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PART 1/3

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

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GLOSSARY

Term or acronym	*Meaning or definition*
Advanced Therapy Medicinal Products (ATMP)	An advanced therapy medicinal product [1] means any of the following medicinal products for human use: • a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC, • a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC, • a tissue engineered product as defined as containing or consisting of engineered cells or tissues, and presenting properties for or being used or administered to human beings with a view to regenerating, repairing or replacing a human tissue.
Allogeneic use	Cells or tissues removed from one person and applied to another [2].
Antibodies	Antibodies are immunoglobulins (Ig). They are large proteins that are found in blood or other body fluids. Antibodies are part of the immune system that identify and neutralise foreign objects, such as bacteria and viruses.
Autologous (transfusion, donation or use)	Blood [3]: Autologous transfusion shall mean transfusion in which the donor and the recipient are the same person and in which pre-deposited blood and blood components are used. Tissues and cells [4]: Autologous use means cells or tissues removed from and applied in the same person.
Blood Establishment (BE)	Blood establishment shall mean any structure or body that is responsible for any aspect of the collection and testing of human blood or blood components, whatever their intended purpose, and their processing, storage, and distribution when intended for transfusion. This does not include hospital blood banks [5].
Bone marrow	See haematopoietic stem cells

[1] Regulation (EC) No 1394/2007 amending Directive 2001/83/EC and Regulation (EC) No 726/2004.
[2] Directive 2004/23/EC.
[3] Directive 2002/98/EC.
[4] Directive 2004/23/EC.
[5] See: Directive 2002/98/EC.

BTC	Blood, tissues and cells
ECDC	The European Centre for Disease Prevention and Control
EDQM	European Directorate for the Quality of Medicine - Council of Europe
EHDS	European Health Data Space
EMA	European Medicines Agency
ESHRE	The European Society for Human Reproduction and Embryology
EU Audits	Audits of the compliance of the national competent authority with legislation for its oversight activities, and done by the Commission (expertise of SANTE Directorate F in food sector, and few new pharma domains)
EUDAMED	European database on medical devices
FAIR	Guiding Principles for scientific data management and stewardship
FMT	Faecal Microbiota Transplants
Gametes	Sperm (spermatozoa) and eggs (oocytes)
GAPP	Facilitatin**g** the **A**uthorisation of **P**reparation **P**rocess for blood, tissues and cells. An EU Joint Action co-funded by the EU Public Health Programme.
GDPR	General Data Protection Regulation
Good Manufacturing Practice (GMP)	Good manufacturing practice shall mean the part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use [6].
Haematopoietic stem cells	Cells in the bone marrow that produce new blood cells. Haematopoietic stem cells are found in bone marrow and in blood collected from the umbilical cord after the birth of a baby. They can also be collected from a donor's blood stream if the donor is treated with particular hormones that cause the cells to move out of the bone marrow into the blood.

[6] Commission Directive 91/356/EEC.

Haemoglobin	A protein found in the red blood cells that is responsible for carrying oxygen around the body. Haemoglobin picks up the oxygen in the lungs, and then releases it in the muscles and other tissues where it is needed. Haemoglobin also contains iron which is critical for it to work properly.
HIV	Human Immunodeficiency Virus
HMA	Heads of Medicines Agencies
Immunodeficiency	A state in which the immune system's ability to fight infectious disease and cancer is compromised or entirely absent.
In vitro fertilisation (IVF)	An assisted reproductive technology (ART) procedure that involves extracorporeal fertilisation.
ITE	Importing tissue establishments
IVF	In Vitro Fertilisation
Joint inspections	Framework where one MS (« host ») with another (« guest ») would inspect together an establishment of the host MS.
JRC	European Commission Joint Research Centre
M	Measure (followed by number)
MD	Medical Device
Medically assisted reproduction (MAR)	Reproduction brought about through ovulation induction, controlled ovarian stimulation, ovulation triggering, assisted reproduction technology procedures, and intrauterine, intracervical or intravaginal insemination with semen of donor.
Medical Device	'medical device' means [7] any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes: - diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease, - diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,

[7] Regulation (EU) 2017/745.

	- investigation, replacement or modification of the anatomy or of a physiological or pathological process or state, - providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations, and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.
Medicinal Product	• Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or • any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis [8] .
NAT	Nucleic Acid Test
NCA	National Competent Authority
NGO	Non-governmental organization
NPV	Net Present Value
Plasma Derived Medicinal product (PDMP)	Medicinal products based on blood constituents which are prepared industrially by public or private establishments, such medicinal products including, in particular, albumin, coagulating factors and immunoglobulins of human origin [9].
PO	Policy Option
SARE	Serious adverse reactions and events
Serious adverse event (SAE)	Blood [10]: Any untoward occurrence associated with the collection, testing, processing, storage and distribution, of blood and blood components that might lead to death or life-threatening, disabling or incapacitating conditions for patients or which results in, or prolongs, hospitalisation or morbidity. Tissues and cells [11]: Any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues

[8] Directive 2001/83/EC.
[9] Directive 2001/83/EC.
[10] Directive 2002/98/EC.
[11] Directive 2004/23/EC.

	and cells that might lead to the transmission of a communicable disease, to death or life threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity.
Serious adverse reaction (SAR)	Blood [12]: An unintended response in donor or in patient associated with the collection or transfusion of blood or blood component that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalisation or morbidity. Tissues and cells [13]: An unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity.
SMCE	Social Multi-Criteria Evaluation
SOCRATES	Social multi-criteria assessment of European policies. A tool developed by the Joint Research Council of the European Commission to support Impact Assessment.
SoHO	Substances of Human Origin
SoHO Entity	An organisation that carries out any activity that directly or indirectly affects the safety, quality or efficacy of SoHO.
SoHO -X	A planned real world data system supporting the revised blood, tissues and cells legislation.
SWD	Staff Working Document
TFEU	The Treaty on the Functioning of the European Union
Tissue Establishment (TE)	Tissue establishment means a tissue bank or a unit of a hospital or another body where activities of processing, preservation, storage or distribution of human tissues and cells are undertaken. It may also be responsible for procurement or testing of tissues and cells [14].
VUD	Voluntary and unpaid donation

[12] Directive 2002/98/EC.
[13] Directive 2004/23/EC.
[14] Directive 2004/23/EC.

1. INTRODUCTION: POLITICAL AND LEGAL CONTEXT

In the European Union (EU), millions of donations of blood, tissues and cells (BTC) are used every year to treat diseases, and to enable essential healthcare interventions, such as surgery, emergency care or cancer care. In most cases, no alternative treatments exist. BTC cover a wide range of substances (red blood cells, plasma, blood-forming stem cells, gametes, and replacement tissues such as corneas or heart valves). Therapies using BTC are highly beneficial, but can also cause adverse reactions in patients and may also be a channel for the transmission of disease. To ensure high levels of public health protection at all stages of the process, from donation and processing to clinical use, the EU adopted a legislative framework for BTC in the early 2000s.

This impact assessment (IA) analyses policy options and measures for addressing the shortcomings highlighted by the evaluation (2019) of the EU legislation on blood, tissues and cells: the Blood Directive 2002/98/EC and the Tissues and Cells Directive 2004/23/EC, and their implementing acts [15] (collectively referred to as "the BTC legislation"). These measures and policy options also take into account the problems caused by, and the lessons learnt from, the impact of the COVID-19 pandemic on the BTC sector, so as to make the BTC legal framework even more effective, future proof and crisis resistant [16].

BTC are not commercially manufactured products, rather the 'market dynamics' depend on donations made by human beings - either during life or after death. Donations from the human body should not be a source of financial gain, in line with the EU Charter of Fundamental Rights [17]. In this context, the sector is mainly organised by public and non-profit organisations that usually set prices for BTC so as to recover their costs [18]. However, in some sub-sectors, such as plasma collection for the manufacture of plasma-derived medicinal products, or Medically Assisted Reproduction (MAR), private companies operating on a for-profit basis also play a significant role. The volumes of BTC, patients and donors involved and the extent of cross-border exchange vary highly from substance to substance (see Annex 8).

Current legislative landscape

While much of the BTC sector is public and organised on a national or regional basis, safety and quality requirements are established in EU legislation since 2002, following the crises in the '80s and '90s when Human Immunodeficiency Virus (HIV) and hepatitis where widely transmitted across the EU by transfusion and treatment with plasma-derived medicinal products (PDMP). The BTC legislation sets high standards of safety and quality for BTC,

[15] For Blood: Directive 2002/98/EC, for Tissues and Cells: Directive 2004/23/EC, see Annex 5. The implementing acts address further specific technical requirements such as provisions on donor eligibility, storage, transport conditions, requirements for traceability, vigilance reporting and import, authorisation of tissue establishments and tissue and cell preparation processes.

[16] This initiative is intended to apply to all substances of human origin (SoHO), but excludes solid organs (subject to Directive 2010/53/EU that remains applicable).

[17] Article 3 of the Charter calls for "the prohibition on making the human body and its parts as such a source of financial gain".

[18] Article 12.2 of the Tissues and Cells directive stipulates that "Member States shall endeavour to ensure that the procurement of tissues and cells as such is carried out on a non-profit basis".

though Member States are allowed, by the Treaty mandate, to set their own, more stringent rules [19]. The BTC legislation sets standards for the donation, collection (procurement) and testing of BTC. For most BTC, this framework also covers the processing and storage in blood and tissue establishments before distribution to hospitals and clinics. For those BTC that serve as starting material for manufactured health products that fall under categories regulated by other Union legislation, including PDMP, advanced therapy medicinal products (ATMP) and medical devices, those last steps (manufacturing, storage, distribution etc.) are regulated under the appropriate legislative framework (e.g. medicinal products (PDMP and ATMP) and medical devices) [20], and there are mechanisms to ensure coherence between the BTC legislation and those adjacent frameworks [21]. The delineations with these other legal frameworks are set by criteria in these other frameworks. The background to the adoption of the BTC legal framework and a detailed description of the framework adopted are provided in Annexes II, III and IV of the BTC Evaluation [22].

More detailed, and regularly updated, guidance on safety and quality of BTC is also available for professionals from expert bodies, such as the European Directorate for the Quality of Medicines and Healthcare (EDQM) of the Council of Europe [23], and the European Centre for Disease Prevention and Control (ECDC) for prevention of transmission of communicable diseases via BTC [24]. The guidelines from the EDQM and the ECDC are, however, not legally binding [25]. A regular dialogue is also established with the European Medicines Agency (EMA) working parties on blood products and on biologicals, in particular for plasma that is further manufactured into PDMP [26]. This dialogue also involves the Inspection Working Party on topics related to oversight.

[19] Article 168(4)(a) of the TFEU stipulates that the Union shall adopt "measures setting high standards of quality and safety of organs and substances of human origin, blood and blood derivatives; these measures shall not prevent any Member State from maintaining or introducing more stringent protective measures".

[20] Directive 2001/83/EC, Regulation (EC) No 1394/2007 and Regulation (EU) 2017/745.

[21] For example, common good manufacturing practices for plasma used to manufacture PDMP are defined in Annex XIV of the EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use. This annex references both blood and pharmaceutical rules.

[22] Evaluation of the Union legislation on blood, tissues and cells {SWD (2019) 376 final} https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/swd_2019_376_en.pdf

[23] The EDQM develops two sets of quality guidance (one on blood and one on tissues and cells) which are strongly referred to in the sector, both by authorities and by professionals. More information on the role of the EDQM can be found in Annex 14.

[24] More information on the role of ECDC for BTC can be found in Annex 15, with examples of up-to-date optional public health measures provided.

[25] With one specific exception concerning the Good Practice Guidelines for blood establishments that have been referenced in an amendment to an Implementing Directive (Directive 2016/1214 amending Directive 2005/61/EC) and are applied in all Member States and adopted in national legislation in some.

[26] It includes the joint development of a dedicated Good Manufacturing Practice (GMP) for "The Manufacture of Medicinal Products Derived from Human Blood or Plasma (so-called "annex 14")".

Political context

This initiative is part of the EU's ambition to build a stronger *European Health Union* [27], so as to: (1) better protect the health of our citizens (including patients, donors and offspring); (2) equip the EU and its Member States to better prevent and address future pandemics (surveillance, data analysis, risk assessment, early warning and response) and (3) improve the resilience of Europe's health systems (sufficient supply of BTC). As part of the European Health Union, there is also a proposal to strengthen the *mandate of the ECDC* [28]. The ECDC is already providing highly appreciated advice on safety to the BTC sector and under this proposal, its role and tasks regarding epidemiological diseases/risks in substances of human origin would be further expanded, by building a network for substances of human origin, that could serve in particular to detect, monitor and report on serious cross-border communicable disease threats posed by substances of human origin (SoHO) (see Annex 15 for more details).

This IA will also feed into the ongoing *evaluation and revision of the pharmaceutical legal framework* [29], undertaken as part of the Pharmaceutical Strategy for Europe. BTC are related to this strategy primarily as essential starting materials for critical medicinal products and because of the regulatory borderlines that exist between BTC and certain categories of products regulated under the pharmaceutical framework. These questions of classification have significant impacts not only on the assessment of benefits and risks, but also on the costs and availability of products and therapies.

This IA looks further into borderline concerns raised during the 2019 evaluation and considers the means available, within the scope of the BTC framework, to strengthen coherence and provide more legal clarity for innovators of borderline and combination therapies. This is done without prejudice to any further measures that may be considered as part of the ongoing Evaluation/IA to inform the revision of the pharmaceutical framework. The BTC initiative does not aim to, and cannot, alter the criteria that define the delineation between the BTC and other regulatory frameworks (pharmaceuticals, ATMP, medical devices etc.), as these criteria are set within the other legal frameworks. However some of the findings of this IA, in particular in relation to the borderlines, could be used for the future work on the pharmaceutical framework. The common aim is to ensure that Europe has a coherent, future-proof and crisis-resistant regulatory system for all complex products that are regulated under more than one legal framework (including combinations of medicines with medical devices or BTC, and BTC as starting materials for medicines).

BTC-based therapies are of key importance for many cancer patients [30]. Any improvements to the BTC framework that can increase the quality, availability and efficacy of blood

[27] https://ec.europa.eu/info/strategy/priorities-2019-2024/promoting-our-european-way-life/european-health-union_en

[28] 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.

[29] Revision of the EU general pharmaceuticals legislation: https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Revision-of-the-EU-general-pharmaceuticals-legislation_en.

[30] Almost all cancer patients need transfusion of blood components in the course of their therapy. Transplantation of haematopoietic stem cells (bone marrow) is the standard therapy for several blood cancers (leukaemia, lymphoma) (see Annex 8).

components for transfusion and of blood stem cell treatments for transplant will thereby contribute to the success of the *EU's Beating Cancer Plan* [31] .

Finally, digitalisation of healthcare systems is ongoing and can allow for significant efficiencies in these public sectors; possible synergies with the creation of an *EU Health Data Space* (EHDS) [32] are also be explored in this IA.

2. PROBLEM DEFINITION

2.1 What are the problems?

After more than 16 years of implementation, and with many new scientific, technical and legislative developments having taken place, the BTC legislation was evaluated in 2019 [33]. The evaluation found that the EU legislation has effectively helped increase safety for millions of patients undergoing blood transfusion, transplantation, or MAR, but it also identified the following five shortcomings/problems [34]:

1. Patients are not fully protected from avoidable risks;
2. BTC donors and children born from donated eggs, sperm or embryos are exposed to avoidable risks;
3. Member States have divergent approaches to oversight;
4. Full potential of innovative therapies is not reached for patients;
5. Patients are vulnerable to interruptions in EU supply of BTC.

While these shortcomings in the first place affect patients treated with BTC, BTC donors and offspring born from medically assisted reproduction (see Annex 8), they also impact upon the 50 national Competent Authorities (NCAs) for BTC [35], their inspectors and staff, and more than 4 600 blood and tissue establishments providing BTC therapies [36]. Other entities working with BTC include 11 000 hospitals, which are impacted through blood banks and/or bedside processes, together with developers of BTC therapies (public healthcare actors and private companies). The problems also affect manufacturers, and developers of therapies using BTC as starting materials.

The evaluation findings (2019) have been further confirmed by the different stakeholder consultation activities carried out in the course of this IA, including the feedback on the Inception Impact Assessment (2020) and the Public Consultation surveys (2021) [37].

