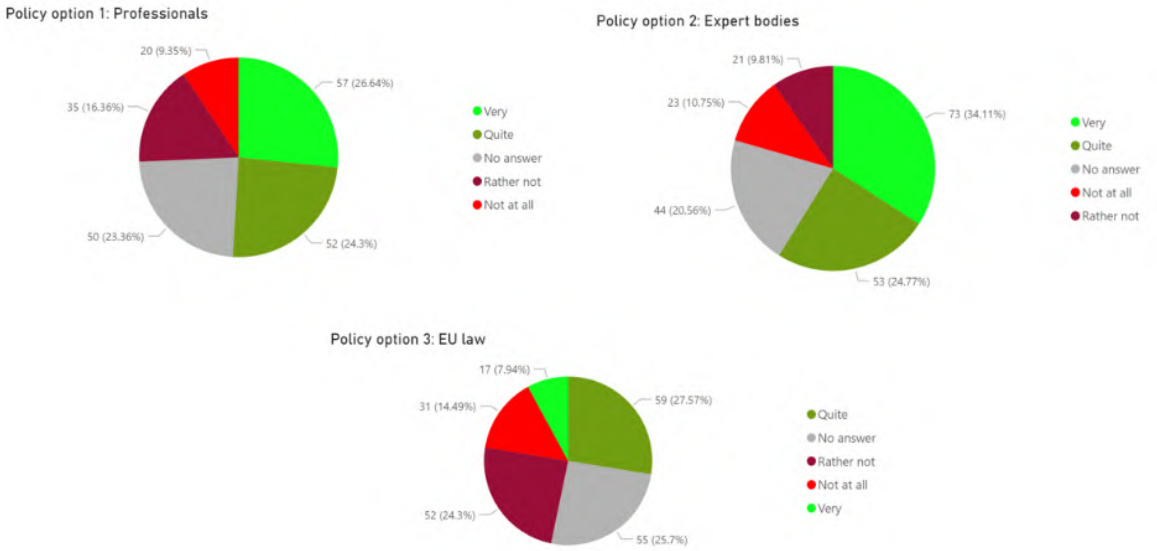
Across all stakeholder categories, the majority of respondents to the Public Consultation indicated that expert bodies (such as ECDC or EDQM) would be their preferred option for setting technical rules to effectively achieve safety and quality for patient protection. However, it is noted that the sub-group of BTC establishments also frequently selected ‘professionals’ for this role, e.g. when asked about setting the rules on the technical characteristics of BTC that will be provided to patients (49 establishments selected expert bodies, while 45 selected professionals in their answers). It also needs to be noted that, when asked about elements that relate to oversight, e.g. criteria/templates to report Serious Adverse Reactions and Events, many respondents believe these should partly be set in EU law.

Figure 18.6. Who should set technical rules to effectively achieve up-to-date safety and quality rules to protect patients? (Public Consultation, n = 214).



To further explore the feasibility of all three options for setting technical rules, respondents were asked to specifically assess the expected cost-effectiveness of each. Answers reflected the preferences expressed previously. Thus, rule setting by expert bodies was considered to be most cost-effective (123 responses of very or quite cost-effective), closely followed by updates by professionals (109 responses of very or quite). Technical rule setting in EU law was considered the least cost-effective (76 responses of very or quite) (Figure 18.7). Analysis by stakeholder groups showed some differences of opinion amongst these groups. Notably, slightly more respondents of blood/tissue establishments considered rule setting by professionals (66 responses) to be (very or quite) cost effective compared to expert bodies (59 responses). National competent authorities with oversight responsibility indicated that expert bodies would be cost-effective.

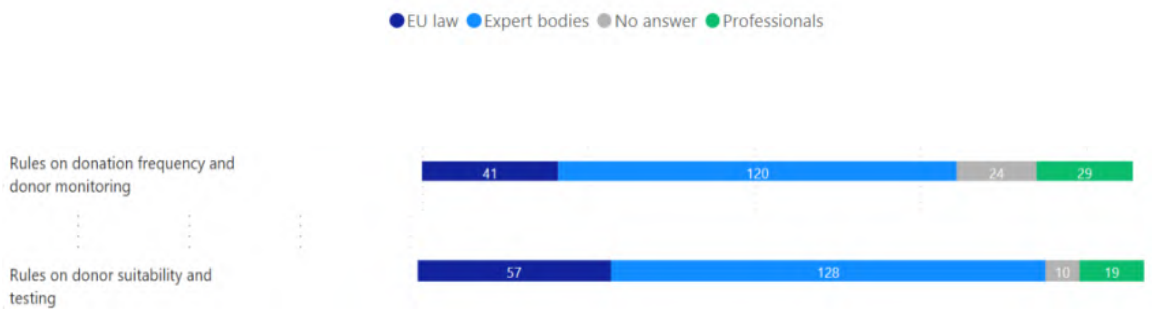
Figure 18.7. Which of the options would overall be most cost-effective to set technical rules? (Public Consultation, n = 214).



18.3.3 Objective 2: Donor and offspring protection

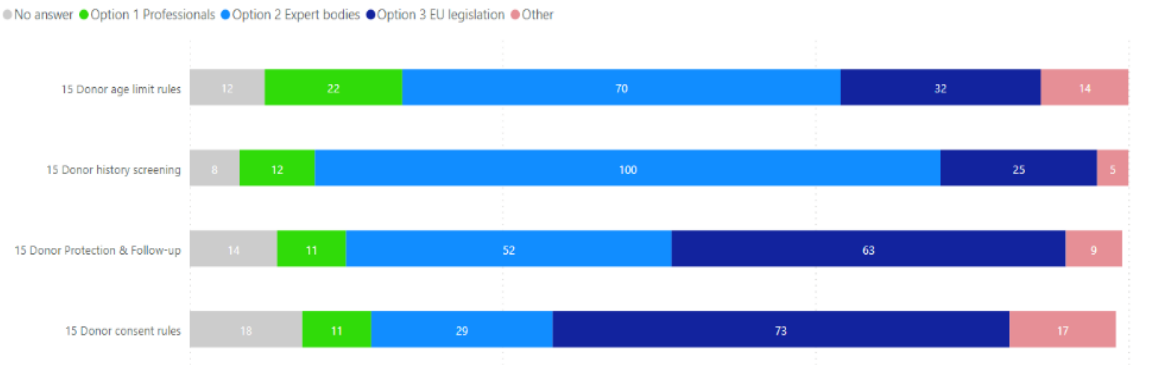
In addition to patient protection, donor and offspring protection also requires the setting of technical rules. Rules for donor and offspring protection could similarly be set by professionals themselves, by expert bodies, or by EU law. Again, the majority of respondents in the Public Consultation indicated that expert bodies (such as ECDC or EDQM) would be the most appropriate for this role (Figure 18.8). However, when comparing these responses to those for technical rules for patient protection, a more significant role was indicated for EU law than for professionals.

Figure 18.8. Who should set out these technical rules [for donor protection] to effectively achieve up-to-date safety and quality rules, based on good science? (Public Consultation; n = 214).



Interestingly, the Targeted Consultation indicated a slight preference that rules on donor protection and follow-up should be set in EU legislation (63 responses) rather than by Expert Bodies (52 respondents) (Figure 18.9). The same tendency was reported on donor/donor family consent rules (73 responses for EU legislation, 29 responses for expert bodies). Preference for Expert Bodies was however reflected by the answers regarding donor age limit rules and donor medical/behavioural history screening (70 and 100 responses for expert bodies, respectively).

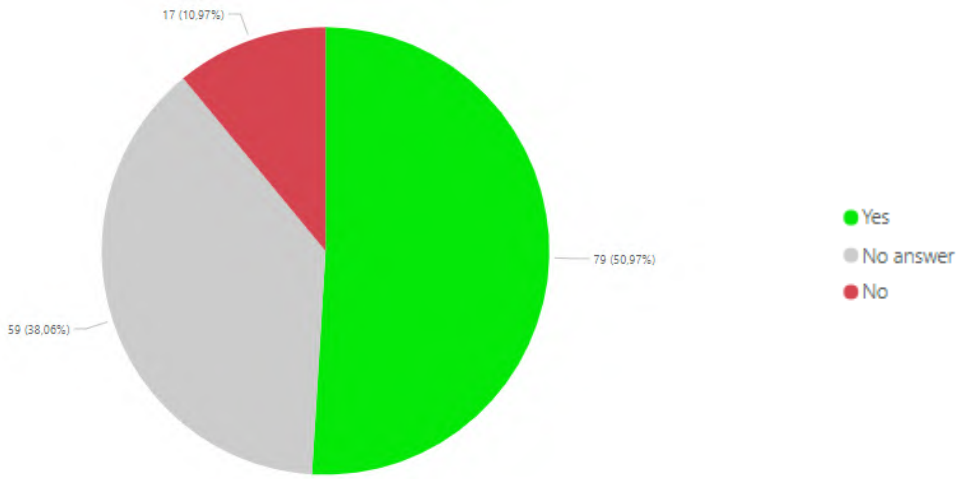
Figure 18.9. Who should set out these technical rules (for donor protection) to effectively achieve up-to-date safety and quality rules, based on good science? (Targeted Consultation; n= 148-150)



18.3.4 Procedural details on Technical Rules

To ensure that revised technical rules could protect all relevant patients and donors, consideration was also given to the need to apply the future framework to any SoHO currently not covered. Of particular relevance here might be novel substances of human origins, such as faecal microbiota transplants or human donor milk. In the Targeted Consultation, around half of the respondents indicated agreement with such an extension of the scope (Figure 18.10). This agreement was generally shared across all stakeholder categories.

Figure 18.10. Should the legislation include in its scope substances of human origin that do not meet the definitions of blood, tissues or cells (e.g. breast milk or intestinal microbiota) but are applied to patients? (Targeted Consultation, n = 155)



Respondents were moreover asked to provide free-text comments on the inclusion of substances not currently included in the BTC framework. Of the 66 answers received, most considered an extension to all SoHO (10 mentions) or all SoHO intended for human application (9 mentions) to be the best option, while 3 responses indicated that any extension of the scope would be inappropriate. Some of the respondents used the opportunity to propose criteria for the decision of in- and exclusion in the future framework and suggested safety and ethical considerations (3 mentions) or risk assessments (4 mentions).