This IA also looks further into the extent of concerns raised regarding the delineation of the borderline between the BTC framework and other legal frameworks, in particular for

[31] https://ec.europa.eu/health/sites/default/files/non_communicable_diseases/docs/eu_cancer-plan_en.pdf
[32] https://ec.europa.eu/health/ehealth/dataspace_en
[33] Evaluation {SWD (2019) 376 final}
[34] Executive Summary of the Evaluation of the Union legislation on blood, tissues, and cells https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/swd_2019_375_summary_en.pdf
[35] For further details on the national competent authorities, see Annex 8 – Table 8.2 (List of BTC Competent Authorities by Member State).
[36] For further details, see Annex 8, Table 8.1: Stakeholder overview.
[37] For further details on the consultation methodology, see Annex 6. Results of the consultation are described in Annexes 2 and 18.

pharmaceuticals and medical devices. Dedicated case studies were developed, and these concerns were also addressed by a broad range of stakeholders in the consultations and discussed with many experts in a workshop (see Section 6.3.2, and Annexes 2, 10 and 18).

Since the evaluation, the COVID-19 pandemic has accentuated several of these shortcomings, in particular regarding the supply of BTC [38] (Annex 9). For example, at the beginning of the pandemic, all fertility treatments in *in vitro* fertilisation (IVF) clinics were postponed until the impact of the virus on pregnancies was better understood. Also, due to the EU's considerable dependency on plasma imported from the US, some patients with immunodeficiencies had to change their PDMP treatment [39]. During the public consultations, stakeholders highlighted that the pandemic had exacerbated the problem of supply dependency (problem 5), and to a lesser extent, the patient protection issue (problem 1) and the divergence of oversight practices (problem 3) [40].

2.1.1 Patients are not fully protected from avoidable risks

EU safety and quality requirements have not been kept up to date with the rapid pace of scientific and epidemiological change [41], and the technical rules defined in the legislation (e.g. specific tests and deferral times for diseases) are now in many cases out of date. This potentially exposes patients treated with BTC to avoidable risks. As a result, the large majority of Member States have adopted more stringent measures to address this gap [42], and as a result, EU legislation is no longer consistently applied [43]. This situation creates legal confusion and unequal levels of safety and quality for patients, and also contributes to creating barriers for the exchange of BTC among Member States [44,45].This affects all BTC, but in particular those that are subject to cross-border exchange like about 15-20,000 units of

[38] Extraordinary COVID-19 meeting of the Competent Authorities for Blood and Blood Components (June 2020) https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/ev_20210603_sr_en.pdf

[39] Reply from the International Patient Organisation for Primary Immunodeficiencies (IPOPI) to a survey conducted by the External Study for the BTC Impact Assessment: "Many of European patient organisations had seen tensions or shortages in their countries during the pandemic […]. This means for patients with primary immunodeficiencies: 35% have had to change brands; 6% had to change route; 12% experienced an increased duration between treatments and 12% had their dosage decreased; no new patients are accepted for Ig treatment (6%); and new patients can't have their treatment (12%)." See Annex 9, section 9.2.1.

[40] Stratification by stakeholder groups revealed no further insights. Public consultation factual summary report, section III, page 6-7, available at https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12734-Revision-of-the-Union-legislation-on-blood-tissues-and-cells/public-consultation_en.

[41] For examples of scientific, technical and epidemiological developments, see Evaluation {SWD (2019) 376 final}, section 5.1.1, p. 29-31.

[42] A 2015 survey found all but 2 Member States (MT and LV) had more stringent requirements for non-reproductive tissues and cells on how to perform (mandatory) testing for HIV, Hepatitis B and C and Human T-Lymphotropic Virus (HTLV). These 25 countries also had additional requirements to test for one or more viral, parasitic or bacterial disease that is not required for in EU legislation. Such maps on tests for reproductive cells or blood were similar.

[43] Evaluation {SWD (2019) 376 final}, section 5.1.1, p. 29-31.

[44] Evaluation {SWD (2019) 376 final}, section 5.5.2, p. 80-81.

[45] See for example position papers submitted by the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) "*F2332668-Final_EUCOPE_Consultation_response_BTC_Revision111220*", by the European Network of Tissue Establishments (eNOTE) "*F2332710-eNOTE_Contribution_-_April_14_2021*" and by the Cord Blood Association "*F1965792-Model_Criteria*", available at 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.

haematopoietic stem cells for transplantation and about 10 million litres of plasma for manufacturing PDMP (see Annex 8, table 8.3).

In addition, some SoHO fall into legal gaps and thus remain unregulated or regulated very differently across Member States. Without appropriate donor selection, collection and testing requirements, the use of unregulated SoHO therapies, such as transplants of faecal microbiota (FMT) or processing and supply of donated breast milk, might put patients at risk of exposure to infectious diseases or toxic contaminants (if the substance is not processed and stored properly), or may involve risky procedures carried out in the home if the treatment is not available in professional medical facilities [46]. It is clear that the inherent risks and need for safe donations of such SoHO, prepared by around 300 establishments across the EU, are equivalent to those for BTC, and require similar measures to ensure their safety and quality [47]. Furthermore, more complex processing of BTC at the bedside of hospitalised patients is happening increasingly [48], and exposes patients to potential risks if no appropriate rules are in place to ensure the safety of the processing steps [49].

2.1.2 Avoidable risks for BTC donors and for children born from donated eggs, sperm or embryos

Measures to protect donors and offspring are very limited in the current legal framework. While many BTC services do monitor donor health [50], and do report adverse reactions, this is organised on a voluntary [51] basis (24 and 17 Member States reported donor reactions for blood, and for tissues and cells respectively in 2020) [52]. Donors (in about 2 350 establishments) can therefore be exposed to risks for their health, in particular those donating

[46] For example, in case of lack of access to faecal microbiota transplants: Nawrat, A., 2021 (- Annex 20).

[47] Keller et al., 2019 (Annex 20) and European Foundation for the Care of Newborn Infants (EFCNI) Working Group on Human Milk Regulation. Making Human Milk Matter - The need for regulation in the European Union. Policy Recommendations. EFCNI; 2020. *"F2332728-2021_01_21_EFCNI_MakingHumanMilkMatter_PolicyRecommendations_final-small"* available at 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.

[48] Procedures, ranging from relatively simple to complex processing of BTC, in which BTC are removed from the patient and returned after processing within a very limited timeframe. For example irradiation of blood: or breakdown of adipose tissue into adipose-derived stem cells.

[49] A position paper submitted by the French Authorities (ARES(2021)2671096) advocated for the regulation of such bedside procedures through a risk-based approach, in addition to a refined scope of the legislation including FMT, breast milk, and blood used for purposes other than transfusion.

[50] Cho & Hiskey, 2021 (Annex 20).

[51] There is currently no obligation to report donor reactions that might impact the health of the donors themselves, see section 2.2.3.

[52] There is overall a growing trend in the number of donor serious adverse reactions (SAR) being reported on a voluntary basis: 2494 blood donor reactions in 2013 (reported by 17 Member States) versus 3821 in 2020 (reported by 24 Member States), summary of the annual reporting of serious adverse reactions and events (SARE) for blood and blood components for 2020 available at: https://ec.europa.eu/health/blood_tissues_organs/key_documents_en#anchor1; 294 tissues and cells donor reactions for donors in 2013 (reported by 15 Member States) versus 903 in 2020 (reported by 17 Member States), summary of the annual reporting of SARE for tissues and cells for 2020, available at: https://ec.europa.eu/health/blood_tissues_organs/key_documents_en#anchor7

often [53] (in about 600 establishments). In addition, for SoHO that are currently outside the scope of the BTC legislation (e.g. FMT and human milk), there is a potential risk of exploitation of donors [54,55]. Nowadays, broad spectrum genetic screening is available to about 1750 MAR clinics to verify the risk of genetic disease transmission by MAR donors (in particular for the about 300 clinics who regularly collect donor gametes) but it is not a mandatory requirement set under EU legislation. For example, there are techniques available for genetic matching of donors and prospective parents, so as to ensure the avoidance of transmission of genetic diseases to the offspring.

2.1.3 Divergent approaches to oversight among Member States

The evaluation has shown that Member States have **divergent interpretations of the oversight provisions**, of the BTC legislation, as they are not specific enough [56]. In particular differences have been reported as regards independence, enforcement powers and technical expertise available in each of the national authorities. This brings differences in the conduction of inspections, in the authorisation of preparation processes (including the extent to which clinical data are assessed for such authorisations [57]) and in the reporting of serious adverse reactions and events (including how to assess seriousness and what data is used as reference [58]). Such differences have also been documented in previous implementation reports on the Blood and Tissues and Cells Directives, and in some Health Joint Actions [59].

This leads to unequal implementation and protection of citizens across the EU, and to a lack of mutual trust between NCAs. This in turn creates barriers to cross-border exchange and prevents availability of optimal (matched) BTC for patients.

2.1.4 Full potential of innovative therapies for patients is not reached

Innovation in the BTC sector is continuous and usually of an incremental nature [60]. Developers (mainly academic/public sector) have flagged two main problems that inhibit them from developing new processes or uses of BTC, while fully ensuring safety, quality and proof of benefit.

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[53] Position Paper of the "Union nationale des associations de donneurs de sang benevoles de la poste et orange (France)" submitted to the Targeted Public Consultation (see Annex 18).

[54] Commercial companies are sometimes involved and offer payment for donation, for example for breast milk https://www.bbc.com/news/uk-england-hereford-worcester-58343016.

[55] For example, donating large amount of milk could impact the mother's nutritional status - Annex 11, section 11.1.

[56] Evaluation {SWD (2019) 376 final}, section 5.2.1.2, p. 42-45.

[57] See for example the experience with COVID-19 convalescent plasma, detailed in Annex 9, section 9.2.2.

[58] These data are reported as absolute values and they do not refer to the total activities performed (usually referred to as denominators), therefore the numbers and trends cannot be used to assess the overall safety of the BTC framework.

[59] Such as EUSTITE European Union Standards and Training for the Inspection of Tissues Establishments https://webgate.ec.europa.eu/chafea_pdb/health/projects/2005204/summary, VISTART Vigilance and Inspection for the Safety of Transfusion Assisted Reproduction and Transplantation https://vistart-ja.eu/home and GAPP Facilitating the Authorisation of Preparation Process for blood, tissues and cells https://www.gapp-ja.eu/

[60] See Annex 12.

Firstly, developers report the **lack of a common authorisation approach for BTC processed or used in new ways** [61]. Changes in BTC preparation processes are continuous and can vary from very minor (e.g., new packaging) to substantial (e.g. de-cellularisation of tissues). Furthermore, many of these changes stem from the increasing use of automation to reduce human error. Authorisation of such incremental changes should be based on sufficient clinical evidence to ensure safety and efficacy, while not requiring disproportionate and unnecessary efforts that would hamper innovation by developers.

Today, changes in BTC preparation processes and uses are authorised in differing ways across the Member States, requiring different levels of clinical evidence. Some Member States are more stringent than others, requiring full clinical trials [62] even for BTC innovations with low levels of risk, while others only require less demanding clinical studies or laboratory validation data alone [63]. It is therefore difficult for BTC developers to identify local requirements, and they sometimes need to repeat and duplicate studies to comply with different local requirements, in order to get the same innovation assessed and authorised in different Member States. For example in 2021, 48 clinical trials were counted to study the use of COVID-19 convalescent plasma [64].

This lack of a proportionate framework can impact safe patient access in two ways: under-regulation creates the risk of treating patients with unproven therapies and in the absence of proper oversight [65], while over-regulation creates the risk of hampering innovation and access with unnecessary and burdensome requirements [66].

Secondly, BTC developers find it **difficult to get legal clarity** regarding whether existing BTC legislative requirements apply to BTC- processed or used in innovative ways, and if so, to what extent. At present, questions can be posed to the Expert Group that brings together national SoHO authorities [67], but this group is not specifically mandated in the BTC legislation

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[61] Lack of appropriate safety and efficacy data has been criticised by stakeholders across different sub-sectors: position statements from the International Society for Stem Cell Research (ISSCR) "*F2332644-ISSCR_Comment_Letter_on_EU_BTC_ Consultations_15 _April_2021*," from the ESHRE "*F2332684-ESHRE_comments_for_TD_2021"* available at 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 and from the European Eye Bank Association (EEBA) "*EEBA_Statement_On_Stem_Cell_Applications_In_The_Treatment_Of_Ocular_Disorders*" submitted to the Targeted Public Consultation (see Annex 18).

[62] The EU Clinical Trials framework (Regulation (EU) No 536/2014) is applicable to medicinal products, regardless whether these are subject to the EU Pharmaceutical framework (Directive 2001/83/EC) or not (like Substances of Human Origin – which are subject to separate EU Directives).

[63] GAPP Joint action – survey with EU National Competent Authorities for blood, tissues and cells.

[64] At least 48 EU clinical trials on CCP, in 16 MS, were registered in the "ClinicalTrials.gov" database as of October 2021; Search of: convalescent plasma | COVID-19 - Results on Map - ClinicalTrials.gov.

[65] See for example Evaluation {SWD (2019) 376 final}, Annex VIII, p.127. The discussions on same-surgical procedure highlight the need for demonstration of efficacy of claims (p. 178).

[66] Clinical trials in the sector – comparison to standard therapy – can cost up to EUR 75 000 (EUR 3 000 per patient). See Annex 5, section 5.4.2.

[67] https://ec.europa.eu/transparency/expert-groups-register/screen/expert-groups/consult?lang=en&groupID=1718

to address such questions and to provide legal clarity [68]. Furthermore, while most BTC-based therapies fall clearly under either the pharmaceutical, medical device or BTC legal framework, the evaluation suggested that in some cases, it is challenging for Member States [69] to decide on which framework's requirements should be applied. Furthermore several BTC can become starting materials for manufacturing therapies under other EU legal frameworks, and in some cases BTC can be combined with therapies regulated under other EU legal frameworks.

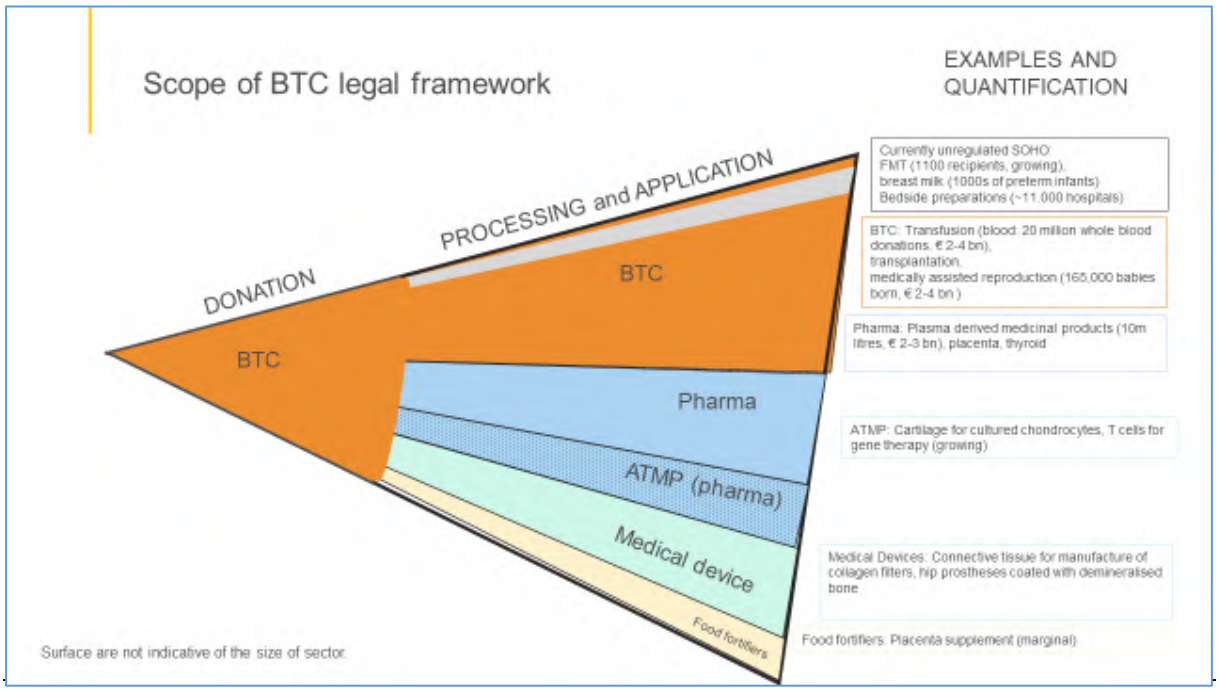

Figure 1: Scope of the EU BTC legal framework

This IA confirmed and substantiated this lack of legal clarity on the borderline. Half of the consulted stakeholders, particularly those representing companies and authorities as well as those representing all other groups [70], raised a lack of legal clarity as an important issue and more than 170 examples where legal clarity is lacking were provided by respondents across all the stakeholder groups [71], in particular in relation to BTC that border the ATMP framework and to unregulated SoHO (see 2.1.1). Furthermore, half of those answering expressed the view that some specific substances that are currently regulated under one legal framework would be better regulated under another [72]. Several borderline cases examined by

[68] Public authorities have also flagged in the public consultation that this mechanism is 'time-consuming' or 'not accessible for developers'. A list of questions and the (slow) process to clarify them in the Expert Group can be found in Annex VIII of the Evaluation {SWD (2019) 376 final}, p. 127-179.

[69] Classifying a substance/product as a BTC or as a medicinal product or establishing which of the respective legal framework applies is primarily a Member State responsibility, but bring very different legal requirements.

[70] NGOs, academia, business associations, EU citizens, others.

[71] Including by professional associations, like the European Blood Alliance (EBA) and the European association of Tissue and Cell Banks (EATCB), and by business associations, like the European Association for Bioindustries (EuropaBIO) and EUCOPE.

[72] These views were especially prominent among respondents from academia or patient organisations. For further details see: Public consultation factual summary report, section III, p. 11. Available at

the external study supporting this impact assessment, confirmed that the choice of legal framework and the requirements that are applicable can have a significant impact, often with effects on patient access (see Annexes 10 and 11 [73]). The borderline case studies reported discontinuation of the development and supply of established (safe and valuable) therapies in the BTC framework, following such re-classifications [74].

These concerns are typically reported where questions are raised as to whether the requirements of the pharmaceutical/ATMP framework are applicable in the hospital settings where many blood and tissue establishments (BE/TEs) are active. This can have two kinds of impacts on safe patient access to therapies:

- Under-regulation: BTC-based therapies are offered without sufficient requirements for safety and quality or any proof of efficacy (often by commercial actors to patients for whom no alternative therapy exists). This issue is described in a position paper published by the Worldwide Network for Blood and Marrow Transplantation [75] and has resulted in calls for a global response [76]. Some of these cases have led to significant, negative media attention which has impacted on the entire sector [77,78].
- Over-regulation: when safe and effective BTC-based therapies are re-classified as ATMP they can no longer be offered by BE/TEs, yet no affordable alternative may be made available by commercial developers [79].

Insufficient legal clarity is also reported where BTC are combined with medical devices or medicinal products, and where BTC are used as starting materials for products that are then manufactured under the medicinal product or medical device frameworks. Stakeholders both from business sectors and from public authorities report significant challenges to comply with technical requirements and oversight in such cases where more than one framework applies

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https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12734-Revision-of-the-Union-legislation-on-blood-tissues-and-cells/public-consultation_en

[73] In particular the case studies for chondrocytes (section 11.7), cultured keratinocytes (section 11.6) and cultured limbal cells (section 11.8) provide examples, with a perspective based on extensive literature review and interviews with leading experts.

[74] Annex 11, in particular section 11.7 (Chondrocytes) and section 11.6 (Cultured Keratinocytes). An illustrative case concerns the development of a new limbal stem cell therapy (section 11.8) used to treat forms of blindness. The development of this therapy was initiated by tissue establishments under the BTC framework. The clinical research results of one establishment were consequently used by a commercial company for an authorisation of the innovative treatment as a pharmaceutical. As a result, all tissue establishments had to halt developments on this therapy. The eventual cost of the therapy offered by a single pharmaceutical company were prohibitively high to allow access to patients, even for the centre that had provided the original clinical data.

[75] Position paper on Unproven Cell-Based Therapies: Current Global Status and Recommendations to the World Health Organization (2018) WBMT-Unproven-Therapies-2020.pdf

[76] Master et al., 2016 (Annex 20).

[77] Notorious stem cell therapy centre closes in Germany: News blog (http://blogs.nature.com/news/page/200?by2=Merck).

[78] Abbott, 2013 (see Annex 20).

[79] This scenario was reported by the Belgian Military Hospital that had difficulties to continue providing patients with cultured skin cells (keratinocytes) to treat burn wound (see Annex 11, section 11.6). Similar experiences are described in a number of the borderline case studies developed by the external study supporting this Impact Assessment (see overview in Annex 10, section 10.2.5).

[80]. The stakeholders' consultations, a dedicated workshop and a series of borderline case studies all point to the lack of cross-sector coordination and consultation as a key driver for limited legal clarity (further detailed in Annex 10). It needs to be noted that the delineation with other EU legal frameworks is however not set within the BTC framework, but set by definitions laid down in these other EU legal frameworks (pharmaceuticals and medical devices). Also, classification decisions are ultimately made by Member State authorities. This has thus led to some situations where different Member States regulate the same therapy under different legal frameworks [81], leading to additional challenges to cross-border exchanges within the EU. This situation can also create issues for importers from third countries that wish to supply multiple Member States.

2.1.5 Patients vulnerable to interruptions in EU supply of BTC

For some essential BTC, the EU is highly dependent on imports to ensure sufficiency [82]. The demand for plasma to treat patients, in particular patients with rare diseases reliant on a steady supply of PDMPs, is higher than the current plasma collection capacity in the EU and results in a high level of plasma import from the US (see Annex 8), equivalent to around 25 % of total plasma needs [83]. A large part of the plasma collected in the EU is collected by the private sector in just 4 Member States and there is a clear recognition that increased collection by the public/non-governmental blood sector is necessary [84].

The sector relies on the willingness and availability of healthy citizens to donate, which can in particular be reduced during public health crises e.g., due to disease outbreaks, such as outbreaks of West Nile Virus in the south of Europe and, more recently, during the COVID-19 pandemic (see Annex 9). Ultimately, patients are at risk of an interruption, or a change, to their treatments.

The current legislation aimed to achieve sufficiency through the application of the principle of voluntary unpaid donation (VUD) but the interpretation of that principle varies across Member States, as well as between the public and private sector. While financial compensation of plasma donors has been shown to achieve high rates of collection, the public sector argues that greater resilience of supply, with less risk for donors, could be achieved by establishing a broader base of donors who donate less frequently without compensation [85].

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[80] 10-20% of respondents find it complex and 50-60% rather complex to meet requirements of more than one legal framework. For further details see Annex 18, Section II.

[81] For examples, see Evaluation {SWD (2019) 376 final}, Annex XVI, Table 2, p. 213.

[82] Evaluation {SWD (2019) 376 final}, section 5.2.6.1, p. 54.

[83] Source: Marketing Research Bureau: The Plasma Proteins Market in Europe — 2017 (https://marketingresearchbureau.com/the-plasma-proteins-market-in-europe-2017/) The EU-28 was importing around 40% of its plasma needs. As the UK, at one point, imported 100% of its plasma due to the risks associated with variant Creutzfeldt-Jakob disease in that country, the dependency now in EU-27 is reduced to around 25%.

[84] Tiberghien, 2021 (see Annex 20).

[85] European Blood Alliance Press release: "Plasma shortage in Europe: proper investment in public blood establishments is the answer, not undermining ethical principles" – October 2021. https://europeanbloodalliance.eu/plasma-shortage-in-europe-proper-investment-in-public-blood-establishments-is-the-answer-not-undermining-ethical-principles/

These diverging views between public and private collectors of plasma have made it even more difficult to define coordinated actions to achieve sufficiency in practice.

2.1.6 Undue burdens

The evaluation showed a general consensus among stakeholder groups that costs associated with the current legislation were justified by benefits for patients. Still, it identified a number of areas for possible regulatory simplification [86]. Most important is the need for a new approach to updating technical *requirements, avoiding the need for legal adoption of new Acts each time a technical standard changes.* In addition, the current framework consists of Directives, and each amendment requires a further transposition by each Member State before it is fully legally binding, which requires further resources and creates further delays, which does not only place additional burdens on the Member States but also leads to differences in transposition and implementation at national level.

The evaluation also highlighted that the costs of implementing some *obsolete and costly donor testing/eligibility criteria are not justified by improved safety* [87]: donor eligibility criteria were not subjected to cost/benefit assessment when introduced and some of them now imply cost inefficiencies [88,89]. Importantly, each donor selection/deferral measure not only has an impact on safety, but also on the (volume of) supply of BTC to treat patients.

The evaluation showed that the costs linked to the *fixed rule on inspection frequency* [90] *was over-burdensome* without proportionate benefits, and identified oversight of the BTC sector as one area for possible simplification [91].

The evaluation also identified limited burdens for downstream manufacturers of products made from BTC, such as manufacturers of PDMPs [92] and ATMP developers [93].

The *absence of a common EU-wide proportionate risk-based authorisation mechanism* for BTC processed or used in new ways creates duplication of effort and a heavy burden (as well

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[86] Evaluation {SWD (2019) 376 final}, section 5.3, p. 57-64.

[87] For example, tattooing, endoscopic examination and acupuncture now carry less risk of disease transmission; age and haemoglobin donation limits are also questioned by experts in the sector. Evaluation {SWD (2019) 376 final}, p. 58. See also Borra, 2016 (see Annex 20) and UK Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO), Donor Selection Criteria report (2017).

[88] Testing of sperm and egg donors and the testing provisions for West Nile Virus in blood donors. Evaluation {SWD (2019) 376 final}, section 5.3.1.2, p. 59.

[89] Situations when the risks associated with contamination and cross-contamination during processing are extremely low to negligible, due to both the length of time of exposure to the processing environment and the mode of application to the patients. Evaluation {SWD (2019) 376 final}, section 5.3.1.3, p. 60

[90] Evaluation {SWD (2019) 376 final}, section 5.3.4, p.63.

[91] Evaluation {SWD (2019) 376 final}, section 6, p.86.

[92] Plasma donated for PDMPs manufacturing undergoes subsequent manufacturing steps, including microbial inactivation. Donor eligibility provisions and costs of donor tests that do not add safety when the plasma is used for PDMPs implies an unjustified burden for these stakeholders. Evaluation {SWD (2019) 376 final}, section 5.3.2, p. 61.

[93] ATMP developers see the costs of complying with BTC import (i.e. from outside the EU) eligibility provisions as inefficient, as the import has to be done via an authorised 'importing tissue establishment' (ITE), which must verify equivalent quality and safety of the tissue and cells to be imported. For imported tissues or cells that are destined for manufacture of ATMP, the ITE must verify the equivalence of the donation, procurement and testing steps. Evaluation {SWD (2019) 376 final}, section 5.3.2, p. 61.

as missed opportunity) for academic developers who normally share newly developed technologies and practices through scientific publications and conferences, allowing for wide access. 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-19 patients, for which currently 48 studies are organised across the EU [94].

Finally, NCAs have been using the existing *digital systems* for reporting (annual reporting of the Serious Adverse Reactions) as well as for notifications (the Rapid Alerts systems for Blood and Tissues & Cells). Some stakeholders organisations have also registries in place and some digital tools to facilitate the work of BE/TEs (see Annex 19, Table 19.1). Another existing tool, the EU Coding Platform (with the TEs Compendium and the EU Tissue and Cell Product Compendium) [95] is maintained by the Commission and used in the sector but is not integrated with other datasets. The available digital tools are fragmented, without common glossaries and taxonomies, and do not allow comprehensive analysis nor efficient pooling and sharing of information. For example, NCAs have reported a high effort needed for their annual reporting (close to 50 person-days per year) [96]. This results in undue burden and loss of efficiency due to the absence of common, or integrated, IT systems.

2.2 What are the problem drivers?

2.2.1 New diseases and developments in science and technology

One of the main drivers for the insufficient protection of patients, donors and offspring born from MAR, is the *continuous, often incremental, development in technologies*, which lead to new methods in collection or processing. Also, the *(re-)emergence of communicable diseases* may require new tests on BTC before they are applied to patients. Finally, scientific knowledge and evidence is also evolving, and so is the view on the most appropriate effective safety and quality requirements to apply. Many of the technical requirements set by the BTC legislation have become outdated and could not be rapidly updated in legislation (estimated to take from 6 months using an emergency legal adoption procedure to at least 2 years using a standard procedure to adopt new legislation or amend an existing Act). By the time an amendment is adopted, it can already be outdated [97].

There are also new and emerging therapies with SoHO (e.g. breast milk and FMT, transplants of other microbiota in the future, transplants of parts of cells or extracellular vesicles), for which it is not always clear whether, and if so which of, the BTC Directives apply.

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[94] https://www.support-e.eu/, while related, these 48 studies are not all duplications, many are also for separate indications.

[95] The EU Coding Platform contains two compendia: (1) the EU Tissue Establishment Compendium, which is a register of all TEs authorised, licensed, designated or accredited by the NCAs; (2) the EU Tissue and Cell Product Compendium, which is a non-exhaustive list of (product codes for) SoHO falling within the definition of either 'tissue' or 'cells'- https://webgate.ec.europa.eu/eucoding/reports/eugcproduct/index.xhtml.

[96] See Annex 5, section 5.1.5.

[97] In 2014 a measure was introduced to allow for Nucleic Acid Amplification Technique (NAT) testing for West-Nile Virus. This would allow to resume collections in areas affected by West-Nile Virus. Shortly after adoption of the legal amendment, planning an individual NAT test, evidence was available that a pooled NAT test would be a more cost-effective alternative test.

Furthermore, new technologies increasingly make it possible to process BTC at the bedside, usually using medical devices. Bedside procedures were however excluded from the BTC framework in 2004 [98], when such procedures were much simpler and did not entail such complex processing steps [99].

With such frequent and sudden changes in epidemiology and technology, it has not proven possible for technical standards defined in EU legislation to be updated in a responsive and timely manner. Despite some minor amendments to update provisions to address new risks [100], the legislation has still not addressed most of the changes.

2.2.2 Increased demand

The *role of commercial actors* has grown as certain BTC are increasingly used as 'starting materials' that are supplied to private companies for the manufacture of medicinal products (such as PDMP) and medical devices such as collagen implants [101]. There has been a steady and significant global and EU increase in demand for PDMP, over 9% per year [102], which translates into an increased need for plasma donations. Consequently, the growing need for donations may also increase pressure on potential donors to donate, and lead actors (both public and private) to increase the incentives for doing so, within the limits imposed by the principle of VUD.

For some *new therapies* (e.g. human milk and FMT), there is also an increasing need for donations, as demand rises in line with an increasing body of scientific evidence on their clinical effectiveness [103].

Finally, *social changes and fertility trends*, as well as new technologies, are driving MAR activities and the need for gamete donors. For example, at the time the legislation was adopted, freezing of donated eggs was highly experimental. This practice has since become routine, opening up possibilities for establishing banks of donated eggs as a commercial enterprise that relies on donors, ideally, from the perspective of the companies, donating frequently.

2.2.3 Regulatory drivers

The current BTC legislation contains only very *limited measures to protect and monitor BTC donors.* In particular, the requirements to report donor adverse reactions are limited to cases where the donor incident had a detrimental impact on the safety or quality of the substances donated (i.e. when there is a possible impact on the health of the recipient), and there is no

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[98] Article 2, paragraph 2(a) of Directive 2004/23/EC.

[99] These procedures are sometimes conflictingly described as "point-of-care" procedures; see for example Hourdet al., 2014 (see Annex 20)

[100] For example, amendment of the Blood Directive to address the emergence of West Nile virus and prevent transmission of this communicable disease by blood transfusion.

[101] Liu, Bingci et al., 2005 (see Annex 20).

[102] Marketing Research Bureau - : The Plasma Proteins Market in Europe — 2017 (www.marketingresearchbureau.com)

[103] Donated breast milk prevents necrotising enterocolitis in pre-term infants (Arslanoglu et al., 2019, see Annex 20); faecal microbiota transplant is used to treat patients with severe bacterial intestine infection due to Clostridium difficile and for a growing number of clinical applications (Baunwall et al., 2021, see Annex 20).

obligation to report other donor reactions that might impact the health of the donors themselves (e.g. fainting after blood donation, or excessive reaction to hormonal stimulation for egg donors). In addition, the legislation contains very *limited and outdated provisions for genetic testing* of egg and sperm donors.

For oversight, the evaluation showed a lack of common provisions in the BTC legislation for verification of effective implementation of inspection, authorisation and vigilance by the NCAs. Equally there is a lack of provisions on expected levels of capacities, skills and independence required of inspectors supervising BE/TEs. The BTC sector is also seeing an increasing number of commercial and multi-national actors that need to be authorised and inspected, as well as a high number of innovations. It can be challenging for some Member States' authorities to have all the skilled resources required to oversee such actors and activities, and sometimes a joined up approach to oversight by NCAs from more than one Member State is needed, but this is not covered in the current BTC frame.

Regarding new BTC preparation processes, the *provisions to assess clinical outcome* (efficacy) in the current BTC legislation *are too generic* [104], and do not allow assessment of incremental innovations in a proportionate way that would be feasible for public sector actors to comply with. While some national authorities might then decide to regulate some therapies under the pharmaceutical framework, the requirements in this framework are often not proportionate to the incremental risk of innovation and it is not feasible for public sector actors to invest in these requirements for a small group of patients [105].