Both the Public and the Targeted Consultation asked respondents for further comments regarding the procedures for rule setting. In the Public Consultation, 105 comments were received. Nineteen of these expressed support for policy option 2 while 2 expressed concerns; for policy option 3, support and concern were expressed by 3 responses each. In addition, these comments highlighted the importance of international harmonization (7 mentions), and the inclusion of GAPP/EUROGTPII into any rule-setting considerations (4 mentions). A significant group of respondents also used this opportunity to call for specific sets of technical rules for individual subsectors (medical assisted reproduction (12 mentions), cord blood (12 mentions), and faecal microbial transplants (5 mentions)).

Responses received to two relevant questions in the Targeted Consultation (96 and 52 responses, respectively) gave some additional insights into the priorities of stakeholders

regarding the process for rule setting under policy option 2. Participants highlighted the fundamental importance of transparency (29 mentions), clear references to the evidence base (24 mentions), and opportunities for stakeholder consultations (21 mentions) as key success factors. Interestingly, responses were split on the importance of geographical representation: While six responses indicated that a balance between Member States would need to be ensured, five responses preferred participation in rule-setting to be based on technical expertise rather than Member State representation. On a separate note, respondents expressed some levels of concern regarding the status of EDQM as a European expert body, highlighting that the scope of Member States was not the same as the EU (8 mentions) and that its current working methods were not sufficiently transparent (4 mentions). Stratifications showed that concerns regarding membership scope came from manufacturers, patient representations, and oversight authorities, while concerns regarding working methods of EDQM came from manufacturers and researchers.

18.3.5 Objective 3: Oversight

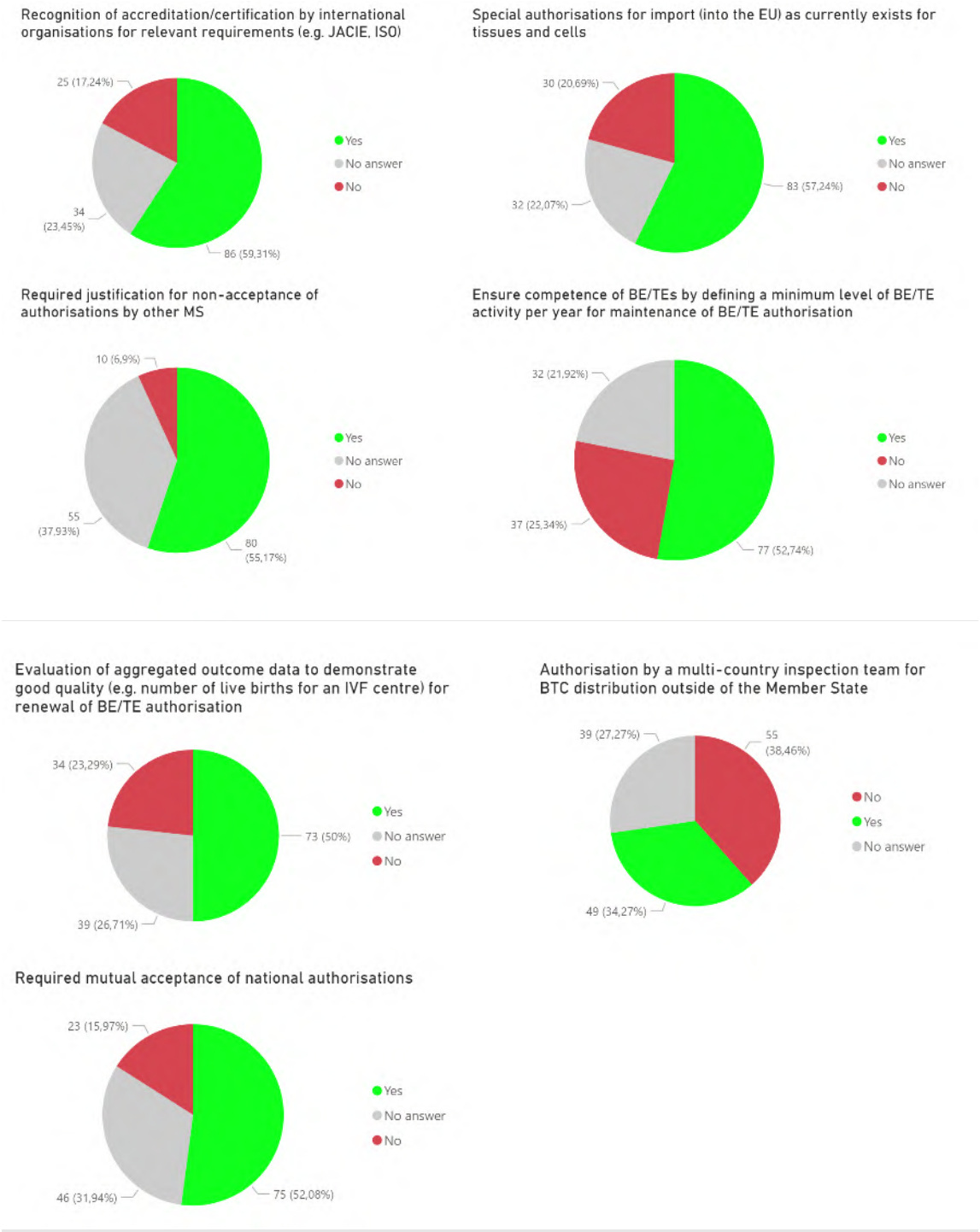
To address the problems resulting from divergent national approaches to oversight, various measures were proposed in the Inception Impact Assessment. In the Public Consultation, respondents were asked to assess the expected impact of introducing oversight principles (meaning that EU law would mandate certain requirements for competence or independence of authorities), European Commission audits of National Competent Authorities, greater collaboration between Member States and a training programme (Figure 18.11). Overall, respondents considered that the proposed measures to strengthen oversight would have positive impacts – average response being 7 on the scale of 1-10 (negative to positive, default value 5).

Figure 18.11. Overview of expected impact of strengthened oversight measures (1 to 10 – negative to positive). (Public Consultation; n = 214).

	Average	Median	Standard deviation
Introducing oversight principles for authorities in EU legislation. The principles might address independence of inspectors, conflicts of interest, and competency requirements for staff in authorities.	7.17	7	1.8
Audits by the European Commission of Member State competent authority control systems (inspection, vigilance, reporting).	6.87	7	2.0
Greater collaboration between Member State competent authorities (e.g. joint inspections, peer audits of inspections)	6.99	7	2.17
EU programme of training of staff in national/regional authorities to agreed guidelines	7.3	8	2.06

In the Targeted Consultation, some further measures were proposed to participants. In most cases, the majority of respondents agreed that some consideration should be given to these proposals as well, although authorisations by a multi-country inspection team for BTC distribution outside of the Member State were rejected by a large group of respondents (Figure 18.12).

Figure 18.12. Which of the following [proposed measures for an improvement of the key requirements for authorisation of blood and tissue establishments] should be considered in legislation? (Targeted Consultation; n= 143-146).



Participants in the Targeted Consultation also indicated a preference that requirements for national authorities be defined and updated by Expert Bodies. When asked about the inclusion of oversight principles in EU legislation, the largest group indicated that 'skill and competence of inspectors and other authority officials' as well as 'lack of personal conflicts of interest of inspectors at each inspection' would increase confidence in oversight practice (122 and 108 respondents, respectively). 'Transparency to citizens'

and ‘adequate administrative capacity’ were also well-received (93 and 91 respondents, respectively) while ‘independence from the regulated sector’ as well as ‘legal mandates to inspectors’ seemed to be slightly less important (76 and 60 respondents, respectively).

To gain a better understanding of the concerns regarding strengthened oversight measures, the Public Consultation asked participants to provide free-text explanations. The 87 answers showed that respondents anticipated an increase in costs (14 mentions), administrative burden (13 mentions), complexity (4 mentions), resource usage and workload (3 mentions respectively). Further concerns were expressed regarding a possible detrimental effect on existing cross-border collaborations within the EU (3 mentions) or with 3rd countries (3 mentions). Finally, the importance of harmonization and coordination was underlined (3 mentions), and a preference was expressed to keep ATMP products under the pharma framework (3 mentions).

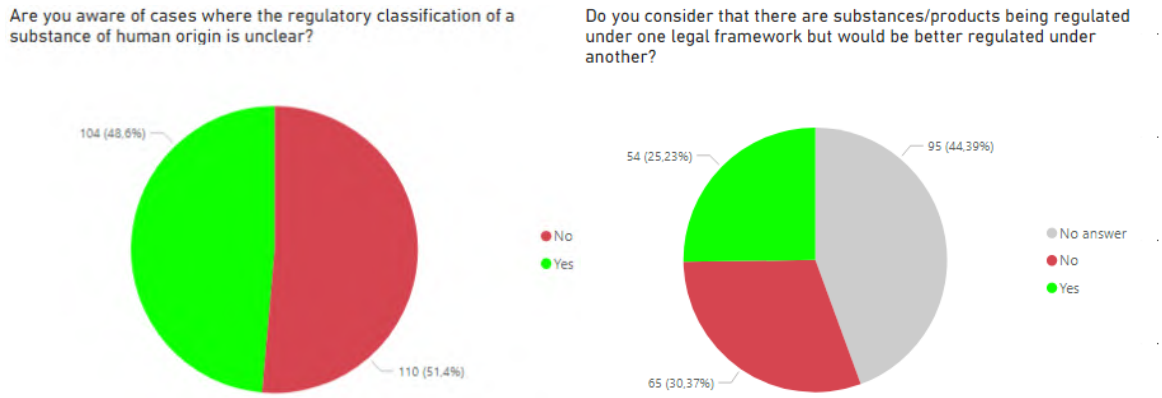
Commenting on the new proposed approach for oversight more generally, a total of 93 free-text comments was received in the Public Consultation. Support was expressed for mutual recognition of inspections (8 mentions) and for the inclusion of general principles in EU law (5 mentions); these supportive comments came largely from public authorities and industry. Large groups of respondents highlighted the importance of special consideration for some subsectors, regarding for example clear criteria for inspectors, training, and financial support in the medically assisted reproduction sector (12 mentions), separate legal categories for perinatal tissues (21 mentions) and faecal microbial transplants (4 mentions). Respondents also remarked that new oversight measures should be flexible enough to allow for risk-based approaches (6 mentions) and ensure coordination between EU level and local inspections (4 mentions).