As there is a borderline and an interplay between the BTC legislation and other frameworks that apply when BTC are used as starting material for manufactured products (see section 1), it is important to understand the *delineation between the legal frameworks*. The scope of the BTC framework is partly a function of the scope defined in these other legal frameworks [106]. Therefore legal clarity is needed on key definitions in adjacent legal frameworks such as as 'industrial process' and an 'intention to place on the market' for medicinal products [107]. Within the pharmaceutical framework, the ATMP regulation sets criteria based on definitions

[104] A "tissue establishment must have access to a nominated medical registered practitioner to advise on and oversee the establishment's medical activities such as […], review of clinical outcomes of applied tissues and cells […]". (Point 3 of annex I of Commission Directive 2006/86/EC).

[105] Stakeholders have expressed differing preferences on how to solve the issue of unclear borderlines, indicating that there is no universal approach as the best option for each substance depends on a variety of factors (see for example position paper by Roche "F2332626-Attachment_to_Roche_submission_to_EU_BCT_legislation_revision_public_consult_Q29" or National Marrow Donor Program (NMDP) "F2264743-National_Marrow_Donor_Program_Comments_EU_directive_04.13.21" available at 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, or the borderline case studies, Annex 11).

[106] Article 2, paragraph 1: Scope of Directive 2004/23/EC on tissues and cells states: "This Directive shall apply to the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells intended for human applications and of manufactured products derived from human tissues and cells intended for human applications. Where such manufactured products are covered by other directives, this Directive shall apply only to donation, procurement and testing."

[107] Article 2, paragraph 1: Scope of Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use.

of ‘substantial manipulation’ or ‘use for a different essential function’ (commonly referred to as ‘non-homologous use’) but excludes ‘non-routine hospital settings’ [108]. The Medical Device Regulation includes in its scope ‘derivatives of non-viable tissues’ [109]. In effect, these are the terms that define whether a particular BTC remains under the BTC framework up to its clinical application or is subject to those frameworks for the later stages of manufacture and supply as ‘products’.

Clarifying scope criteria and definitions set by other frameworks must be addressed under these frameworks through relevant initiatives such as the revision of the pharma legislation but requires good coordination across the legislative frameworks concerned.

Furthermore, while there are many instances of national collaboration between different sector authorities [110], it is often complicated for BTC developers to ask for EU-level advice on how to interpret these legal definitions (with the exception of the scientific criteria for ATMP, for which a dedicated committee exists to provide advice).

The *absence of a legally mandated EU-level advisory mechanism* in the BTC sector, equivalent to that in the pharma [111] or medical device sectors [112], also complicates EU-level exchanges of views between sector authorities, and can hamper the provision of clear and uniform advice to developers and national authorities.

Under the current legislation, Member States are obliged to encourage the achievement of sufficient supply through VUD, but there are *no concrete measures laid down to protect or increase supply*. Policies to manage donation rates and stock management fall within the remit of health service management at Member State level. However, the lack of EU supply monitoring provisions and of such provisions in each of the Member States makes it difficult to predict EU supply interruptions and thus to take appropriate action to mitigate the risks to patients. The legislation is also lacking provisions for ensuring preparedness for sudden disruptions.

Finally, the article 168(4)(a) of the Treaty of the Functioning of the EU (TFEU), gives the Union a strong mandate to set high common standards of quality and safety, while also allowing Member States to implement more stringent national measures, in line with subsidiarity and national decisions on the organisation of healthcare. As explained in section 2.1.1 (problem 1), adhering to the standards set in the Directives, which have not been kept up to date, does not provide for optimal safety and quality of BTC. Consequently, Member States have used their right to implement more stringent measures to protect patients treated with BTC, often reflecting the guidelines of expert bodies such as the EDQM and the ECDC. This has led to a complex mosaic of requirements for BE/TEs to comply with if they wish to supply BTC to hospitals/patients in more than one Member State and to suboptimal access for patients to their best matching BTC therapy.

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[108] Article 2, paragraph 1(c): Definitions – and Article 28, paragraph 2: hospital exclusion – of Regulation (EC) N° 1394/2007.

[109] Article 1, paragraph 6(g): Subject matter and scope – Regulation (EU) 2017/745.

[110] In 21 EU Member States the national authority competent for blood, tissues and cells is the same as the national competent authority for pharmaceuticals.

[111] Committee on Advanced Therapies – Regulation (EC) No 1394/2007.

[112] Working Group on Classification under the Medical Devices Coordination Group.

2.3 How will the problem evolve?

The BTC evaluation suggested that these trends, drivers and problems would continue to gain importance as climate change and increased travel promote the spread of communicable diseases and science and technology continue to advance and bring new medical and commercial possibilities. Communicable disease outbreaks will have a negative impact on BTC donation rates, often because sections of the donor pool become ineligible to donate due to possible exposure. In this context, having an ad-hoc view on the supply situation will become ever more important for policy making and risk management, to ensure effective responses and continued supply of safe BTC.

There is an overall increasing demand for many BTC therapies, e.g. for IVF (10% more cycles/year [113]), so the impact on patient, and donor, protection will grow over time. Also the use of substances such as FMT is expected to increase [114] and trends are observed towards increasing use of medical devices for processing BTC at the bedside [115]. Although the devices used are appropriately certified, concerns were raised about the need for appropriate requirements and oversight of BTC applied to patients in those circumstances outside the quality management system of an authorised BTC establishment. These concerns were raised in the BTC evaluation and during meetings with NCAs [116]. In the absence of updated and harmonised rules for safety and quality of BTC used in these circumstances, it can be expected that the divergence among Member States' practices will further increase.

The demand for PDMP and plasma is expected to continue its growth, and EU patients are set to become even more dependent on plasma collections from outside the EU, mainly the US.

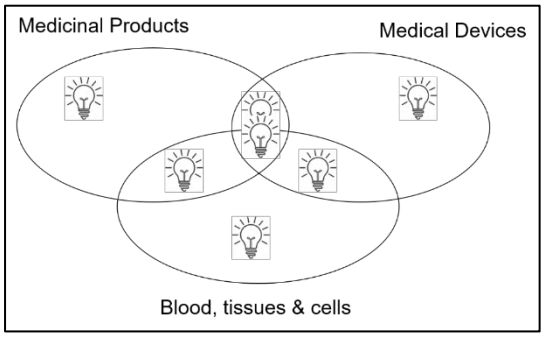

Figure 2: Innovation crosses legal frameworks

Horizon scanning [117] indicates an increase in borderline therapies for which it is not clear which is the applicable legal framework and/or which multiple legal frameworks will need to be applied. Although many of the substances/products currently situated on regulatory borderlines are autologous, and cross-border exchange is not frequent at this stage, this is likely to change as innovation in both the BTC and the ATMP fields move forward. Overall, it is expected that innovation will lead to an increasing number of borderline cases, combination products and BTC that become starting materials for other therapies.

[113] ESHRE statement: European pregnancy rates from IVF and ICSI 'appear to have reached a peak'. News release 25.06.2019 https://www.eurekalert.org/news-releases/543795.
[114] Wortelboer & Herrema, 2021 (see Annex 20).
[115] Alves & Grimalt, 2018; Simonacci et al. ,2016; Oliven & Shechter, 2001 (see Annex 20).
[116] Evaluation {SWD (2019) 376 final}, section 5.4.2.3, p.72-73.
[117] EMA/Innovation task force, Borderline Classification Group of Heads of Medicines Agencies.

3. WHY SHOULD THE EU ACT?

3.1 Legal basis

The BTC legislation has a strong legal mandate based on Article 168(4)(a) of the TFEU. As a shared competence with the Member States, and in line with the principle of subsidiarity, this Treaty Article gives the EU a mandate to set out measures establishing high standards of quality and safety for BTC while allowing Member States to maintain or introduce more stringent protective measures. Member States remain responsible for decisions of an ethical and organisational nature, such as allowing the donation of certain BTC or deciding who may access BTC therapies (e.g. access to IVF therapies), and for the implementation of the VUD principle. When a Member State chooses to allow a particular new practice (such as testing or storage of embryos) the safety and quality of this practice are then regulated by the EU BTC legislation.

Furthermore Article 168(1) of the TFEU, ensuring a high level of human health protection can also be explored as a basis for the new initiative, as an additional legal basis, in particular to facilitate stronger common measures to support the sustainability of the BTC supply, as well as for protection of donors and of offspring from MAR.

Treaty articles related to the Single Market are not considered appropriate to legislate substances of human origin, which are subject to the prohibition on making the human body and its parts as such a source of financial gain (art 3.2.(c) of the EU Charter of Fundamental Rights).

3.2 Subsidiarity: Necessity of EU action

Ever-evolving disease threats, such as Zika and Hepatitis E, which can both be transmitted through BTC, or more recently COVID-19, constitute cross-border threats to public health. In addition, the exchange of BTC between Member States and with third countries is necessary for ensuring optimal patient access and sufficiency of supply, and in many cases it is essential when a donor needs to be specifically matched with a recipient [118]. The extent of cross-border exchange is considerable, although it varies highly from substance to substance, as shown in Annex 8. For some, such as blood components for transfusion, it is minimal (under 1% for rare blood units) although exchanges can also happen more widely during emergencies. There is a continuous and significant exchange and import of plasma for PDMP manufacture and almost half of all haematopoietic stem cell transplants (bone marrow) involve a donation made in another country to improve the genetic match. There are substantial cross-border shipments from some EU hubs where gamete collection is organised (leading sperm banks in Denmark supply to many countries, Spanish IVF clinics collect and supply egg-cells to many other countries).

Increasing cross-border exchanges of BTC necessitate ever-closer cooperation between a number of health professional groups and authorities to ensure that BTC remain traceable from the donor to the recipient and vice versa. While a common EU compendium already

[118] For many BTC, a match is to be ensured between donor and recipient before use, for example to verify immunological compatibility (like grouping for blood). Hence, while a certain BTC might be available locally, use of a similar BTC from abroad might be required to ensure matching and optimal outcome.

exists with all TEs authorised by their national authorities, the many more stringent national requirements and differences in oversight create de-facto barriers to cross-border exchange. EU action is therefore required to reinforce the framework, increase trust and facilitate that patients in all Member States can benefit equally from safe and effective BTC.

In addition, there are different practices regarding donor monitoring or reporting of activity and supply data (see section 5.1), and the current situation differs significantly per Member State: four large Member States (DE, FR, IT, ES) already have a lot of oversight measures in place, on the other hand, there are a significant number of smaller, and less well resourced, Member States where the implementation of common EU measures will require more efforts, but will also bring more benefits in terms of strengthening the safety and quality of BTC.

3.3 Subsidiarity: Added value of EU action

The evaluation concluded that *"in general, the Directives improved the quality and safety of BTC in a manner that would not have happened, or would have happened more slowly, without EU legislation*". Indeed, significant efforts to raise safety and quality to a common level were made across the EU following the adoption of the legislation. But as technical requirements have failed to keep pace with change over the years, standards have diverged and the evaluation highlighted that "*more stringent national requirements, although permitted by the Treaty, limit the EU added value, particularly in terms of exchanges between Member States"* [119].

The COVID-19 pandemic highlighted the risks of supply interruptions, the need for adequate donor and recipient protection, and the need for rapid and adequate authorisations of health innovations in the BTC sector (see Annex 9). By providing a framework for cross-border cooperation, based on a common set of rules, and connected to sector-specific expertise, EU-level measures are best placed to address such issues effectively.

Overall, for the five problems highlighted, more collaboration and support among the NCAs would help to address these issues, would bring simplification and would improve the effectiveness of the legislation and the efficiency of its implementation. Sharing information across Member States at NCA level, e.g. on the supply of critical BTC, authorisations of preparation processes, or results of the inspection of an establishment, would help other Member States. Surpluses for a certain BTC should be transparently notified, and authorities could re-use preparation process authorisations already given (by assessing that the procedure is equivalent, without performing again a complete risk assessment or re-assessing the clinical evidence provided) (see Annex 12). The burden associated with this data sharing can be significantly reduced by the provision of an EU digital platform where data can be entered directly by operators and accessed by authorities.

Also, some sector-specific expertise might not be easily available in all Member States. Providing for a common framework that supports joint practices among Member States will promote simplification and efficiency.

[119] Evaluation {SWD (2019) 376 final}, section 5.5, p 78.

4. OBJECTIVES: WHAT IS TO BE ACHIEVED?

4.1 General objectives

The overall objective of this initiative is to ensure a high level of **health protection** for EU donors, recipients and offspring and ensure safe and effective **access** to BTC therapies. As new technologies or risks will continue to emerge, it is desirable that the future BTC framework is more effective, **future proof, crisis resistant and agile** enough to accommodate new trends and continue providing appropriate safety and quality requirements. As the evaluation identified a number of areas for possible **simplification** (see paragraph 2.1.6), areas for improving the efficiency of the BTC legislation and simplifying its implementation by all stakeholders will also be explored.

4.2 Specific objectives

The EU BTC legislative framework should therefore:

1. Ensure safety and quality for patients treated with BTC therapies and maximise protection from avoidable risks linked to BTC.
2. Ensure safety and quality for BTC donors and for children born from donated eggs, sperm or embryos.
3. Strengthen and allow for harmonisation of oversight practices among Member States.
4. Facilitate the development of safe and effective innovative BTC therapies.
5. Improve the resilience of the sector, mitigating risk of shortages.
6. (horizontal) Foster the use of efficient digital solutions.

It should be noted that objectives 1 and 2 are closely linked, as they both involve setting technical rules for safety and quality to better protect EU citizens. In addition, some measures would be synergetic between both objectives: for example, by including substances not yet in the scope of the BTC legislation, such as breast milk and FMT, this will increase the safety and quality of those substances and therefore better protect patients, but also better protect donors of such substances.

Furthermore, throughout the revision process, many parties underlined that the VUD principle remains very important for the BTC framework and should be retained in revised legislation [120].

[120] Various position papers on this topic were submitted to the public consultation by the Associazione Volontari Italiani del Sangue (AVIS) "*F2332686-AVIS_Statement_on_the_revision_of_BTC_ legislation*", by the European Network of Tissue Establishments (eNOTE) "*F2332710-eNOTE _Contribution_-_April_14_2021*", by the International Federation of Blood Donor Organizations (IFBDO/FIODS) "*F2332731-IFBDO-FIODS__position*", available at 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, and by the European Committee on Blood Transfusion (CD-P-TS) from the EDQM "Art._21_Oviedo_guiding_principles.pdf" through the targeted consultation (see Annex 18), as well as by the French authorities outside of the formal consultation process (ARES(2021)2671096). It should be noted that stakeholders at times differ in their exact definition of VUD, especially regarding the extent to which possible compensations are compatible with a generally unpaid donation.

5. WHAT ARE THE AVAILABLE POLICY OPTIONS?

5.1 What is the baseline from which options are assessed?

The baseline is a "no policy change" scenario, with the current EU Directives on BTC remaining in force, while some Member States continue to develop and apply more stringent rules as they have done in the past [121]. In the baseline situation, the expert bodies already providing guidance on SoHO, such as the EDQM (Annex 14) and the ECDC (see Annex 15), will also continue working in the field.
The Commission proposal for a strengthened mandate for ECDC [122] already includes some new or reinforced tasks in the field of SoHO intended to prevent the transmission of communicable diseases via BTC. Those include in particular epidemiological surveillance for SoHO relevant communicable diseases; preparedness and response planning, risk assessments and provision of non-binding recommendations and options for risk management; supported through a dedicated network of experts and authorities in substances of human origin (see Annex 15). Throughout the IA, the assumption will be made that this proposal, which is currently under negotiation, will be adopted without major changes regarding these tasks.

As stated in section 2.3, it is expected that the underlying problems will persist, and even be exacerbated, as the drivers will not disappear (increased demand for many BTC therapies, science and technology bringing new medical and commercial possibilities, and communicable diseases possibly (re)-emerging). It is likely, as mentioned above, that in the face of these trends, and in the absence of EU action, some Member States will take further more stringent measures, to mitigate the absence of updated safety and quality rules at EU level, resulting in an increased divergence in practices followed at national level (see section 2.2.3).

As noted in section 2.1.1, the situation is not the same in all Member States, as some had put in place more stringent measures to protect patients. There are also different practices regarding BTC donors' protection, with increased follow-up and monitoring on a voluntary basis of donor reactions. This demonstrates that monitoring has been introduced at a national level, either on a voluntary or a mandatory basis, and there is support and willingness of professionals and authorities to monitor and to share the data. There are also different practices in place in Member States as regards preparation process authorisation (as explained in section 2.6), and it was estimated that 19 Member States, covering 82% of all BTC establishments in the EU [123], already have such practices in place (though with different approaches). A similar proportion of Member States is estimated to already use risk parameters to schedule inspections, combining the current fixed-frequency inspections with more frequent controls for certain establishments. Regarding actions to mitigate risks of shortage, some Member States already have emergency preparedness and contingency plans

[121] On that basis, position papers submitted by authorities from Germany argue that maintenance of the baseline in their Member State is preferable over any of the policy options suggested.
[122] Proposal for a regulation of the European Parliament and of the Council amending Regulation (EC) 851/2004 establishing a European Centre for disease prevention and control.
[123] See Annex 5, section 5.1.5 (estimation based on Member States' responses to a dedicated survey carried out by the External Study for the BTC Impact Assessment).

in place. In a recent survey done by the EDQM on blood emergency/contingency planning [124], out of the 20 Member States who replied, 16 had plans in place to ensure the continuity of blood supply.

5.2 Description of the policy options

Measures are proposed for each of the objectives, with different policy options being explored where technical expertise will be essential for the measures, safety and quality rules or guidance, to be kept up to date. There is a need for those rules that protect patients, donors and offspring (objectives 1 & 2) to be flexible enough to accommodate changes quickly (a new epidemiological threat, a new technology available for testing, new scientific evidence, etc.). Such expertise can also be leveraged to update guidance for the authorisation of innovative BTC (BTC prepared or used in new ways) (objective 4), and for the design of preparedness plans (objective 5). **Three policy options** have been identified and explored as alternative ways of specifying such more technical rules (see Annex 13 for details on the specific objectives, policy options and measures, and results).

The **three options** differ as regards to the roles and responsibilities of regulators and stakeholders (it should be noted that under each policy option, NCAs inspect the blood and tissue establishments):

- Under **policy option 1 – decentralised regulation:**
  blood and tissue establishments
  - define their own internal technical standards, and guidance, according to their local needs, evidence review and risk assessments;
  - design the risk assessments on novel processes following inter/national or standards from other bodies;
  - develop monitoring and notification systems and contingency plans.

- **Policy option 2 - joint regulation,** builds on the expertise available in established expert bodies, such as the EDQM and the ECDC, which:
  - define technical standards and guidance. Under this option, EU legislation would refer to the latest technical standards of these expert bodies.
  - define the requirements for the novel preparation processes risk assessments;
  - provide technical guidance on monitoring and notification systems and contingency plans.

  Member States may impose more stringent requirements or introduce a temporary derogation if the national, epidemiological situation requires it. In both cases, the EC must be notified.

- Under **policy option 3 – central regulation:** EU legislation:

[124] The survey was conducted as part of the Blood Supply Contingency and Emergency Plan (B-SCEP) project, the results will be published soon.

- sets the technical standards. The legislation will be revised, with the support of a new expert committee, when risks and technologies evolve, to keep the rules up to date;
- defines the requirements for the novel preparation processes risk assessments;
- develops monitoring and notification systems and contingency plans.

Member States may impose more stringent requirements or introduce a temporary derogation if the national, epidemiological situation requires it. In both cases, the EC must be notified.

In addition, a set of common measures to achieve the different objectives are proposed (see below). The table below gives an overview per objective of all measures, specifying those that differ according to the policy option. For the purposes of detailed costing and impact assessment, the measures are further broken down and codified in Annex 16.

	Objective	**Key measures**
1	Ensure safety and quality for patients treated with BTC therapies and fully protect them from avoidable risks linked to BTC	**M1A** - Fill regulatory gaps (e.g. FMT, breast milk) **[common]** **M1B** - Up-to-date technical rules **[differs by policy option]**
2	Ensure safety and quality for BTC donors and for children born from donated eggs, sperm or embryos	**M2A** - Set donor and offspring protection principles in law **[common]** **M2B** - Up-to-date technical standards for donor and offspring protection **[differs by policy option]**
3	Strengthen and allow for harmonisation of oversight practices among Member States	**M3A** - Set principles and new practices for oversight in legislation (e.g. independence of authority, risk-based inspections) **[common]** **M3B** - Provide EU support (EU audits of authorities, training,) **[common]**
4	Facilitate the development of safe and effective innovative BTC therapies	**M4A** - Create BTC mechanism to advise on applicability of BTC legislation and liaise with equivalent MD and (AT)MP mechanisms **[common]** **M4B** - Risk-based authorisation BTC processed or used in new ways, including clinical data when justified, with guidance **[differs by policy option]**

5	Improve the resilience of the sector, mitigating risk of shortages	**M5A** – introduce supply monitoring and notification rules **[common]** **M5B** – Require emergency preparedness plans with guidance **[differs by policy option]**
Horizontal	Foster the use of efficient digital solutions	EU development of an interoperable digital platform for publishing relevant information and data exchange; linking existing local, national and EU systems [125.], with 3 different implementation: **M6A.** Upgrade **M6B.** Upgrade and connect **M6C.** New single system

Table 1: Overview of key measures assessed

For **objective 1**, the common measure consists in including in the scope of the framework all SoHO applied to human persons for therapeutic or other purposes [126] (measures M1A), with specific exceptions [127]. There will be no change in the delineation with other EU legal frameworks (it is rather the pharma and medical device frameworks that define the delineation). Thus, this measure will **address the gaps** in the current legislation for substances of human origin, such as breast milk and FMT [128,129], and the trend towards increased processing of BTC at the patient's bedside. The technical rules will be kept up to date (M1B); either by the BTC establishments (Policy Option 1), by expert bodies (Policy Option 2) or by regularly revised legislation (Policy Option 3). It needs to be added that the basic act will only organise for how technical rules are set, but not set technical rules itself. These will be set in later implementing acts and/or guidance – according to the Policy Option chosen.

For **objective 2**, **principles** will be laid down in EU legislation for the protection of BTC donors and MAR offspring and will include mandatory reporting on serious adverse reactions and events (donors can be exposed to health risks for the purposes of donation, for example the egg-cell donors that must be pre-treated with hormones) and allow self-reporting of

[125] Such links between systems create opportunities for simplification and automation, which should result in user-centric processes supported by digital technology. The Once-Only Principle should allow public administrations in Europe to reuse or share data and documents that people have already supplied, in a transparent and secure way – while protecting privacy. Tool 28 Better Regulation Toolbox.

[126] It is noted that in a 'Note to the Commission by the French BTC Authorities' (ARES(2021)2671096), the view was expressed that BTC should not be used for cosmetic purposes and therefore should be excluded from the scope of the EU BTC legislation. In the light of the evidence that BTC are regularly used for these purposes (e.g. so-called 'vampire facials'), these purposes are included so that there are safety and quality rules in place when the treatments are allowed in a Member State.

[127] Organs, autologous substances re-applied during the same surgical procedure without processing and substances that, later in the pathway from donation to clinical use, are regulated under other EU frameworks, such medicinal products manufactured from BTC.

[128] See footnote 49.

[129] Other substances currently not regulated, such as blood for purposes other than transfusion (e.g. serum eye drops), extracellular vesicles (although there is currently no approved use worldwide); this will allow the framework to be future-proof by regulating substances for which clinical use may emerge in the future.

adverse outcomes by BTC donors [130] (common measures, M2A). **Technical rules for donor and offspring protection** will be kept up to date (M2B), either by the BTC establishments (Policy Option 1), by expert bodies (Policy Option 2) or by regularly revised legislation (Policy Option 3).

For objective 3, all measures are common for the three policy options. P**rinciples to strengthen oversight** (M3A) will be established in legislation to provide assurance that NCAs carry out their functions in an independent and transparent manner and with adequate skills and resources. In addition, **new and more efficient oversight measures** (M3B) to enhance oversight will be introduced, such as joint inspections, risk-based scheduling of inspections, and organisation of EU audits of national oversight systems. The oversight of BE/TEs and other relevant entities will overall follow an approach proportionate to the risks (see annex 16: Details of the measures and policy options) [131]. Measures supporting joint practices, such as joint inspections of establishments (those providing BTC to many Member States, or those having a specific technology/process in place) will bring simplification and efficiency for the NCAs.

For objective 4, to facilitate innovation, two measures were assessed. The first is a **risk-based approach to authorise changes in the preparation and use of BTC** (M4B, differs according to policy option). Such approach is tailored to the incremental innovation in the public BTC sector ensuring safe access to effective therapies and avoiding under- as well as over-regulation. This measure will extend an existing requirement for tissues and cells [132] to blood and strengthen it in the light of the many new ways that BTC are now processed (some examples are given in point A of Annex 12 where a detailed description of this measure is provided) [133]. An assessment [134] will be performed by the establishment to identify the level of novelty and risk associated with the proposed change. There will be a requirement for clinical evidence to be collected by the establishment, and assessed by the authority, when the degree of risk or novelty warrants this. Clinical evidence requirements could range from intensified monitoring of possible side-effects to clinical follow-up and investigation plans with comparisons to standard therapies, in a manner equivalent to clinical trials in the medicinal product framework at the highest risk level.

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[130] Improved reporting means in particular providing for more harmonised definitions and common IT tools. It should be noted that the Czech authority, in its position paper, suggested removing the binding format of SARE reporting forms so that each Member State can use their own form.

[131] The risk-based approach responds to concerns regarding increased costs, administrative burden, and complexity that were expressed by national competent authorities. Further details: Annex 2, section 3.4.

[132] A preparation process authorisation requirement already exists in Directive 2004/23/EC, and Directive 2006/86 refers to the possible use of clinical data for this authorisation.

[133] The risk-based approach responds to concerns regarding over-regulation and overlaps with existing requirements in other frameworks that were expressed in the stakeholder consultation by 26 respondents representing industry and tissue establishments. Overall, 73% of respondent expressed support for the introduction of requirements for demonstrating quality, safety, and efficacy. Further details: Annex 2, Section 3.5.

[134] The Euro-GTP II tool can be used to assess relevant risks such as immunogenicity, graft rejection, toxicity or carcinogenicity. The tool was developed by tissue and cells professionals in a EU-funded action (www.goodtissuepractices.eu)

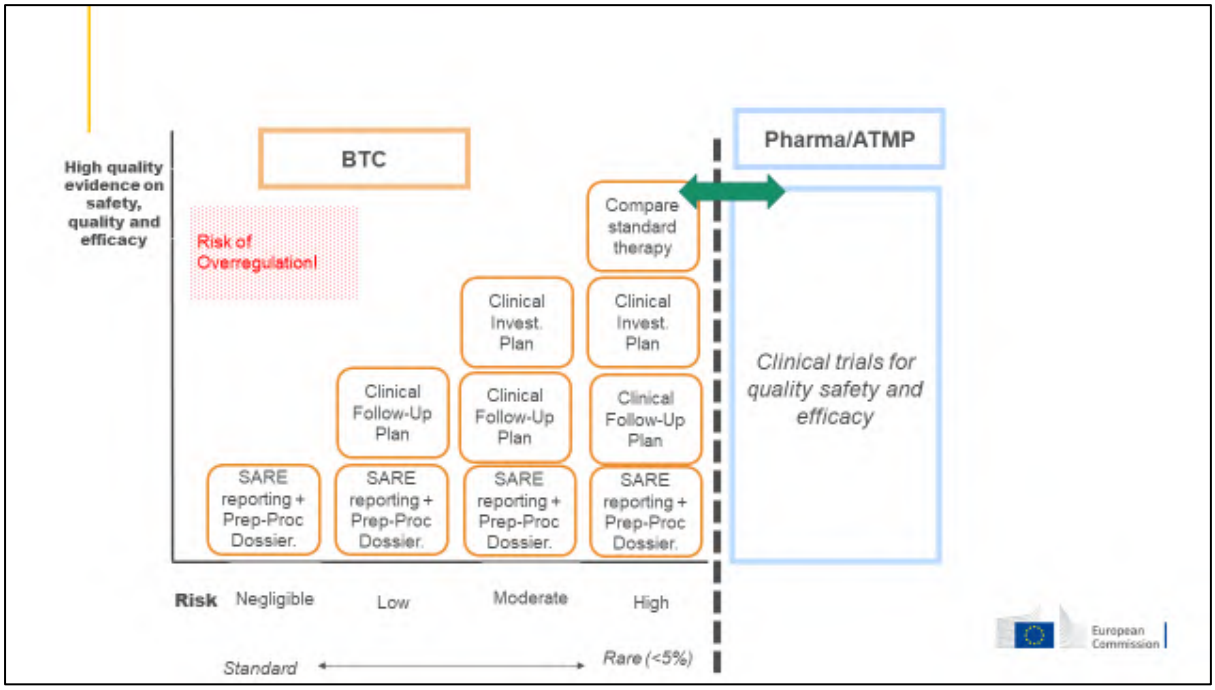

Figure 3: New BTC requirements on safety and efficacy, proportionate to incremental levels of innovation in BTC sector

The clinical trials framework is already used in the EU for newly developed BTC preparations in many Member States [135]. Technical standards for the performance of risk assessments and for the clinical evidence gathering protocols to be followed will be developed either by the establishments (Policy Option 1), provided by expert bodies (Policy Option 2) or defined in EU legislation (Policy Option 3).

The second measure under objective 4 (common to all options, M4A) is to establish an expert group that can give **advice on whether and which BTC requirements are to be applied** to ensure safety and quality of a BTC preparation. Such expert group will not make any change to the scope of the EU BTC legislation, and will only provide advice on the applicability of the EU BTC legislation, not on the application of other EU legal frameworks. In the few cases where the provision of advice would relate to regulatory borderlines with other EU legal frameworks, in particular when classification is unclear or when BTC are used as starting materials or in combination with devices or pharmaceuticals (see section 2.1.4), this mechanism will coordinate with equivalent mechanisms in these other legal frameworks [136] to provide for coherent advice. The evaluation had underlined that supporting coherent processes for the classification of BTC processed or used in new ways could simplify the work of authorities [137]. It will therefore also be important to define rules of procedure on e.g., when (triggers, criteria), how (efficient communication channels) and within what timeframes (delays) the expert groups/mechanisms in different EU legal frameworks will coordinate their

[135] See footnote 62.

[136] Innovation Task Force in EMA and Borderline Classification Group of HMA for pharmaceuticals, the Committee on Advanced Therapies for ATMP, the Working Group on Classification for Medical Devices.

[137] Evaluation {SWD (2019) 376 final}, section 6, p. 86.

views. While such rules of procedure cannot be set in a basic act, the tools to do so will be laid down in the basic act.

It needs to be reiterated that no measures are proposed to change definitions or criteria that delineate the border with other legal frameworks. These definitions are set within these other legal frameworks (see section 2.2.3) and any potential revision of those would have to be assessed in the relevant legislative initiative (see section 7.4). Keeping to the current delineation, where this framework applies to all BTC, unless another Union legal framework applies, is a future-proof approach that will allow to accommodate for such possible revisions in these other frameworks. The proposed advisory and consultation mechanism will continue to be useful and effective should the delineation be changed through future initiatives in other frameworks. It also needs to be reminded that, ultimately, classification decisions are made by Member State authorities.

For objective 5, the first measure (common to all options, M5A) is to introduce supply **monitoring** (for all BTC) **and notification obligations** (for those BTC that are critical for patient treatment [138]). A second measure (differing according to the options, M5B) is to require **crisis preparedness plans to be place** [139]. While the EU has no mandate to intervene directly in supply management, reliable monitoring and notification of shortages would help Member States detect sudden drops in supply of BTC, trends towards shortages or dependencies on other Member States or on third countries, and would help them to take appropriate mitigation actions. This monitoring should also address critical devices needed to collect or process BTC [140] and take into account the importance of BTC for the sustainability of the supply of medicines manufactured from BTC [141].

When the BTC legislation was adopted, one objective was to achieve sufficiency through *the VUD principle*. In this IA, a number of stakeholders, generally representing those working in blood and tissue establishments in the public sector, called for a more stringent enforcement of the principle [142] while others, particularly the commercial plasma collectors, called for a more liberal interpretation and for allowing the coexistence of both donation models

[138] For example, blood is considered as a critical BTC, as it is a life-saving substance that has no alternative while bone grafts are not, as a range of alternatives are available.

[139] From the EDQM B-SCEP survey, to ensure the continuity of blood supply, 11 Member States considered there is a need for legislation outlining the obligations for emergency preparedness and contingency planning and 15 considered a need for defined guidance or recommendations on emergency preparedness and contingency planning.

[140] Improved monitoring and data collection could also be helpful to trigger emergency measures in other relevant sectors, such as Medical Devices, and is thus an important pre-condition for stable supply chains (see position paper submitted by Roche: "F2332626-Attachment_to_Roche_submission_to_EU BCT_legislation_revision_public_consult_Q29" available at 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).