18.3.6 Objective 4: Innovation

To allow for high levels of innovation with patient benefit, a clear understanding of potential barriers faced by innovators in the sector is needed. Previously identified challenges related to unclear regulatory classifications of substances were confirmed as almost half of the respondents (48%) in the Public Consultation, including a high number of National Competent Authority respondents, indicated that they are aware of cases where the regulatory classification of a substance of human origin is unclear (BTC establishments 48%; manufacturers of products based on BTC 53%; National Competent Authorities 62%).

Approximately a quarter of the respondents to the Public Consultation considered that there are substances/products being regulated under one legal framework that would be better regulated under another (Figure 18.13). There were slight variations between categories of respondents; notably, almost 40% of respondents from academia or patient organisations reported problems of this nature.

Figure 18.13. Clarity and application of regulatory classifications (Public Consultation, n= 214).

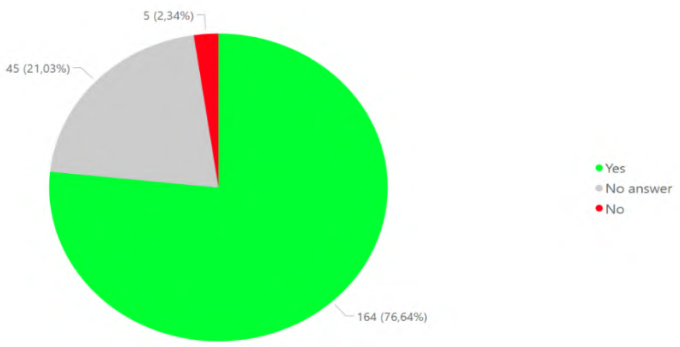


In the Targeted Consultation, respondents were moreover asked to specify whether they had experience developing treatments at the borderline of frameworks. 49% (72 respondents) indicated that they did and were prompted to give further information (Figure 18.14). This indicated significant complexities in understanding which frameworks were applicable, obtaining guidance or confirmation thereof, and obtaining acceptance from other Member States.

Figure 18.14. How easy have the following aspects been when developing therapies that are at the borderlines with other EU regulated frameworks? (Targeted Consultation, n= 58-71).

When considering different measures to address the problem highlighted in Figures 18.13 and 18.14, respondents to the Public Consultation tended to agree that the set-up of an EU-level structure or committee to advise Members States on whether a substance falls under the BTC legislation would have positive impacts, the average response being 7 on the scale of 1-10. There were slight variations across the categories of stakeholders, but considering the number of respondents the difference is not meaningful [31].

Furthermore, the overwhelming majority of respondents to the Public Consultation indicated that such an EU-level structure or committee, if established, should co-ordinate decisions with the equivalent committees in the medicinal product and medical device frameworks (Figure 18.15).

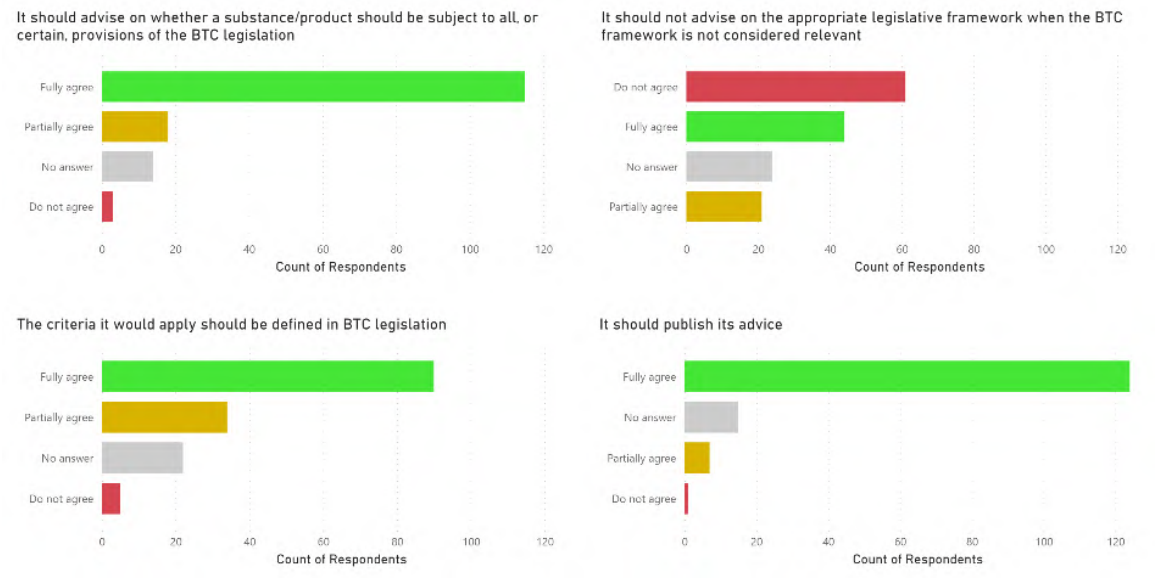


[31] Total average is 7.02; average response of NCA 7.24; BE/TE and healthcare providers 6.99; patients 6.95; manufacturers 6.88.

Figure 18.15. If an EU level structure or committee were established, do you consider that it should co-ordinate decisions with the equivalent committees in the medicinal product and medical device frameworks? (Public Consultation, n= 214).

In the Targeted Consultation, more specific proposals were made and strong majorities supported that such a mechanism should advise whether a substance or product should be subject to all or certain provisions of the BTC legislation, that it should work based on criteria defined in the BTC legislation, and that it should publish its advice. Respondents were more divided and overall less supportive that the same mechanism should advise on the appropriate legal framework when the BTC framework is not considered relevant (Figure 18.16).

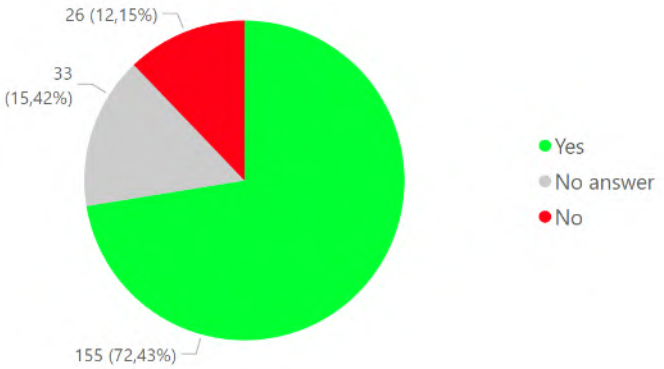
Figure 18.16. If an EU mechanism were introduced to advise on whether, and if so which, BTC requirements should apply to a substance/product, what is your view on the following statements regarding its possible role? (Targeted Consultation, n= 147-151).



Further remarks made on such a mechanism were largely positive, focussing on increased harmonization with its added benefit in facilitating exchange between Member States and improved guidance for local authorities. Some concerns were expressed, highlighting that advice should be set up to prevent "shopping" for advice and to maintain global harmonization of criteria for ATMP.

To effectively regulate innovation in the BTC field, respondents agreed that legal requirements should be introduced in EU legislation for demonstrating safety, quality, and efficacy when BTC are prepared or used in new ways (Figure 18.17). Support for such requirements was expressed by the majority of respondents across different types of organisations, including public authorities (85%), citizen/patient organisations (80%), academic/research organisations (71%) as well as companies/business associations (60%). Breaking down the responses by sector, the support is strongest in the blood sector (81%), followed by tissues & cells (77%). A slightly weaker majority of the respondents in the pharmaceuticals sector (57%) also support this approach.

Figure 18.17. Should legal requirements be introduced in EU legislation for demonstrating safety, quality and efficacy when blood, tissues and cells are prepared or used in new ways? (Public Consultation, n= 214).



Those who indicated that such authorisation requirements would not be necessary were prompted to explain their reasoning, and indicated mainly that overlaps with the existent frameworks on Medicinal Products or Medical Devices should be avoided. In the Targeted Consultation, these views were reflected once again. Here, participants were also asked to estimate the potential financial and administrative burden on a scale of 1 to 10. On average, this burden was estimated at 6.2 for blood and tissue establishments and 5.7 for competent authorities and clinical users.

The targeted consultation made some specific suggestions as to what these authorisation practices could look like. Participants indicated agreement that these should be risk-proportionate (104 fully agree, 10 partially agree), conditional on clinical evidence (86 fully agree, 19 partially agree), and that clinical outcome registries could be included in this (70 fully agree, 40 partially agree). They further indicated that preparation process authorisations should be publicly registered (64 fully agree, 41 partially agree) and shared and mutually recognized between Member States (53 fully agree, 52 partially agree). Their application should be specific to intended clinical applications (60 fully agree, 37 partially agree). When asked whether such authorisations should be applied if changes applied only to the mode of clinical application, participants were largely in disagreement (10 fully agree, 38 partially agree).