[141] The existing link between blood and plasma as starting materials for biological medicinal products was also recognized by the European Parliament in their resolution on shortages of medicines: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52020IP0228&from=EN.

[142] An example is the EBA Press release: "Plasma shortage in Europe: proper investment in public blood establishments is the answer, not undermining ethical principles" – October 2021. https://europeanbloodalliance.eu/plasma-shortage-in-europe-proper-investment-in-public-blood-establishments-is-the-answer-not-undermining-ethical-principles/

(compensated and uncompensated) [143]. The latter group of stakeholders noted that the tissues and cells Directive, unlike the blood Directive, specifically permits compensation of donors for expenses and loss of income [144] and call for this approach to be generalised across all BTC sectors. The only viable option regarding the VUD principle, from a legal and political point of view, is to maintain it (see also section 5.3). Still its definition and implementation will harmonise the differing versions existing today between the Blood and Tissues and Cells Directives, and be adapted the so-called principle of 'financial neutrality' recommended by the DH-BIO committee of the Council of Europe on this topic [145] that has received broad consensus. In this way, the VUD principle will be maintained but it will be clarified that Member States may set fixed allowances to compensate donors so that financial disincentives to donation are removed.

This option to maintain and harmonise the VUD principle mitigates the risks of financial disincentives and is not only of ethical nature but also strikes a balance between safety and supply. Regarding safety, the risk is that highly remunerated donors can come to rely on the associated income and may hesitate to reveal relevant risk factors during donor screening, to avoid deferral and loss of income. This might also lead to safety risks for the donors themselves related to overly frequent donation. Regarding a sustainable supply, the reliance of the current blood supply on millions of unremunerated blood donors in the EU has demonstrated, not least during the COVID-19 pandemic, that these donors continue donating even in challenging circumstances, when their level of motivation even increases. In contrast, donor payment models typically result in reliance on a small pool of high frequency donors, where a loss of motivation or eligibility to donate can have a damaging impact on supply [146].

The horizontal objective of fostering the use of efficient digital solutions (objective 6) in the new BTC legal framework (SoHO-X platform) builds on the digital measures under each of the previous objectives: development of an IT platform with quality and safety requirements (objectives 1 and 2); supporting oversight (objective 3); for the sharing of authorisation information (objective 4) between Member States, which will facilitate the responsible uptake of and access to new BTC therapies across the European Union; for the exchange of information on supply (objective 5). This data in the BTC sector can become ***valuable digital assets*** in the areas of public health and process innovation in the sector. There is a clear

[143] Kluszczynski et al. (2021) *Value Considerations for Plasma-Derived Medicinal Products (PDMPs) in Europe.* White-paper-key-economic-and-value-considerations-for-plasma-derived-medicinal-products-PDMPs-in-Europe_Vintura-and-PPTA.pdf

[144] Article 12 of Directive 2004/23/EC.

[145] Council of Europe Committee on Bioethics (DH-BIO) Guide for the implementation of the Principle of Prohibition of Financial Gain with respect to the human body and its parts, as such, from living or deceased donors, available at https://rm.coe.int/guide-financial-gain/16807bfc9a.

[146] For example, a 25% drop in plasma donations was recorded in US remunerated plasma collection during the first COVID-19 wave (second trimester of 2020), while some public blood services (such as the BE Red Cross) managed to increase plasma donations in the same period.

potential for improving data flows for reports on BTC-related activities, e.g., on serious adverse reactions and events, on supplies, as well as on the outcomes of BTC [147].

The technical implementation of the SoHO-X platform can be done via:

- Upgrade (M6A): add missing elements to the existing systems as individual components – no links/ no interoperability.
- 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.
- 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 [note that it will be possible to link this data platform to adjacent legal frameworks, where appropriate (such as for clinical trials, communicable diseases, medical devices …)].

These three possible implementations should be considered as 3 sub-options for each of the 3 policy options (as they could be combined with each of the 3 policy options).

Many of the measures proposed to achieve the objectives will bring simplification through the *use of digital tools* and platforms linking with each other in a more harmonised way. This initiative will also seek to extend and harmonise their use, allowing key data to be reported only once but used by multiple actors for different purposes. In this way, for instance, BTC donation and use data can be used for sufficiency monitoring, but also for estimating the frequency of adverse outcomes.

5.3 Options and possible measures discarded at an early stage

Regarding the choice of the legal instrument, maintaining Directives was discarded as it had been demonstrated, during the evaluation, to result in high variability in the interpretation and implementation of the rules, causing a lack of clarity and challenges for inter-Member State exchange, which is one of the problems this initiative aims at solving. A **Regulation** is considered the only suitable format for the new legal act, considering that a key element of the proposal is to establish harmonised measures for Member States and organisations involved in collection, testing, processing, distribution, application of substances of human origin, from donors to patients. Furthermore, a Regulation avoids the burden associated with the transposition of Directives which require Member States to adapt their national law accordingly This sector is mainly public and payment to authorities for inspections and authorisations is not common and consequently resources of NCAs are limited. The possibility for more national stringent requirements, as foreseen in the Article 168(4)(a) of the TFEU, will ensure that the high standards set in an EU Regulation can still be complemented by measures needed to accommodate for national specificities in how healthcare is organised nationally.There are EU legal precedents where Regulations are used even with a legal basis where Member States can implement more stringent measures [148].

[147] See Annex 19.

[148] Besides public health, the TFEU allows stricter measures at MS level in the areas of consumer protection, social policy and environment. An example of this is the Regulation (EU) No 517/2014 of the European

A number of further options were discarded early in the process as their impacts were largely undesirable and there was little, if any, support for them among stakeholders.

No change to the legal acts; only **reactive amendments of the implementing directives to address only the most urgent needs** for updating of safety and quality provisions. This option would not fully protect patients against future risks and would not address the drivers of the problems.	**No change in the legal acts, only encouragement of Member States to work together to agree voluntarily** on oversight principles, authorisations of new preparation processes, classification decisions, crisis preparedness. This option would increase divergence between Member States and reduce the possibility of cross-border exchange.	A **SoHO regulatory agency,** at EU level, setting safety and quality rules and/or issuing central authorisations for BTC processed or used in new ways (similar to the EMA for medicines). This option is generally considered not realistic, disproportionate and too costly for the size of the sector (as compared to food and pharmaceuticals that each have a dedicated agency).

Table 2: Discarded options

As noted in paragraph 5.2, there are some domains where the scope for EU action is limited, particularly when *ethics or organisational aspects* are concerned. For example, some stakeholders called for measures to ensure equal access to MAR technologies [149]. This is not addressed in the policy options as it is Member States that have the legal competence to permit, or not, certain procedures on the basis of ethical considerations.

Regarding the advisory mechanism on scope of BTC, some actors [150] call on the EU to go further by establishing one *common cross-sector EU advisory platform*, but this falls outside the scope of the BTC revision. However, the creation of a BTC advisory mechanism will significantly facilitate such a further step, if this measure is adopted through another mechanism.

On the topic of *plasma dependency*, there were calls for greater investment in expanding dedicated *plasma collection* programmes, increasing donor pools as well as other important measures such as training programmes to avoid plasma wastage or unnecessary prescription, or the inclusion of *patient blood management measures* [151]. While the EU has supported

Parliament and of the Council of 16 April 2014 on fluorinated greenhouse gases (with Article 192 of the TFEU as legal basis).

[149] Comments submitted to the consultation surveys mainly by TE's active in the MAR field as well as a patient/donor organisation.

[150] Position paper submitted by the French health authorities (ARES(2021)2671096) and Proposal submitted by the Danish Minister for Business, Industry and Financial Affairs and the Danish Business Forum for Better regulation (Proposals for Simplification of EU Legislation:). https://ec.europa.eu/info/sites/default/files/proposals-simplification-eu-legislation-danish-ministry-industry_en.pdf), page 4.

[151] Various position papers submitted by: the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE,) "*F2332668-Final_EUCOPE_Consultation_response_BTC_Revision111220*", a Spanish healthcare provider (Baron, et al., 2020 (see Annex 20), and the International Foundation for Patient Blood Management (https://www.ifpbm.org/images/EU%20PBM%20Manifesto%20February%202020%2024.pdf).

cooperation between Member States and professional associations to address issues such as these in the past (e.g. support to plasma collection [152], work on Patient Blood management [153]), regulatory measures in these fields fall outside the scope of EU legal competence (as they relate to national competence to organise healthcare).
Many stakeholders noted a limitation of the measure proposed for objective 5 due to the fact that none of the proposed measures directly intervenes in or seeks to steer supply [154]. However, the proposed measures will allow for Member States to recognise and address supply shortages, and link to further EU initiatives, which may take proactive steps to enhance supply (e.g., Structured Dialogue on supply systems for pharmaceuticals, European R&I Partnership for Pandemic Preparedness [155]).

Finally, it became clear early in the process that abandoning the current principle on **voluntary and unpaid donation** (VUD) was not a viable option, from a legal and political perspective, as it would be contrary to with the Article 3 of the EU Charter of Fundamental Rights that prohibits the commercialisation of the human body. Moreover, keeping the differing versions from the blood and the tissue and cell Directives [156] would not help reaching harmonisation in the sector.

6 WHAT ARE THE IMPACTS OF THE POLICY OPTIONS?

6.1 Screening of impacts and identifying and scoring criteria

Social (health outcomes), economic, digital impacts and impacts on fundamental rights were identified in a first screening and through a mixed method, consisting of literature review, workshops, and surveys. The full list of criteria, methodological notes for scoring and impacts (by criteria and by policy option) can be consulted in Annex 4, Table 4.1. This table was used as input for the multi-criteria decision analyses (see section 7.1).

The impacts of the options were assessed in an iterative process, taking into consideration the assessment of sector experts, through targeted workshops bringing together stakeholders and

References to this concept were also made by different stakeholders responding to the public consultations as an additional measure to support a sufficient supply in the EU, see Annex 2 section 3.6.

[152] https://ec.europa.eu/commission/presscorner/detail/en/ip_21_50

[153] The European Commission has published guidance on the implementation of Patient Blood Management in 2017, based on the WHO definition of Patient Blood Management as "patient-focused, evidence based and systematic approach for optimising the management of patients and transfusion of blood products to ensure high quality and effective patient care". https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/2017_eupbm_authorities_en.pdf.

[154] See Annex 2, section 3.6.

[155] https://ec.europa.eu/info/sites/default/files/research_and_innovation/funding/documents/ec_rtd_he-partnerships-pandemic-preparedness.pdf

[156] **Directive 2002/98/EC (Blood) Article 20:** "Voluntary and unpaid blood donation: Member States shall take the necessary measures to encourage voluntary and unpaid blood donations with a view to ensuring that blood and blood components are in so far as possible provided from such donations."; **Directive 2004/23/EC (Tissues and cells) Article 12:** "Principles governing tissue and cell donation: Member States shall endeavour to ensure voluntary and unpaid donations of tissues and cells. Donors may receive compensation, which is strictly limited to making good the expenses and inconveniences related to the donation. In that case, Member States define the conditions under which compensation may be granted."

experts, and including a validation process with the three lead experts of the external study supporting this IA.

- Quantification of the impacts was possible mostly for economic impacts, using the standard cost model.
- Where the ultimate impacts could not be quantified (in particular for social and digital impacts), qualitative and quantitative intermediary criteria were used. Such criteria make good proxies for eventual health impacts of the policy options in terms of infections prevented, or quality-adjusted life-years.

In addition to the objective criteria, the preferences and expectations of the stakeholders were also considered. Criteria capturing stakeholders' opinions are clearly indicated as such in Table 4.1 (Annex 4).

Table 3 contains examples of criteria used, their scoring and the corresponding outcome (impact).

Dimension	**Impact type**	**Specific Objective**	**Criterion**	**Scoring**	**BL**	**PO1**	**PO2**	**PO3**
Social	Public health	1 - patient protection	Agility of the regulatory system to respond to avoidable risks:	**Minimum** time required to update/issue technical guidance in an **emergency situation** on safety and quality by the relevant experts in all MS (months)	6-12	1-36	1-6	7-12
Social	Public health	2 - protection of BTC donors and offspring	Agility of the regulatory system to respond to avoidable risks	baseline = Engagement of experts with the relevant expertise and resources for the updates/issuing of technical guidance on safety and quality - inconsistent; across MS and BE/TEs depending on their size and available resources + consistent expertise available to all MS +++ high quality expertise available to all MS	=	-	+++	+
Economic	Public health systems - sustainability	3 - oversight	Efficiency of the oversight - the extent to which the inspections are proportionate to the risks of activities	Number of MS using a consistent risk-based approach in overseeing blood, tissues and cells establishments	12	27	27	27

Table 3: Examples of impacts, criteria and their scoring

6.2 Social-health impacts

When assessing the reduction of avoidable risks for patients (objective 1), the assumption is that if **up-to-date technical provisions for ensuring a high level of safety and quality for recipients (M1B)** are available in a timely manner, the avoidable risks for patients will be minimised (e.g. no obsolete protocols are used for testing). In addition, if those rules are consistent across Member States, it will allow a similar protection for all citizens, wherever they are treated in the EU. Key criteria used include: *time needed for updates (regular and in crisis), available expertise and coherence across Member States*.

Analysis of the social/health criteria shows that the baseline option does not provide for such timely updating of technical provisions. Delays to update rules take at best 1 year, half of that in emergency situations.

Analysis of the social/health criteria shows that, compared to the baseline:

- In option 1, large, well-resourced establishments will be able to mobilise expertise quickly to revise guidelines, but smaller ones would not have these capacities and lag behind. Larger establishments could therefore respond much quicker than smaller establishments – overall this would result in even more divergence between establishments and between Member States than under the baseline.
- Under option 2, technical guidelines can be updated by expert bodies and applied by establishments in a short timeframe (1 month in case of an emergency provision; 6-12 months for more substantial revisions), mobilising scientific expertise across the EU.
- With option 3, a central EU secretariat would need to work with a new committee(s) of experts (similar to those working with expert bodies as under option 2) that would develop the technical standards. A legislative amendment would be needed for each change or update, adding a minimum of 6 months to the procedure, while reducing the scientific independence of the process. Even in an emergency situation the update would go through an approval procedure adding at least 6 months compared to option 2 (see Table 4).

Another key improvement for patient safety can be achieved by **filling the existing legal gaps in the BTC framework (M1A)**.[157] Making 300 FMT and breast milk establishments subject to the BTC framework will allow to address similar concerns on donor safety [158], and to improve the protection of thousands of recipients of FMT and for pre-term infants receiving breast milk. In the public consultation, 82% of those who expressed an opinion supported the inclusion of these substances in the legislation [159]. Similarly, the obligation for hospitals and healthcare providers to register bedside processing of BTC, where similar levels of safety and quality are expected compared to processing in BE/TE, and consequently report

[157] These areas: FMT, breast milk and bedside processing are currently the only legal gaps that were identified. By setting the scope of the new framework as substances of human origin, excluding solid organs, the framework will be future-proof and cover new technologies that might be created. Though it is not possible to assess costs at this point of time.

[158] Smith et al., 2014 (See Annex 20).

[159] Annex 18: Section II, Figure 15.10.

occurrence of adverse reactions, will allow authorities to take appropriate actions to ensure safety and quality for patients in these settings. Over 80% of respondents to the public consultation expressed support to regulate such bedside procedures, though a majority felt they should be subject to less stringent requirements, in particular when these are taking place in operating theatres during surgery [160]. This measure would substantially improve the *consistent EU-wide protection of patients* ensuring safety, quality and efficacy of such therapies.

The impact of the proposed measures on the **protection of donors and offspring through up-to-date technical provisions** (objective 2 – **M2A-B**) is assessed largely using the same criteria (*timely availability of high quality and consistent technical rules*, see Table 4), and the options perform in a similar way as for objective 1.

Access to safe and effective innovative treatments (objectives 4 and 5) depends strongly on broader factors that characterise the health systems of the Member States, such as budgets available and ethical decisions, and that are outside the competence of the EU. The measures do not directly impact supply but rather facilitating Member States to identify and manage supply crises. However, a number of measures will contribute to access and continuous supply:

- the borderline case studies suggest that having appropriate and proportionate legal requirements for innovative BTC (BTC used or prepared in new ways) reduces costs and, with that, increases the feasibility of reimbursement and access (see Annex 10).
- EU-wide monitoring of critical BTC supplies (including inter-Member State exchanges and imports), for those BTC where a shortage would impact health of citizens, and notification of the authorities in case of significant drops.
- Mandatory development and maintenance of preparedness plans to deal with such crisis situations and manage sudden shortages.
- All measures that harmonise technical standards and increase inter-Member State trust in oversight, will facilitate inter-Member State exchanges of BTC. This is an important factor as transfer of BTC from one region to another can be an essential element of a crisis response, particularly when the crisis is caused by an epidemiological outbreak in one geographical area.