18.3.7 Objective 5: Supply

On the topic of sustainability of the supply of BTC, stakeholders were asked to assess the expected impact of proposed measures. Overall, respondents considered that the establishment of mandatory EU monitoring and routine reporting of sufficiency data (including rapid notifications in case of sudden significant supply drops) would have positive impacts. The average responses for the measures are 7 on the scale of 1-10 (1 being no impact and 10 being a significant positive impact). Respondents also indicated an increase of administrative burden and costs for such measures (with an average response of 6 on a scale of 1 to 10 in both cases, where 1 indicated low burden or cost and 10 a very significant burden or cost). The answers given to the Targeted Consultation generally mirrored these assessments. Other measures selected as helpful to address a sudden drop in supply (crisis) were co-operation amongst BTC establishments (selected by 117 respondents), notification to the EU level with collective response co-ordination (93) and notification to the National Competent Authority with a national response (72).

To allow for further suggestions on measures to address sudden drops in supply, participants in the Public Consultation were asked for free-text comments. The 26 comments received included some suggestions repeated by multiple respondents, mainly EU support for exchange of substances between Member States (5 mentions) and a reference to the conclusions drawn by the EMA task force on supply (4 mentions). In addition, the creation of ECDC standards for Patient Blood Management was advocated (3 mentions). References to the EMA Task Force came mostly from manufacturers and stakeholders involved in plasma-derived medicinal products.

Around 65% of respondents indicated that mandatory preparedness/contingency plans would bring some, or many, improvements, with around 20% of respondents not responding to this question. This support was strongest among National Competent Authorities, of which around 80% indicated that they would expect some or many improvements, followed by BTC establishments and healthcare providers (around 60%) and manufacturers (around 40%).

Some concerns on the topic of preparedness/contingency plans were specified in the provided free-text answers, these centred mostly on potential harmful effects on the intra-EU flow of plasma or concerns regarding over-prescription. These concerns came from manufacturers or representations of professionals in the pharmaceutical sector.

Additional proposed measures tended to receive significant support, with the exception of provisions allowing export bans. However, participants also tended to agree that these additional measures would be associated with financial and administrative burdens for stakeholders and authorities (Figure 18.18).

Figure 18.18. Overview of agreement with and expected burden of proposed measures to ensure sufficiency of BTC supply in EU countries. (Targeted Consultation, n= 141-144). Suggestions ordered (top to bottom) by percentage agreement with appropriateness.

	Appropriateness			Financial/Administrative burden			
	Yes	No	No answer	Low	Significant	High	No answer
Promotional donation campaigns	115	2	26	19	**69**	11	44
More trust, collaboration and exchanges between Member States	97	2	44	**45**	38	8	52
Investment in establishment equipment and staff	95	11	36	2	33	**61**	47
EU platforms for the exchange of BTC between Member State establishments	81	17	44	14	**45**	31	52
Reduced wastage	76	20	48	**56**	19	6	62
More appropriate policies for use in clinical settings	66	14	60	31	**41**	6	64
Supply planning at the regional, national or EU level	64	46	30	12	**55**	14	61
Provisions to allow export bans	32	52	56	15	15	18	92

Stratification of respondents revealed some further insights in this case. For example, Blood and Tissue Establishments were more likely to anticipate a high burden associated with EU platforms for improved exchange of substances between Member States while manufacturers tended to expect a low burden associated with promotional donation campaigns.

Participants were also questioned specifically on their attitudes to allocation of BTC according to clinical need. On this point, the widest support was expressed for leaving establishments to collect and provide BTC according to demand (42 of 88 answers) or creating requirements at national level under the guidance of clinicians (37 of 88 answers).

In the 93 concluding comments on supply sufficiency received in the Public Consultation, considerable support was expressed regarding EU measures to help exchange between Member States (7 mentions) as well as beneficial effects of updated and harmonized technical rules (6 mentions). Stratification showed that especially public authorities seemed supportive of improved exchanges between Member States. On the other hand, concerns were raised regarding the effectiveness of contingency planning (4 mentions). A significant group of respondents expressed concern that supply of tissues in medically assisted reproduction may be threatened if donor testing rules were made too complex (12 mentions). Again, national Patient Blood Management plans based on ECDC standards were raised as an additional opportunity to benefit supplies (5 mentions), as well as removing disincentives for donors (4 mentions) and limiting waste of any substances of human origins (3 mentions) [32].

[32] The responses to this question also included a coordinated response on cord blood and perinatal tissues, recommending harmonization and relaxation of rules applicable to cord blood (19 mentions).

ANNEX 19: SOHO-X – DIGITAL PLATFORM

19.1 Introduction

This annex on the Digital Systems in the sector of Blood, Tissues and Cells (SoHO-X) informs and complement the impact assessment on the costs and impacts of the proposed three digital sub-options.

19.2 Digital Check

The digital check tool was used to identify the precise digital aspects or ICT needs of the BTC revision.

DIGITAL CHECK	
Are the expected evolution of the problem and the baseline significantly influenced by digital technologies?	Yes. • Digital technologies play an increasing role in the innovation in the sector – many such technologies are on the border with other regulatory frameworks, in particular medical devices • Information necessary for timely and efficient crisis management is limited due to lack of interoperable data reporting requirements
Does a particular policy option respond to problems only in the physical world (and not in the digital world)?	No. All policy options include a digital component.
Might the option considered be incoherent with the EU's digital policies currently in place (such as eGovernment action plan[247], reuse of existing solutions for electronic identification, signature, delivery and invoicing), under development or revision, and might the option have an impact on digital infrastructures/service levels (see sub-section 19.5.3 below)?	No, because all the proposed options for possible future platforms would represent an evolution of part of the solutions currently active, taking a specific place in the IT ecosystem and bringing additional features and enhancement to the services currently provided.
ICT systems / solutions	
Is there a need to support the initiative by establishing new or revising existing ICT solutions? Is there a need to develop, migrate and/or operate any kind of new or existing IT system, network or service over the internet or private networks. It could be that ICT is in the core of the legislation or a supporting driver of it.	Yes, the possible future ICT solution would need to meet additional needs – on particular in terms of collecting data, reporting and/or establishing connection to existing platforms with interfaces for data exchange. The solution would also implement data analytics features and would provide all the tools to monitor the data, such as reports and dashboards.
Is there a need to establish new or change existing business processes that handle information/data in an electronic/automated manner? "Business process" means a sequence of activities to produce a specific result. Today, most of those activities can	Yes, for all objectives • Manage technical requirements for safety and quality • Reporting on activities, safety, quality, efficacy, supply (from health providers as well as blood and tissue establishments, clinical societies,

be automated by IT systems and tools and executed through electronic workflows that collect, store, retrieve, consult, filter, exchange, report data (text, image, or video)	possibly directly patients/donors) • Information sharing and reports related to oversight • This could be also a good opportunity to review the existing business processes in order to optimize them and, as consequence, improving the overall performance of the system. • Most of the recent IT solutions provide the possibility to design and implement automatic workflows, which would reduce both the time needed to complete a process and the likelihood to have human errors.
Is there a need for managing information electronically in a secure manner or with respect to data protection regulation that would mandate specific ICT measures? Sensitive data must be treated with care. If any option refers to such a need, it is highly possible that special IT security measures should be taken to ensure exchange, integrity and confidentiality of this data, such as encryption, secure hosting, limited access, etc.	Yes, the data managed refers to health information and must be considered sensitive data; personal-level health data is needed to assess the safety, quality and efficacy of BTC procedures.
Would business processes require secure identification and authentication mechanisms or electronic trust services (c.f. eIDAS Regulation)	Yes, the access to the platform must be granted after a registration process. Only registered users will be able to perform specific business processes such as data upload process or data export process, especially those that include personal health data. Further authorization and data visibility could be granted according to specific roles that would be assigned to specific users.

Table 19.1: Digital check.

19.3 Impact Assessment

The Impact Assessment proposes specific measures related to IT/digitalisation for each of the policy options and each of the 5 gaps identified.

The following figure and table show the existing systems and map them in relation to the policy options/measures.

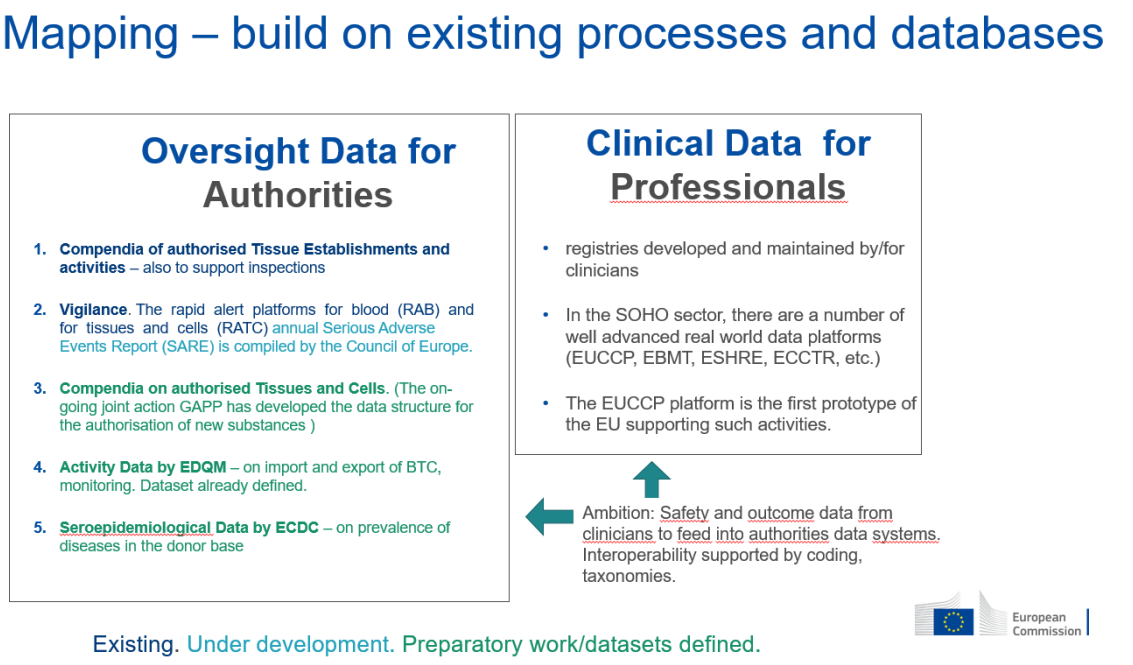


Figure 19.1: Mapping data usage in the SoHO Sector.