Introducing a **risk-based authorisation scheme for BTC processed and used in new ways (M4B),** with proportionate requirements for evidence of safety, quality and in particular efficacy, is a measure that is strongly supported and all stakeholder groups that expressed an opinion [161] considered that it would significantly facilitate innovation. Not only is this *evidence of risk/benefit useful* for authorities overseeing safety and quality, but it will also support the assessment of the added value of new BTC therapies by local/national policy

[160] Annex 2, Section 3.2.Opposing views came from 4 competent authorities, one blood establishment and 2 other respondents.

[161] Breaking down the responses by sector, the support is strongest in the blood sector (81%), followed by tissues and cells (77%); the majority of the respondents in the pharmaceuticals sector (57%) also support the statement. There is a particularly strong support from public authorities (85%) and citizens/consumer organisations (80%). 60% of companies and business associations and 71% of academic/research organisations expressed support. See Annex 18, Section II.

makers responsible for healthcare organisation and budgets. The usefulness of using selected evidence from clinical outcome digital registries, as proposed by the GAPP Joint Action [162], is widely acknowledged [163]. The possibility of publishing a list of authorised processes, as well as of sharing such evidence amongst BTC establishments and Member States' authorities are strongly supported [164] and expected to further facilitate access to innovation. Providing common guidance to implement such a risk-based authorisation scheme, through expert bodies (option 2) or centrally (option 3), further harmonizes the use of this approach, and hence improves equal access for patients across the EU to safe and effective BTC processed and used in new ways. With option 1, establishments would have to conduct risk assessments and propose clinical studies without such common guidance.

A **BTC legal advisory mechanism (M4A)** would help clarify EU-level regulatory pathways for BTC innovation across public and private sectors, and publication of its advice [165] is expected to facilitate the development and supply of newly developed BTC, through increasing regulatory clarity. In particular, improved clarity would create an environment in which public sector (and academic) BTC establishments would be more prepared to invest in the development of innovative BTC treatments and organise for more local (diversified) supply - thus *further improving patient access to innovation* (see also section 6.3.2). While it is important to underline that this initiative will not change the delineation between the BTC and other EU legal frameworks, there is an almost unanimous view that such an EU-level BTC legal advisory mechanism should interact and coordinate with equivalent structures/committees in these other EU (medicinal product and medical device) legal frameworks [166]. Many Member States have such coordination already established at national level [167], but it is lacking at EU level [168] where it would enable more EU-wide consistency. Note that the ongoing work on the revision of the pharmaceutical framework is exploring a similar, corresponding measure to provide EU-level advice on the applicability of the pharma legislation, in coordination with advisory mechanisms in other legal frameworks (such as medical devices or BTC). Note that this exercise does not look into altering the criteria that define the delineation with other Union legislation, nor into changing the applicable legal framework for certain therapies. Rather, the continuation of the current approach to apply this legal *framework* unless *an*other Union leg*al framework* applies, allows to ensure that no therapies based on SoHO go without safety and quality requirements. This flexible approach

[162] www.gapp-ja.eu

[163] Over 60% of respondents agree fully or partly to use clinical outcome registries as source of evidence. Dissenting views came from some BE/TEs, although their majority agreed. For further details, see Annex 18, Section II.

[164] Over 85% of respondents expressed support for these two possibilities. Dissenting views came from public authorities as well as other stakeholders. For further details, see Annex 1518, Section II.

[165] With the exception of one industry stakeholder, all respondents to the targeted public consultation believe advice should be published (see Annex 18
, Section II, Figure 15.15).

[166] See Annex 2, Section 3.5.

[167] In 21 EU Member States the BTC national competent authority and pharmaceutical national competent authority are hosted by the same organisation.

[168] Views expressed in a dedicated workshop "Borderlines with Other Regulated Frameworks: Classification Advice and Interplay" with authorities and stakeholders from BTC, pharma and medical device sectors. See summary in https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/icf_summarynotes_stakeholder-workshops_en.pdf.

is future-proof towards possible changes in other Union legal acts (e.g., through the pharma revision), where the delineation criteria are set.

Case studies have shown that patients access to some BTC has been limited by regulatory classification decisions, even though such therapies could have been provided with sufficient quality, safety protocols and clinical follow up, often at a lower price [169]. The availability of a risk-based pathway could allow for some BTC-preparations that have been regulated as medicinal products in some Member States (e.g. serum eye drops) to be regulated under the requirements of the BTC framework, with an expected impact on their eventual cost and access [170].

As regards resilience of the sector and mitigating risk of shortages (objective 5), the stakeholders in the sector recognise some benefit of measures for monitoring and notifications, while however also flagging concerns of an increased workload. **Monitoring and notification measures for a limited set of critical BTC (M5A)** [171] are thus proposed in response to these concerns, to ensure benefits in terms of information for policy makers and transparency, and in case of sudden drops in supply [172]. Option 2 and option 3 in particular are assessed as providing *consistent, timely and comprehensive information* to Member State authorities. Around 65% of respondents to the public consultation consider that making **crisis preparedness plans mandatory (M5B)** would bring improvements [173] in the *resilience of supply* in case of crisis. Providing common guidance on preparedness under option 2 and option 3 in particular are assessed as generating benefits through consistent standardised preparedness plans; with option 1, establishments will have to develop their individual plans.

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[169] The case studies included a series of examples where a reclassification of a BTC as an ATMP resulted in tissue establishments having to stop an activity and hospitals not subsequently having access to an authorised ATMP alternative for their patients. An example was the culturing of keratinocytes for the treatment of burned patients where cell culture was concluded by the Committee for Advanced Therapies to be a 'substantial manipulation'. Had the discussions that led to that recommendation involved a consultation with a BTC advisory mechanism, it is quite probable that the recommendation might have been different and that cultured keratinocytes would still be widely available for burn patients from skin banks around the EU.

[170] Literature review and expert interviews in the borderline case studies reported this possibility when discussing impact on cost, access and innovation of therapies that originally were classified as BTC but then re-classified. For further details, see Annex 11 (in particular sections 11.7: Chondrocytes, 11.6: Cultured keratinocytes and 11.8: Cultured limbal cells).

[171] The critical BTC are those for which a lack of supply would put patients at significant risk. For this IA, the following BTC were considered as 'critical': blood, plasma, cornea, skin, cardiac valves, pancreatic islet cells, and hematopoietic stem cells.

[172] Overall, stakeholders considered that monitoring and reporting would improve transparency for citizens and information for policy makers, as both were given an average rating of 7 on a 10-point scale (10 being positive impact). The effect on transparency for citizens was rated negatively (lower than 5) in 14 responses, mostly from companies/businesses and to a smaller extent from NGOs, academia, and public authorities. The effect on information for policy makers was rated low 7 times, from public authorities, companies/businesses, academia and an NGO. Annex 18, section II.

[173] This support was strongest among NCAs, 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%). See also Annex 18, Section II.

Objective	Criterion	BL	PO1	PO2	PO3
Obj 1-2	Availability of timely information for risk management on serious adverse reactions and events for patients, donors and offspring	=	++	++	++
Obj 12	Ability of the regulatory system to respond to avoidable risks - mobilising relevant scientific and technical knowledge in the BTC sectors	=	-	+++	+
Obj 1-2	Agility of the regulatory system to respond to avoidable risks - time required for regular updates (in months)	12-180	1-36	12	48
Obj 1-2	Agility of the regulatory system to respond to avoidable risks - minimum time required for updates in emergency situation (in months)	6-12	1-36	1-6	7-12
Obj 1-2	Consistency of regulatory practice across the EU - geographical scope	=	-	+++	+++
Obj 1-2	Mobilising relevant scientific and technical knowledge in the BTC sectors for the updates of guidance	=	-	+	+
Obj 1	Stakeholder confidence on the effectiveness of options in achieving patient protection from all avoidable risks	=	+	+++	++
Obj 2	Stakeholder confidence on the effectiveness of options in achieving protection of donors and offspring from all avoidable risks	=	+	+++	++
Obj 4	Safety of BTC processed or used in new ways - evidence on the safety and efficacy is available demonstrating the clinical efficacy outweighs the risk.	=	+++	+++	+++
Obj 4	Impact on patients' access to BTC processed or used in new ways with proven added value	=	++	++	++
Obj 5	Resilience of the BTC supply: availability of information to anticipate and manage shortages/risks of interruption	=	+	+++	+++
Obj 5	Resilience of the BTC supply: preparedness to ensure effective and timely response to manage shortages	=	+	++	++
Obj 5	Access - Stakeholder judgement on the expected effectiveness of options in achieving Objective 5	=	+	++	++

Table 4: Summary of expected impact of policy options along different social impact criteria; = no difference, - negative impact, + some improvement, ++ significant improvement, +++ major improvement

6.3 Economic impacts

6.3.1. Costs

The costs were calculated using the standard cost methodology for all measures (as described in Annex 5), identifying initial one-off ("adjustment") costs and recurrent administrative costs, and by key stakeholder group. For sake of simplicity, this report presents *annual Net Present Value (NPV) costs*, based on the net present values of the one-off costs and the administrative costs for a period of up to 10 years. A standard discount rate of 3% is used [174,175]. The details of the calculation, unit costs, and the administrative and one-off costs by each measure and policy option are presented in Annex 5. *The detailed breakdown of costs by*

[174] $NPV = \sum_{i=0}^{i=n} \frac{B_i}{(1+r)^i} - \sum_{i=0}^{i=n} \frac{C_i}{(1+r)^i}$; where the Costs and Benefits in a given year i are C_i and B_i respectively over the policy/project lifetime of n years (starting in year 0).

[175] The social discount rate is used to compare costs and benefits that occur in different time periods from the point of view of society. See Better Regulation Tool Box 61.

measure is available in the interactive dashboard. Costs and savings will mainly fall on the BE/TEs (including future ones), other new SoHO entities (e.g., hospitals, to be registered), NCAs (oversight role), and EU institutions.

One particular challenge was to identify and attribute costs in public settings (public administrations, hospitals) where real hospital costs are often absorbed in overall budgets and unaccounted for. This explains the high variety of costs reported through the study survey, for example for inspections these (time) efforts range from 2 days (direct activities) to 365 days (including daily costs of quality assurance, maintaining records, training, Hazard Analysis and Critical Control Points - HACCP development etc.). Sector experts, both from NCAs and from public establishments, were therefore brought together to identify and agree on reasonable average values and validate key assumptions that have been used to calculate costs (for more details, see Annex 5).

It needs to be noted that typical BE/TEs are, while of the size of an SME, of a public nature. It has been considered in the drafting and assessment of the proposed options and measures that these establishments have limited (legal) resources to devote to compliance with different national regulations, which complicates the supply of BTC across borders in compliance with regulations of different Member States. Establishing common, EU-wide requirements is therefore considered of benefit for these actors. Only a few for-profit 'small and medium-sized enterprises' (SMEs) will be directly impacted by the initiative; these are mostly establishments found in the sub-sector of MAR (private IVF clinics). Therefore, no further SME test was conducted.

Finally, the cost calculations took account of differences between Member States. In particular the size of Member States plays a role, with 4 large Member States (DE, FR, IT and ES) accounting for 63% of EU BE/TEs and having already many of the proposed measures in place (see Annex 5). While it was harder to use this experience to quantify benefits, this situation has had a significant influence on the calculation of the baseline, and of the additional costs for the proposed measures/options in such countries, compared to other Member States that have no comparable measures in place to date (see also section 5.1 - baseline).

Some measures, allowing for more coordination and less duplication, might even entail a saving for those countries that have them already in place (fall under the baseline). Though a conservative decision was taken not to include these savings here, they are however listed as potentials for simplification under section 8.

Costs of key measures to protect patients from avoidable risks - Objective 1

Under this objective, costs for the following key measures are taken into consideration:

The creation and maintenance of **up-to-date technical rules for safety and quality of recipients (M1B)** addresses one of the main undue burdens flagged (section 2.1.6). Costs for this vary across the policy options:

- In option 1, an extra cost of EUR 6.0 m is expected for the BE/TEs. Large and well-resourced establishments would have the resources, however, for smaller ones this would be a more substantial burden. There are additional costs of inspection of appropriateness and implementation of these standards by NCAs to verify whether these requirements are

indeed appropriate for each establishment: this would cost an extra EUR 0.8 m compared to the baseline. EU institutions' efforts would be limited to general coordination support (EUR 0.1 m).

- In option 2, expert bodies would be co-funded by the EU budget and is expected to cost an additional EUR 0.7 m for the EU, compared to the baseline. However, the extra costs for establishments would then be limited to EUR 3.0 m, while the extra costs for verifying implementation during inspections would be limited to around EUR 0.4, as establishments and authorities can rely on common EU standards.
- Option 3 implies higher costs for the EU budget (EUR 1.2 m) as it cannot rely on co-funding with expert bodies. Costs for establishments and authorities are similar to policy option 2.

Member States are expected to report in a common, transparent way on additional (more stringent – option 2 and 3) national requirements (measure M1.3). This is expected to impose only a negligible cost, if this information can be extracted or referenced from the published national rules.

An indirect economic benefit of having up-to-date rules is that these allow for savings on the application of obsolete rules and testing, an undue burden (see section 2.1.6), which is illustrated under section 8.

Filling the legal gaps and covering *unregulated SoHO* (such as FMT and breast milk) **(M1A)** is estimated to require one-off costs for submission and assessment of an authorisation request, and subsequently annual reporting and inspection costs (EUR 1.7 m). These extra costs fall mainly (75%) on a group of about 300 new establishments [176] and partly (25%) on their authorities.

Furthermore, the regulation of *bedside processing of BTC*, through a light approach [177] that will require a registration and annual activity and vigilance reports – will incur an extra cost of about EUR 6.2 m for around 11 000 hospitals (registered entities [178]) in the EU. This cost amounts to around EUR 500 per hospital and takes into account a significant saving achieved through the establishment of an EU data platform to support this reporting. This measure will also bring an additional verification cost for authorities (EUR 0.5 m). An investment in the central IT registration tool (EUR 0.2 m) will facilitate registration and reporting for healthcare providers.
The expanded scope towards Substances of Human Origin (excluding organs), might bring future new therapies to be covered. It is however not possible at this moment to specify these, nor the benefit and cost of regulating them under the new framework.

[176] This number is assumed to stay relatively stable in future as, on the one hand the application of a legal framework will cause some centres to discontinue activities, and on the other hand the interest for these therapies is increasing.
[177] For further details on the Graded Approach, see Annex 16.
[178] This task could be supported by hospitals blood banks, present in most EU hospital in order to organise supply and administration of blood to different hospital departments and already familiar with compliance with BTC legislation.

Costs of key measures to protect donors and offspring - Objective 2

To **include the protection of donors and offspring within the legal framework (M2A)** will require all establishments working with donors or with assisted reproduction to *report on SAR* in donors and offspring. This is already happening today, on a voluntary basis in the majority of EU Member States for donors (baseline - 24 Member States for blood and 17 Member States for tissues and cells), but it will need to be organised in most Member States for offspring (only 2 Member States implementing already). This will generate an extra cost for 2 300 establishments [179] estimated at EUR 5.5 m, and another EUR 0.3 m for their authorities. Furthermore, establishments working with certain categories of donors [180] will have to *organise medium/long-term monitoring* of safety and health outcomes. Outcome monitoring will also be required for offspring born from donated gametes or embryos. This is estimated to cost EUR 3.6 m per year for about 900 involved establishments [181], and EUR 0.1 m for their authorities.

The three policy options have been explored to provide for **up-to-date technical rules for safety and quality of donors and offspring (M2B)** and estimated to bring following costs:

- Option 1: it will be more expensive for 2 350 establishments working with donors and 1 770 working with MAR to identify appropriate technical rules for their local setting/activities, and then implement them (EUR 5.1 m) – the costs of this requirement may be difficult to cover for smaller establishments [182]. This option will also entail extra costs for the NCAs to inspect whether these technical rules are appropriate for the local setting, and well implemented (EUR 0.5 m). Like for objective 1, EU costs will be limited to EUR 0.1 m for coordination support.
- Options 2 and 3: When these establishments can directly implement technical rules prepared centrally (option 3) or jointly (option 2) this cost (person-days) remains limited for establishments to EUR 4.1 m. There is also a verification cost for authorities (during inspections) though for implementation only (0.2 m). There is an extra cost for the EU for coordination to develop technical standards, which us higher if rules are prepared centrally (EUR 0.9 m for option 3) than jointly (EUR 0.5 m for option 2).