Specific Objective	Measure	Existing systems
1. Increase patient protection from all avoidable risks	M1.4 EU development components of IT platform for quality and safety requirements	**EBMT** • The purpose of the Registry is to provide a pool of data to EBMT members to perform studies, assess epidemiological trends, and ultimately improve patients' lives. • Save and improve lives of patients with blood-related disorders through innovation, research and the advancement of cellular and stem cell-based therapies. **EuroGTP II** • Intends to provide practical tools which will assist Tissue Establishments and Organisations Responsible for Human Application, to assess the risk of BTC for the implementation of technical requirements defined for the assessment and verification of the quality, safety and efficacy of therapies with human T&C. **RAB / RATC** • The rapid alert platforms for blood (RAB) and for tissues and cells (RATC) give to Member States' competent authorities the possibility to effectively launch alerts to each other and/or to request information in case of an alert or crisis.

2. Increase protection of BTC donors, and children born from donated sperm, eggs or embryos, from specific risks	M2.4 The European Commission will develop the relevant component of an IT platform for quality and safety requirements	**ESHRE (GDPR)** • Registry on medically assisted reproduction. Anonymisation of patient: in order to overcome the identity problem, clinical centres identified the treatment rather than the individual, in this way you can anonymise the data and the ID attached stands for a treatment rather than a patient.
3. Strengthening and harmonisation of oversight among MS	M3.6 EU development components of IT platform for oversight	**EDQM** • Development of standards and guidance • Harmonising data collection exercises in the field of tissue and cells in Europe. **EU Coding Platform / Compendia** • EU Coding Platform provides the Single European Code (SEC) tool to standardise information concerning Donation Identification Sequence and tissue/cell products (Product Identification Sequence) using a standard fixed length alphanumeric code. • EU Coding Platform contains two compendia: - EU Tissue Establishment Compendium: the register of all tissue establishments which are authorised, licensed, designated or accredited by the Member States' competent authority. - EU Tissue and Cell Product Compendium: it is a non-exhaustive list of (product codes for) substances of human origin which fall within the definition of either 'tissue' or 'cells'.
4. Facilitate the development of safe and effective innovative BTC therapies	M4.7 EU will develop an exchange (IT) platform for NCAs to exchange info regarding (novel) process authorisations (the platform would be used for (voluntary) acceptance of authorisations among MS) This includes clinical evidence collected by clinicians with the support of learned societies	**EuroGTP II** • Interactive assessment tool to compute the level of risk of data uploading through an algorithm. **GAPP** • Development of tools able to facilitate the work of authorization of blood, tissue and cells establishments. • Provide a structure that can be used by competent authorities for assessment purposes independently from any national or international framework. **EBMT** • The EBMT registry collects data for research and development of new and improved transplant, cell therapy and immunosuppression procedures, and to improve the quality of these

		procedures through the accreditation of treatment units.
5. Improve the resilience of the sector, mitigating risk of shortages of critical BTC therapies	M5.4 The European Commission will develop the relevant component of the (IT) platform for exchange of information on supply and activity	**EUCCP** • Gather information across Member States about blood plasma with Covid antibodies to support a study on the effectiveness of plasma as Covid therapy. • Gather information about blood plasma with Covid antibodies in order to help distribution of the plasma itself. **EBMT** • Share all knowledge associated with the transplantation of haematopoietic stem cells from all donor sources and donor types including basic and clinical research, education, standardisation, quality control, and accreditation for transplant procedures. **ESHRE** • ESHRE provides guidance that enhances safety and quality assurance in clinical and laboratory procedures.

Table 19.2: Existing systems relevant to the achievement of each objective.

19.4 Implementation

In the implementation of the measures above, the following **three sub-options** have been identified:

1. **Upgrade (M6A)**
   Add missing elements to the existing systems as individual components – no links/ no interoperability.
2. **Upgrade and connect (M6B)**
   Add missing elements to the existing systems as individual components – plus an additional layer to extract, link and analyse the data.
3. **New single system (M6C)**
   Create a new unified system – which includes a revamp of the existing elements as well as the addition of the new elements.

Focusing on the mentioned options, there are some considerations that can be reported here.
The option M6A would upgrade each platform implementing features of data analytics or other features according to what is actually needed. Option M6A would not include features allowing data exchange and aggregated analysis.
Unlike option M6A, Option M6B would imply that each existing system has to be evolved both regarding their own features and in relation to their ability to exchange data

with other systems belonging to the same area (SoHO). This kind of "distributed evolution" requires high levels of coordination among all the platforms in order to get the needed standardization so that data could be exchanged keeping its semantic meaning and being consistent across all the systems. Even if the specific upgrade required for each system (interfaces, layers for data integration and analysis) would not be very challenging, a relevant effort will be required by the definition and the implementation of a shared mechanism that would allow data analytics features. In fact, performing data analysis on such distributed system could be not easy due to possible integration and alignment issues.

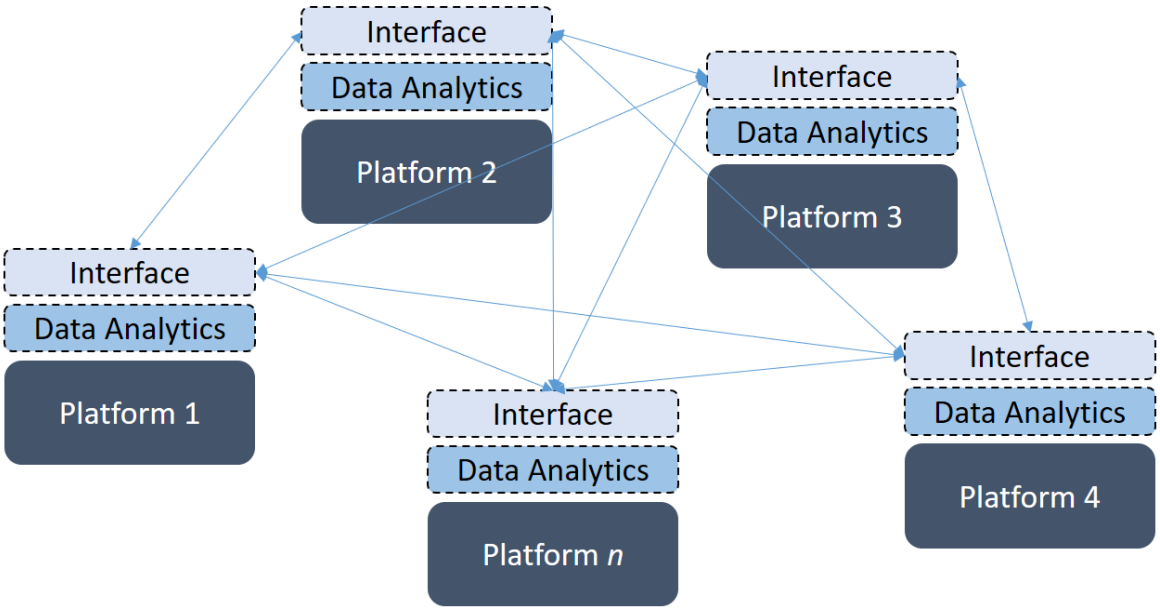


Figure 19.2 Graphic representation of Option M6B. Boxes with dotted lines are the additional components to upgrade the existing platforms.

On the other hand, option M6C would provide "by design" a common place where data could be collected and "harmonized" before being used for the intended purposes. A centralized solution would also make easier the management of topics like security and performance. In some cases, a source platform could be also replaced by the single system itself, allowing the direct input of data from a specific source (health authority, clinician, etc.) and skipping the intermediary role of a dedicated platform. This would be a hybrid approach, meaning that the single platform would act both as collector of data coming from external registries and as point of data input.
Option M6C would also solve the problem of keeping the final solution aligned to the most recent technologies: since there will be a single system which gathers all the data from different platforms, it will be sufficient to evolve only this system to have the latest technology available.
Please refer to the next paragraph for a more detailed analysis of the benefits coming from the implementation of a single platform.

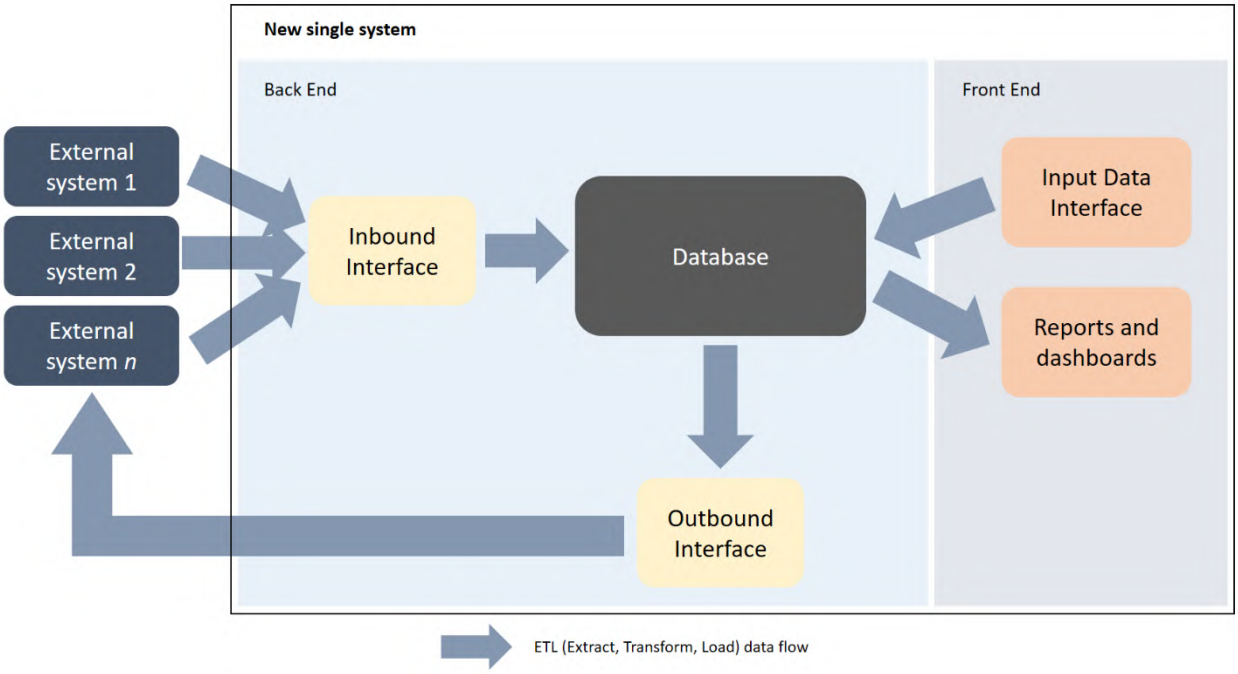


Figure 19.3: High-level single system architecture for Option M6C

The choice of moving to a new single system brings other relevant choices about the nature of the future solution. For example:

- On-premise or Cloud
  A first critical decision would be related to the hosting of the IT infrastructure, which could be kept onsite and managed directly or through a third-party. A different approach would be going for a Cloud solution, meaning that the IT infrastructure will be housed offsite, delegating the monitoring and maintaining activities to an external entity.
- Make or buy
  The technology to create the future solution may come from a traditional development environment or from a platform that would provide an ecosystem of modules and services to be adapted to the requested needs. In the first case the future solution would be developed from scratch (make), requiring high effort in the first phase. In the second case the solution would be created configuring specific modules and using the infrastructure provided (buy). This option would reduce the initial effort required to set up the new system, but implies higher running costs (licenses).

19.5 Impacts of the three options for platform SoHO-X

19.5.1 Interoperability

Option M6A

Due to the non-existence of links between the systems, option M6A would not improve interoperability and would not allow the implementation of best practices for systems architectures, data management and semantic definition of data.

Option M6B

The solution depicted in Option M6B makes possible the communication among the existing platforms, but only in a reading mode. This would not achieve an interoperability among systems, because from a specific platform it would possible only to get data from another platform without being able to integrate that information in a broader view. Also, being a single-way link, there will be no way to share back relevant information belonging to the same context.

Option M6C

A single platform would standardize all the different formats of data coming from external systems, allowing a consistent and integrated view of all the relevant data.
Also, keeping all the SoHO platforms connected to a single systems means making viable a direct access to relevant information from a single point, which is the best way for healthcare systems to improve patient safety and security, to be always updated about any possible emergency, to respond quickly and effectively to new issues.
Sharing information on oversight activities would also increase transparency and mutual trust across Member States.

19.5.2 Data analytics

Option M6A

Option M6A would introduce Data Analytics features only within the platform itself (where needed), meaning that option M6A would not bring benefits in terms of data aggregation and analysis among platforms.

Option M6B

Adopting Option M6B would make possible to have a view of data belonging to other platforms by interrogating each one of them and getting the data exposed by the specific interface. This solution will not implement a comprehensive view of the SoHO landscape because of multiple systems which in fact will not interact.
In this scenario it would not be possible to implement a Data Analytics feature for the whole SoHO environment because data will remain fragmented and spread across systems.

Option M6C

A single system would avoid these difficulties and increase efficiency both in functional and operational terms. A comprehensive data model would allow to keep monitored the current situation of specific themes and to react quickly and in an effective way to any problem that would rise. Such solution would be achieved by implementing advanced data sharing features and thus realizing a “Real-Time Visibility” of data across platforms. Automatic dashboards and reports will be the basic tools to enable monitoring and forecast activities, to activate alert settings and to exploit the potential of having a broad visibility of information.

In the SoHO specific context, availability of clinical data and up-to-date information are necessary to ensure continuous innovation and that the patients only receive treatments that are safe and effective.

19.5.3 Access Security

Option M6A

Each platform will keep the security policies already in place to grant accesses to their registered users.

Option M6B

The direct access of a user to a generic platform will use its current security policy, specific for each platform.
As showed in in the previous chapter, a link between the interfaces of two platforms will make available data of a platform to a user who accessed a different platform. The user will be able to access only the data that the specific interface will present and only in a reading mode.
The user who from the platform "A" will be able to reach the data of platform "B" will have a role with the grants to access specific data from other specific platforms. This solution implies that different visibility rules must be agreed in advance among the owner of the platforms and each visibility rule must be associated to different roles in each platform. Also, any policy change of a single platform will trigger a redefinition of roles and grants for all the users of other platform.

Option M6C

The unification of the access policies within a single system would improve the security of the data through the definition of roles and visibility to be assigned to specific users.
Implementing an "Identity and access management" (IAM) practice in one single system would bring several benefits:

- Any change to the security policy of a specific platform which shares data with the single system can be easily reflected in a change of the visibility granted to one or more role defined in the single system. This would have immediate effect on the access privilege of all the users impacted.
- Security admins of the single system will be able to enforce security policies across all platform modules and applications. With common policies, it will be easier to monitor accesses, identify violations and revoke access when needed.
    - Many regulations (including the Sarbanes-Oxley Act, HIPAA, PCI DSS and GDPR) have data security, privacy and protection mandates that directly relate to IAM. The administrator of the single system would be able to prove compliance, and be able to verify protections for data, including who has access to it, how that access is protected, processes for revoking access and how passwords are managed.

The implementation of such security policies may also solve an issue raised by some key users of existing platforms, which is related to the circulation of clinical data among registries different from the one where the data has been originally submitted. If the new single system would also operate as single input system for different entities, it will be

sufficient to assign specific grants to specific users in order to make available relevant data to the right users.

19.5.4 Data management

Option M6A

Each platform will keep using their own current data management policies.

Option M6B

As mentioned in the previous paragraphs, the interfaces that in Option M6B will be available in each platform will make possible to access specific data from other platforms, but this solution will not implement an integrated and consistent database.
The solution provided by Option M6B will rather be a distributed database, having no checks on its own consistency. Data analytics features will be applicable only to subsets of data, without being able to provide a comprehensive view.

Option M6C

A single system would implement a single, integrated and consistent database, able to support data analytics features. Data integrity checks will be part of the solution, providing accurate and comprehensive view of data quality. Also, it will be possible to highlight any deviation from data quality standard and to track back the issue to the data source for correction.
The single system would be a federated model, which would allow data to stay locally in the original registries without the obligation on Member States and other entities to restructure their databases in order to be compliant. It would also provide automated data flows for real-time updates from all the relevant registries and allow a more effective, simpler and faster way to input data.
A common problem raised by key users of the platforms currently active is related to the long time needed to input data into the registries. A new single platform could solve this issue by providing a more flexible and user-friendly interface to input data. An additional feature to be discussed may also be the possibility to input data in multiple registries at once through the access to the single system, submitting data in an entity-driven or patient-driven session.

19.5.5 Resilience

Option M6A

Resilience features will remain the same, as specified in the level of service agreed for each platform.

Option M6B

Resilience features will remain the same, as specified in the level of service agreed for each platform.

Option M6C

Depending on the technology and on the implementation strategy that will be chosen, the new single system will be designed with specific features (e.g. Disaster Recovery solution), which will allow the solution to react to critical situations. A resilient approach will include responding quickly to an issue, minimizing damages, providing continuous operations with a pre-defined level of service.
Such resilience features will only applicable to the single system solution and its data. No additional resilience feature will be provided for existing platforms and for their data not imported in the single system.

19.5.6 Easiness in evolution

Option M6A

Upgrades or evolutions on existing platforms could be performed with no impact on other systems.

Option M6B

Similarly to Option M6A, upgrades or evolutions could be easily performed on specific platforms, but, in this case, issues related to mutual compatibility will raise. In order to keep all the platforms able to communicate to each other, every change must take in consideration (ex-ante or ex-post) how the features related to data exchange or data aggregation would be impacted.

Option M6C

Having a single system makes easier to manage its evolution independently from the other systems which would keep working as source of data. The only dependency would remain the need to adapt the interfaces between systems, where and if necessary.
The evolution would be not only about technology, but would also include the concept of scalability, which is the ability of a process, system or organization to grow and manage increased demand. The concept connotes the ability to accommodate an increasing number of elements or objects, to process growing volumes of work gracefully, and/or to be susceptible to enlargement.

19.6 Assessment table

Preliminary expert assessment of the performance of the three options:

Criteria	**M6A: Upgrade** Add missing elements to the existing systems as individual components – no links/ no inter	**M6B: Upgrade and connect** Add missing elements to the existing systems as individual components – plus an additional layer to extract, link and analyse the data	**M6C: New single system** Create a new unified system – which includes a revamp of the existing elements as well as the addition of the new

			elements.
Interoperability: the extent to which the system allows a consistent and integrated view of all the relevant data	Missing connections among the systems would result in lack of interoperability and would prevent from the implementation of best practices.	This option would allow communication among platforms but only in reading mode, without making possible the integration of information.	A single system would standardize all the different formats of data coming from other platforms, allowing a consistent and integrated view of all the relevant data and promoting the interoperability among these platforms.
	0	+	++
Data analytics: the extent to which the solution allows analysis of data originating from multiple sources	Data Analytics features to be introduced only within the platform itself, no benefits in terms of data aggregation and analysis among platforms.	Data would remain fragmented and spread across systems. It would not be possible to implement a Data Analytics feature for the whole SoHO environment.	A single system would allow a comprehensive data model which would make possible advanced Data Analytics tools (alert settings, monitoring and forecast activities) together with features such as "Real-Time Visibility" of data, automatic dashboards and reports.
	0	0	++
Security requirements: the extent to which security of the data is ensured through the definition of roles and visibility to be assigned to specific users	Each platform will keep the security policies already in place to grant accesses to their registered users.	The direct access of a user to a generic platform will use its own security policy, but grants to access data from other platforms must be agreed in advance and managed during the time.	"Identity and access management" (IAM) in one single system would improve the security of the data through the definition of roles and visibility to be assigned to specific users.
	0	+	++
Data management: the extent to which the system can ensure data quality	Each platform will keep using their own current data management	Interfaces of each platform will make possible to access specific data from other platforms, but this	A single system would implement a single, integrated and consistent

	policies.	solution will not implement an integrated and consistent database.	database, able to support data analytics features. Data integrity and quality checks will be part of the solution, as well as automated data flows for real-time updates.
	0	+	++
Resilience: the extent to which the system can react to critical situations.	Resilience features will remain the same, as specified in the level of service agreed for each platform.	Resilience features will remain the same, as specified in the level of service agreed for each platform.	A single system would react responsively to critical situations (e.g. disaster recovery). A resilient system is expected to respond quickly to an issue, minimizing damages, always providing continuous operations.
	0	0	+
Easiness in evolution: technology and scalability	Upgrades or evolutions on existing platforms could be performed with no impact on other systems.	Upgrades could be easily performed on specific platforms but mutual compatibility issues may raise.	A single system makes easier to manage the evolution independently from the other systems. It must be noted that the single interfaces should be adapted to the evolution of the central system.
	+	+	

Table 19.3: Assessment table.

19.7 Cost estimation

This chapter introduces a proposal for a tool to estimate the one-off cost of implementing the three options. In the tables here presented are listed the basic features that the solutions described for options M6 A, B and C would have.

For each of these features has been estimated:

- Man days needed for analysis, design, build and unit test;
- Number of units needed (orange column).

The last column shows the total amount of man days required for each feature. Varying the units required (orange column) - the value can be also zero if the feature is not required - the calculated man days will vary accordingly.
Please note that the man days estimated may vary accordingly to the target technology that will be chosen. For example, if a low-code platform ("Buy" option) will be selected as solution, the man days required for "build" activities may decrease.

Assumptions

- The estimation tool includes only the following project phases: Analysis, Design, Build, Unit Test
- Cost of the IT infrastructure or platform access (licenses) not included
- Cost of a single man day: 400€ (based on EC contract rates, taking in account the skill mix)

Estimation of other costs

- Project Management: 11% of the "one-off cost" to be considered for project management (Gartner)
- Requirements gathering: : 18% of the "one-off cost" (estimation from literature and similar projects)
- Integration Test and User Acceptance Test: around 40% of the "one-off cost" (estimation from literature and similar projects)
- Maintenance: 30% of the "one-off cost" to be considered for the "Yearly ongoing cost" (Gartner)

19.7.1 Option M6A

Front End / Back End	Description	Task name	Task details	Analysis / Design (man days)	Build / Unit Test (man days)	Total per Unit	N. Unit	TOTAL (N.* Tot Unit)
Front End	Access to reports and dashboards	x-system -Dashboard/Report	Dashboard/report on System x (low complexity)	3	2	5	8	40
			Dashboard/report on System x (medium complexity)	5	3	8	10	80
			Dashboard/report on System x (high complexity)	9	5	14	8	112

In the case here proposed the total amount of man days is 232. Estimating an average cost of a man day with a standard skill mix to be EUR 400, the current cost estimation for the activities described above would be EUR 92 800.

19.7.2 Option M6B

Front End / Back End	Description	Task name	Task details	Analysis / Design (man days)	Build / Unit Test (man days)	Total per Unit	N. Unit	TOTAL (N.* Tot Unit)
Front End	Access to reports and dashboards	x-system -Dashboard/Report	Dashboard/report on x-system (low complexity)	3	2	5	8	40
			Dashboard/report on x-system (medium complexity)	5	3	8	10	80
			Dashboard/report on x-system (high complexity)	9	5	14	8	112
Back End	Interfaces for data exchange (Design)	Unique Standard Interface Design (same for each x-system)	Staging Area design (one for all the x-system)	15	0	15	9	135
Back End	Interfaces for data exchange (Build)	Unique Interface Design (build in each x-system)	Staging Area build (one for each x-system)	0	5	5	35	175
Back End	Data flows from external systems to interface	Inbound Flows (from x-system to interface)	ETL initial load (low complexity)	10	5	15	5	75
			ETL incremental load (low complexity)	2	3	5	5	25
			ETL initial load (medium complexity)	15	10	25	9	225
			ETL incremental load (medium complexity)	2	3	5	9	45
			ETL initial load (high complexity)	20	15	35	4	140
			ETL incremental load (high complexity)	2	3	5	4	20
Back End	Data flows from interface to external systems	Outbound Flows (from interface to x-system)	ETL import from interface vs x-system (low complexity)	5	3	8	1	8
			ETL import from interface vs x-system (medium complexity)	10	5	15	4	60
			ETL import from interface vs x-system (high complexity)	20	10	30	3	90

In the case here proposed the total amount of man days is 1 230. Estimating an average cost of a man day with a standard skill mix to be EUR 400, the current cost estimation for the activities described above would be EUR 492 000.

19.7.3 Option M6C

Front End / Back End	Description	Task name	Task details	Analysis / Design (man days)	Build / Unit Test (man days)	Total per Unit	N. Unit	TOTAL (N.* Tot Unit)
Front End	Access to reports and dashboards	SoHO-X single system -Dashboard/Report	Dashboard/report on SoHO-X (low complexity)	3	2	5	8	40
			Dashboard/report on SoHO-X (medium complexity)	5	3	8	10	80
			Dashboard/report on SoHO-X (high complexity)	9	5	14	8	112
Front End	Interface to input data in the SoHO-X system	SoHO-X single system -Front-End Input Data Interface (IDI)	IDI to load file/data into SoHO-X (medium complexity)	10	5	15	5	75
Back End	Internal data flow between data input interface and database	SoHO-X single system data flows - ETL from IDI to SoHO-X DB	ETL IDI inbound (medium complexity)	15	10	25	5	125
Back End	Internal data flows between database and interfaces for external systems	SoHO-X single system data flows: -ETL from Interface to SoHO-X DB -ETL from SoHO-X DB to interface	ETL inbound (medium complexity)	15	10	25	12	300
			ETL outbound (medium complexity)	10	5	15	3	45
Back End	Database	SoHO-X single system -Database Design and Build	DB Design logical and physical	40	10	50	1	50
Back End	Interfaces for data exchange	SoHO-X single system -Interface Design and Build	Staging Area Design for inbound and outbound flows	10	5	15	15	225
Back End	Data flows from external systems to SoHO-X	Inbound Flows (from x-system to SoHO-X)	ETL initial load (low complexity)	10	5	15	5	75
			ETL incremental load (low complexity)	2	3	5	5	25
			ETL initial load (medium complexity)	15	10	25	9	225
			ETL incremental load (medium complexity)	2	3	5	9	45
			ETL initial load (high complexity)	20	15	35	4	140
			ETL incremental load (high complexity)	2	3	5	4	20
Back End	Data flows from SoHO-X to external systems	Outbound Flows (from SoHO-X to x-system)	ETL import from SoHO-X to x-system (low complexity)	5	3	8	1	8
			ETL import from SoHO-X to x-system (medium complexity)	10	5	15	4	60
			ETL import from SoHO-X to x-system (high complexity)	20	10	30	2	60
Back End	Internal data flow to archive	SoHO-X single system Data replacement flows	ETL for data replacement (archiving or deleting)	2	2	4	10	40
Back End	Monitoring	Monitoring and reporting	Monitoring data flows processes	10	20	30	1	30
			Discarded reporting, re-submitting processes	20	15	35	1	35

In the case here proposed the total amount of man days is 1 815. Estimating an average cost of a man day with a standard skill mix to be EUR 400, the current cost estimation for the activities described above would be EUR 726 000.

19.7.4 Interface setup cost for source platform

Referring to the estimation presented for Option M6C, it could be interesting to focus on the costs from the perspective of a single source platform.
The interface setup activities to be performed on source platforms are described (in terms of effort) in the following rows:

Front End / Back End	Description	Task name	Task details	Analysis / Design (man days)	Build / Unit Test (man days)	Total per Unit	N. Unit	TOTAL (N.* Tot Unit)
Back End	Data flows from external systems to SoHO-X	Inbound Flows (from x-system to SoHO-X)	ETL initial load (low complexity)	10	5	15	5	75
			ETL incremental load (low complexity)	2	3	5	5	25
			ETL initial load (medium complexity)	15	10	25	9	225
			ETL incremental load (medium complexity)	2	3	5	9	45
			ETL initial load (high complexity)	20	15	35	4	140
			ETL incremental load (high complexity)	2	3	5	4	20
Back End	Data flows from SoHO-X to external systems	Outbound Flows (from SoHO-X to x-system)	ETL import from SoHO-X to x-system (low complexity)	5	3	8	1	8
			ETL import from SoHO-X to x-system (medium complexity)	10	5	15	4	60
			ETL import from SoHO-X to x-system (high complexity)	20	10	30	2	60

More specifically, the interfaces that would be used to send data from source platforms to the single system are the ones described in the Task "Inbound flows":

Front End / Back End	Description	Task name	Task details	Analysis / Design (man days)	Build / Unit Test (man days)	Total per Unit	N. Unit	TOTAL (N.* Tot Unit)
Back End	Data flows from external systems to SoHO-X	Inbound Flows (from x-system to SoHO-X)	ETL initial load (low complexity)	10	5	15	5	75
			ETL incremental load (low complexity)	2	3	5	5	25
			ETL initial load (medium complexity)	15	10	25	9	225
			ETL incremental load (medium complexity)	2	3	5	9	45
			ETL initial load (high complexity)	20	15	35	4	140
			ETL incremental load (high complexity)	2	3	5	4	20

This means that - taking in account the effort to set up only the interfaces to send out data from source platforms - the total man days required are 530.

The estimation performed for Option M6C takes in account 12 different types of data for 18 different data flows, from x-systems to SoHO-X. The number of source platforms may vary, but according to this sizing is possible to include about 10 external platforms in the design of the centralized system.
Combining all the numbers above, the estimated average cost for setting up an outbound interface for a single platform would be about EUR 21 200 (53 man-days at a EUR 400/day rate).

19.7.5 Cone of uncertainty

The cost estimates foresee a degree of variability as stated by the "Cone of uncertainty" theory (see figure below). As documented by this theory, the degree of accuracy for the development costs estimations is directly linked with the software development stages of a system and with the corresponding available knowledge in terms of detailed requirements and specifications. In fact, at early stages of a system implementation, the level of knowledge on system requirements and specifications is lower than at subsequent project stages. This uncertainty in the knowledge affects directly the "cost estimation accuracy", causing more variability in the real costs and therefore increasing the error in the cost estimation process.
According to this theory, being at an early stage, the final cost could result increased or decreased up to four times if compared with the current cost estimation.
In our specific case, it will be very unlikely that the cost will be four times higher (or lower) than the value estimated. The most likely values for the final cost will be the closer ones to the current cost estimation. Hence, for the purposes of the present feasibility study, we can assume that the final cost may range between 67% and 150% of the estimated cost.

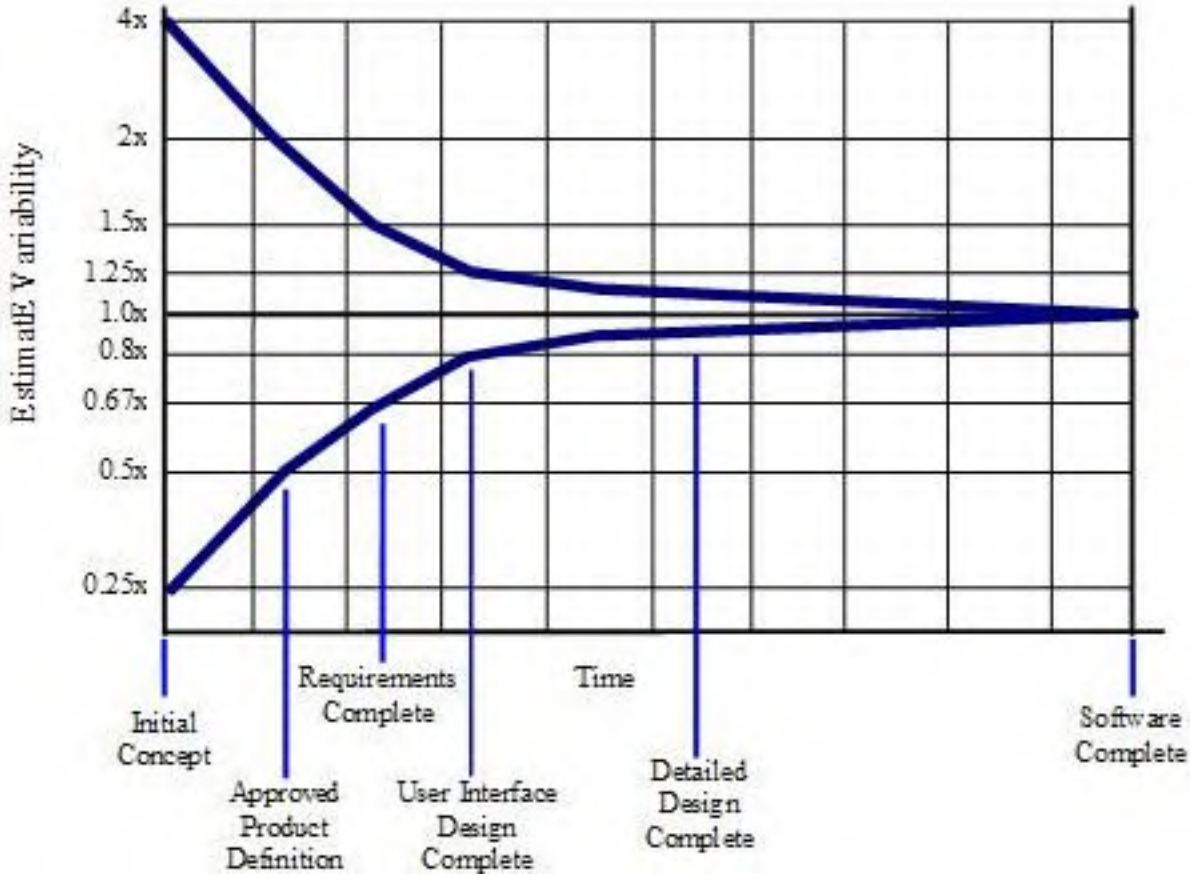


Figure 19.4: Cone of uncertainty.

19.7.6 Table of costs

Cost of implementing the system (in EUR)	**M6A: Upgrade** Add missing elements to the existing systems as individual components – no links/ no interoperability.	**M6B: Upgrade and connect** Add missing elements to the existing systems as individual components – plus an additional layer to extract, link and analyse the data.	**M6C: New single system** Create a new unified system – which includes a revamp of the existing elements as well as the addition of the new elements.
Cost for analysis, design, build and unit test phases	92 800 (232 man days)	492 000 (1230 man days)	726 000 (1815 man days)
Additional costs (Requirements gathering, Project Management, Integration Test and UAT)	64 960	344 400	508 200
Total estimated cost	**157 760**	**836 400**	**1 234 200**
Estimated yearly cost	27 840	147 600	217 800

for maintenance activities			
Range of estimation uncertainty: 67% - 150%			

19.8 Conclusions and next steps

The present feasibility study addresses the most relevant topics that would lead to the implementation of a single system for SoHO area. In this preliminary analysis, themes like digital checks, options for implementation, impacts (benefits) and costs have been discussed.
One of the main takeaway of this study is that a single system for SoHO area would be a strongly recommended option in order to bring together the several contributions in terms of data and knowledge from many different sources and, as consequence, to have a unified view of the whole SoHO environment. In this way it would be also possible to perform data analysis, share knowledge and be ready to react to issues that may rise.

List of next steps:

- Workshops
  As part of the feasibility study, two more workshops will be scheduled. The subjects will be the interoperability among SoHO platforms and the validation of the outcomes of the study itself.

- High Level Requirements
  A thorough session dedicated to the collection of the High Level Requirements (functional and not functional) should be scheduled in order to get a more detailed picture of the target system and be able to proceed with its formal definition.
  The participants to that meeting should the people who in fact will use the future single platform in order to make possible the gathering of meaningful requests and contributions to the design of the solution.

Annex 20: Bibliographic references

Abbott, A. *Italian stem-cell trial based on flawed data*. Nature, 2013. https://doi.org/10.1038/nature.2013.13329.

Alves, R. and Grimalt, R. *A Review of Platelet-Rich Plasma: History, Biology, Mechanism of Action, and Classification*. Skin Appendage Disord, 2018, 4:18-24. doi: 10.1159/000477353

Arslanoglu, S. et al. *Fortification of Human Milk for Preterm Infants: Update and Recommendations of the European Milk Bank Association (EMBA) Working Group on Human Milk Fortification*. Front Pediatr, 2019, 22 (7:76). doi: 10.3389/fped.2019.00076.

Baron, D.M et al. *Patient blood management during the COVID-19 pandemic: a narrative review*. Anaesthesia, 2020, 75, 1105-1113. doi: 10.1111/anae.15095.

Baunwall, S.M.D. et al. *The use of Faecal Microbiota Transplantation (FMT) in Europe: A Europe-wide survey*. Lancet Regional Health Europe, 2020, 9(100181), https://doi.org/10.1016/j.lanepe.2021.100181

Borra et al. *Blood donor deferral: time for change? An evidence-based analysis.* International Journal of Clinical Transfusion Medicine, 2016, 4: pp. 55–66. DOI:10.2147/IJCTM.S84521

Cho, J & Hiskey, M. *Editorial: Plasmavigilance: Source plasma joins the call to arms*. Transfusion 2021, 61(10), pp.2803–2805, https://doi.org/10.1111/trf.16668.

Hourd P, Chandra A, Medcalf N, et al. *Regulatory challenges for the manufacture and scale-out of autologous cell therapies.* 2014 Mar 31. In: StemBook [Internet]. Cambridge (MA): Harvard Stem Cell Institute; 2008-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK201975/

Liu, Bingci et al. *The Use of Type I and Type III Injectable Human Collagen for Dermal Fill: 10 Years of Clinical Experience in China*. Seminars in Plastic Surgery vol. 19,3 (2005): 241–250. DOI: 10.1055/s-2005-919719.

Master, Z. et al. *Unproven stem cell interventions: A global public health problem requiring global deliberation.* Stem Cell Reports, 2016, Volume 16(6), pp. 1435-1445. https://doi.org/10.1016/j.stemcr.2021.05.004.

Nawrat, A. Exploring the challenges of regulating faecal microbiota transplants. Medical Device Network, 2021. Available at https://www.medicaldevice-network.com/features/exploring-the-challenges-of-regulating-faecal-microbiota-transplants/

Oliven A, Shechter Y. *Extracorporeal photopheresis: a review*. Blood Rev. 2001 Jun;15(2):103-8. doi: 10.1054/blre.2001.0155.

Simonacci F, Bertozzi N, Grieco MP, Grignaffini E, Raposio E. *Autologous fat transplantation for breast reconstruction: A literature review.* Ann Med Surg (Lond). 2016, 12, pp. 94-100. doi:10.1016/j.amsu.2016.11.012

Smith M, Kelly C & Alm E. How to regulate faecal transplants. Nature, 2014, Volume 506, pages 290–291.

Tiberghien P, *Increasing unpaid plasma collection by blood establishments to ensure availability of plasma–derived medicinal products and blood components in Europe*, Transfusion Clinique et Biologique, 2021, 28(4), pp. 331-333, https://doi.org/10.1016/j.tracli.2021.09.004.

Wortelboer, K. and Herrema, H., Shedding light on dark matter faecal microbiota transplantation in Europe, The Lancet Regional Health – Europe, 2021, https://doi.org/10.1016/j.lanepe.2021.100187.