Costs of key measures to strengthen oversight - Objective 3

All measures explored here are horizontal, and do not differ per policy option. This objective will require efforts both for the national authorities that oversee the sector and for the EU to support these authorities.

The introduction of **principles and new measures for oversight (M3A)** entails several elements. Oversight p*rinciples* (e.g., the need for independency and adequately skilled staff) are expected to bring an extra organisational cost for half of the authorities (EUR 0.5 m). The

[179] 25% of 2350 establishments working with donors and 95% of 1800 IVF establishments.

[180] Where donation implies some risk to the donor, e.g. it involves hormonal treatment, an invasive collection procedure they are required to donate repeatedly and frequently.

[181] Donor monitoring for 250 plasma collection centres, 50 sperm/oocyte banks, 300 HSC banks and offspring reporting for 300 IVF establishments.

[182] The burden on defining such rules and putting in place such a system brings a fixed costs and is a relatively independent of the size and turnover of the establishments' activity. Therefore, for smaller establishments, these costs are proportionally a larger share of their budget.

risk-based scheduling of inspections, to replace the fixed-frequency inspection rule that was flagged as bringing an undue burden (section 2.1.6) is expected to be cost-neutral, as modelling confirmed that it is possible to inspect all establishments with adapted frequencies of high, medium and low complexity inspections [183] with the same number of person-months as required for the current regime of standard inspections every second year. This will significantly increase efficiency of oversight.

Furthermore, the NCAs will also be able to organise *joint inspections,* bringing in colleagues from other Member States, for example to inspect an establishment using a rare technology. These are estimated to cost authorities about EUR 0.1 m and the EU about EUR 0.5 m, in order to fund extra time for staff, travel and translations. The organisation of *EU audits* on national oversight systems would cost the EU around EUR 0.5 m.

Additional measures for **EU support (M3B)** are proposed for coordination including an IT platform (EUR 0.4 m), and training (EUR 0.8 m).

Costs of key measure to facilitate innovation - Objective 4

The introduction of a **risk-based authorisation mechanism for changes in BTC preparations and use (M4B)** will require the proportionate [184] collection and assessment of clinical evidence on safety and efficacy. Sensitivity analysis [185] shows that these costs vary radically based on the extent of data collection (adverse occurrence reporting can be organised for EUR 500, but clinical investigations, clinical evaluations or clinical trials are more costly, potentially going up to EUR 15 000 - 75 000), driven by the number of patients, as well as the number of data to be recorded (see Annex 12). These costs of data collection on outcomes of patients in the clinic can be a heavy burden on the BTC sector. However, where real world data registries and electronic health records of the hospitals can be used for such (secondary) decision-making by NCAs, the reporting costs would radically drop, underlining that digital health investments can be leveraged. Allowing for the wider use of clinical trials, for high-risk innovations, by national BTC authorities can be considered as an efficient way to ensure safety and efficacy of high risk BTC preparations. In several countries these BTC authorities are already using clinical trials, and in many countries the same as the authorities in charge of pharmaceuticals.

Eventual calculations estimate the cost for healthcare providers (collecting clinical evidence) to be around EUR 3.6 m and for authorities around EUR 0.8 m. Costs for providers and authorities will be a bit higher under option 1 – where they cannot rely on common guidance. The EU will bear costs of about EUR 1.0 m for IT, support and coordination, as well as for developing common technical guidance. The latter part will be EUR 0.2 m more expensive in case of stand-alone development (option 3), and EUR 0.2 m lower in case of no development

[183] Currently (baseline) each establishment (regardless its size, complexity or safety-record) is required to be inspected every 2nd year. A risk-based scheduling of inspections would allow, with the same number of inspection man days, to (a) inspect 10% establishments with highest complexity twice per year, (b) 30% of establishments with medium complexity every second year (like today) and (c) 60% of establishments with low complexity every fourth year.

[184] This lack of proportionality was flagged as an undue burden (see section 2.1.6).

[185] Sensitivity analyses allows to assess impact in cases where some parameters remain uncertain, for example by introducing minimum and maximum values for these parameters in quantifications (see Annex 4).

of common guidance (option 1) vs joint development (option 2). These costs fall mainly on 8 Member States without an established approach for assessing such innovations.

An important consideration that is not included in the calculations here is the potential saving on the 19 Member States with an established baseline for healthcare providers and authorities. This can bring a significant potential for savings (see section 8) for those countries with existing practices (70%), thanks to the sharing of data, assessments and collaboration for identical processes, allowing to reduce the duplication of effort across different Member States. Experience from other fields shows that smaller Member States can particularly benefit from reusing this information [186]. While we followed a conservative estimate here, it might be argued that, at EU level, such savings would offset the costs for healthcare providers and authorities.

The new **BTC legal advisory committee (M4A)**, including members of national BTC authorities, can be run efficiently through online exchanges and meetings, with support from EU staff (secretariat and organisation of regular physical meetings). This committee can also meet with equivalent committees and groups in other EU legal frameworks (e.g., Committee on Advanced Therapies in EMA). The overall costs for these committee meetings and time of expert staff in national authorities is estimated to be EUR 0.5 m, and is a cost counted for the EU (considering 7 meetings per year and additional 3 meetings with other sector authorities [187]).

Costs of key measure to avoid supply disruptions - Objective 5

The introduction of **supply monitoring and notification rules (M5A)** is applicable on establishments whose supplies are considered critical for the patient safety and impact [188]. This measure is expected to subject to the policy options:

- Under option 1, in absence of common guidance, the cost for the 2 500 concerned establishments is EUR 6.5 m. The cost for authorities of EUR 0.1 m is relatively low as they are only expected to be involved in rather few occasions when sudden supply shortages are notified. There is also a support cost at EU level of about EUR 0.7 m for coordination, including IT support.
- Under options 2 and 3 the cost for the 2 500 concerned establishments is reduced to EUR 4.2 m, with a similar low cost of EUR 0.1 m for the authorities. The cost for EU coordination, including IT support, and updated guidance is EUR 0.8 m EUR under a joint regulation policy option (option 2), and increases to EUR 0.9 m under a fully centralised policy option (option 3).

It needs to be noted that the costs for establishments includes a high one-off cost to invest in digitalisation (EUR 16.6 m in options 2 and 3), which then allows a significant reduction in

[186] SWD/2018/04: Commission Staff Working Document Impact Assessment Strengthening of the EU Cooperation on Health Technology Assessment (HTA) Accompanying the document Proposal for a Regulation of the European Parliament and of the Council on health technology assessment and amending Directive 2011/24/EU.

[187] This is a conservative estimate, as probably many meetings can be organised efficiently and at less cost in a virtual format.

[188] This corresponds to all blood establishments, 60% of non-reproductive tissue establishments, but excludes reproductive tissue establishments (IVF establishments).

annual administrative costs to monitor and report shortages (EUR 3.1 m, or less than EUR 1 300 per establishment supplying critical BTC).

The **requirement of preparedness plans (M5B)** for all BE/TEs, which will then allow to respond when shortages are notified, is also subject to policy options.

- In option 1, the establishments are to define individual crisis preparedness plans. The absence of a central standard makes it difficult to rely on common ICT solutions; and it is also estimated that it will require a lot of time for the set-up and revision of preparedness plans. These measures bring a significant extra cost of EUR 7.0 m for establishments, partly due to the need for each of them to bring in expertise. Costs for Competent Authorities to evaluate the crisis preparedness plans are estimated at EUR 0.3 m. The cost for EU coordination is EUR 0.2 m.
- Under options 2 and 3, establishments can rely on central standards for their crisis preparedness plans. This is expected to significantly reduce effort on the set-up costs – which is particularly significant for smaller establishments. Calculations therefore show overall costs for establishments to be limited to EUR 0.7 m, while a cost of EUR 0.3 m will be incurred by authorities to verify preparedness plans in the establishments. The cost of EU coordination and to prepare common guidance is EUR 0.3 m under option 2 and EUR 0.4 m under option 3.

It needs to be noted that the investment in common guidance under option 2 (and 3) still brings a significant one-off cost for the establishments (EUR 11.7 m) but then allows for an annual administrative saving of EUR 0.5 m compared to the baseline. This saving is not possible under option 1.

Considerations for offsetting costs for key stakeholders

In order to facilitate implementation of the different measures across the five objectives, some EU support measures are suggested to offset costs for authorities, establishments, entities and clinical societies during initial adjustment (around EUR 24 m) and later during the implementation phase (EUR 6 m per year) (see Annex 17 for more details).

6.3.2 Innovation and research

Two measures (M4A and M4B) are proposed to facilitate innovation by defining a clear and proportionate regulatory pathway that is tailored to the actors (mainly public sector bodies) in the BTC sector. The impact of these measures is assessed against 5 criteria, in comparison to the baseline (Table 5).

The proposed **risk-based approach to authorising changes in BTC preparations or use (M4B)** offers an opportunity to enhance efficiency and balance safety and access by ensuring sufficient levels of safety and quality for BTC with lighter oversight requirements when justified by a low level of risk or novelty. In most cases, with negligible risks, current safety monitoring requirement might be considered sufficient. However, where high risks are identified, or the process is particularly novel, the requirements for demonstration of safety and efficacy in the patient would be more coherent and comparable to those applied in other frameworks, like to authorize pharmaceuticals, requiring clinical comparative studies. As well as scoring well against the criteria of improving process authorisations and *facilitating innovation in the public sector* where these developments normally occur, the measure also

contributes to *cross-sector consistency and coherence*. This is therefore considered a key element needed to ensure that patients can access safe therapies of proven benefit (for access benefits see also section 6.2). There is broad support that such legal requirements should be introduced in EU legislation for demonstrating safety, quality and efficacy when BTC is prepared or used in new ways [189].

Supporting innovation, with proportionate requirements, is particularly effective in this sector, as results are generally *published and circulated* openly so that many BTC establishments can implement improved processes once they have been developed and authorised in one establishment (third criterion in Table 5). The availability of a *data-sharing* platform for developers and authorities will allow for further sharing and leveraging of data, in line with existing practice of open innovation and partnerships applied by the public academia and professional societies [190], as well as with European Research Policy. This improved transparency of research data will not only increase regulatory efficiency, it will also allow professionals to provide patients across the EU with wide and fast access to the BTC that are processed or used in new ways and are shown to be safe and effective.

An advisory mechanism on the application of the BTC legal requirements (M4A) is expected to facilitate innovation by *increasing legal clarity and consistent advice to BTC developers and authorities across the EU (regulatory coherence)* [191]. Such an advisory mechanism would help clarify EU-level regulatory pathways for BTC *innovation across public and private sectors,* and the *transparency* brought by publication of its advice [192] is expected to facilitate the development and supply of newly developed BTC. In particular, improved clarity would create an environment in which *public sector (and academic) BE/TE* would be more prepared to invest in the development of innovative BTC treatments and organise for more local (diversified) supply - thus further improving patient access to innovation (see also section 6.2). No fees for applicants are foreseen.

In addition, such an EU-level mechanism should interact and coordinate decisions with equivalent mechanisms in adjacent legal frameworks [193]. This cross-sectoral collaboration will *improve the cross-sector consistency of advice on regulatory requirements* and will also provide a much-needed channel of effective communication for agreeing on technical requirements when BTC are the starting materials for products subsequently manufactured under pharmaceutical or medical device frameworks or when BTC are combined with

[189] 155 respondents answer that new legal requirements should be introduced for demonstrating safety, quality and efficacy when BTC are prepared or used in new ways, while 26 respondents (mostly from companies and businesses, but also from academia and NGOs) disagree. For further details see Annex 18, Section II.

[190] Most professionals in (academic) blood and tissue establishments are member of professional societies such as EBMT, ESHRE, EATCB, EEBA or EBA. Most of those societies have as mission to support research and dissemination of progress, for example through medical journals, conferences or joint data platforms.

[191] 127 respondents to the public consultation expect a (very) positive impact of having such an advisory committee, compared to 7 respondents expecting a negative impact (see Annex 2, Section 3.5).

[192] Almost all respondents to the targeted public consultation believe advice should be published (see Annex 18, Section II, Figure 15.15), dissenting view from one company.

[193] 164 respondents to the public consultation and 123 respondents to the targeted consultation consider such coordination and interaction necessary, with 5 dissenting views from 1 NCA and 4 private sector stakeholders and 1 dissenting view from an NGO, respectively (Annex 2, section 3.5).

medical devices or medicinal products before human application [194]. Such EU-level coordination amongst sector-authorities will for example allow to develop an approach to facilitate import of BTC that are starting materials for ATMP, one of the undue burdens that was flagged (section 2.1.6). It will however be important to ensure efficient mechanisms of coordination as expressed by some important actors [195].These aspects are further elaborated in Annex 12.

In addition, measures to **fill legal gaps (M1A)** for SoHO not currently regulated under the BTC framework and those BTC processes carried out in surgery or next to the patient (bedside) will extend these positive impacts on legal clarity and facilitation of innovation also to those therapies that previously were unregulated. This benefit will be enhanced by the provision of a data sharing platform at EU level.

Objective	Criterion	BL	PO1	PO2	PO3
Obj 4.	Regulatory coherence: the extent to which there is clarity as to the regulatory framework to which the substance/product belongs (including for products that move from one framework to the other and currently unregulated products)	=	++		
Obj 4.	Regulatory coherence: the extent to which there are consistent/comparable regulatory requirements for BTC, including coherence across legal frameworks (BTC, pharma, med tech)	=	++		
Obj 4.	Impact on innovation in the BTC sector: extent to which measure facilitates R&D (fostering partnerships across the public and private sector; transparency of research: circulation of data, research results or researchers; transparency of R+D costs)	+ [196]	++		
Obj 4.	Impact on innovation in the BTC sector: public sector innovation	=	++		
Obj 4.	More consistent and better improved national process authorisations: number of Member States sharing data on national authorisations	=	++		

Table 5: Summary of expected impact on innovation; = no difference, - negative impact, + some improvement, ++ significant improvement, +++ major improvement. See complete table in Annex 4 for details on scoring

Of note, apart from the requirements for the novel preparation processes risk assessments (defined by BE/TEs, or by expert bodies, or set in EU law according to the policy option), the measures on innovation are common across the options and therefore the three options score equally.

[194] The workshop on "Borderlines with other Regulated Frameworks: Classification Advice and Interplay" (9th of June 2021) concluded that effective communication between relevant authorities in different sectors is essential. For a summary, see https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/icf_summarynotes_stakeholder-workshops_en.pdf.

[195] Views in particular expressed by the Committee on Advanced Therapy, the advisory mechanism in the field of advanced therapy medicinal products.

[196] Private actors are in parallel expected to benefit from the initiatives expected under the pharmaceutical framework.

6.3.3 Sustainability of public healthcare budgets

The common measures are foreseen to impact positively the sustainability of healthcare budgets that go beyond the administrative efficiencies described above (which principally impact publicly funded authorities and also publicly funded BE/TEs).

Firstly, there is a broader *digital impact* (see section 6.4) which will bring administrative efficiency for actors and authorities.

The new authorisation and data reporting processes will also improve *availability of better evidence/data* for national/local decision-making to ensure the effective use of BTC. This evidence may also be used in settings that go beyond overseeing safety and quality: not only for treatment protocols and guidelines; but also for pricing and procurement of technologies/services for health providers or even in more formalised health technology assessment processes [197] (i.e. helping to identify the most cost-effective BTC), helping *national budget* holders in their pricing and reimbursement decisions and also in the conditions and rationalisation for use of BTC therapies. A good example is the study and use of convalescent plasma for the treatment of COVID-19 [198,199].

Thirdly, there are opportunities for healthcare cost savings by *correcting requirements faster when safety and quality measures become obsolete* (M1B and M2B). Across all policy options, technical requirements for testing and processing would reflect the best available evidence; no outdated tests/procedures, nor those of unproven value, would be authorised. This will impact BTC supply in two ways: as well as reducing costs, it will also mean fewer deferred donors and less discarded BTC [200].

Fourth, *public health research savings* can be made from the possibility to have risk-based, proportionate evidence collection for the authorisation of BTC processed or used in new ways (M4B). Not all new therapies need full clinical trials; the evidence generation for incremental changes (e.g. changes in the packaging, adjustments in the testing) remains proportionate to the risks [201]. Where clinical trials would typically cost up to EUR 600 000 in the BTC sector, evidence for innovations with a medium level of risk could be collected

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[197] The European Bone Marrow Transplant Society (EBMT) is engaged in dialogue with the European Health Technology Assessment bodies to explore how clinical outcome data from the EBMT registries can be used when assessing the value of new cell-based therapies (https://www.ebmt.org/ebmt/news/ebmt-and-eu-joint-action-health-technology-assessment)

[198] A recent example is the assessment of convalescent plasma, collected from recovered COVID-19 patients (hence containing COVID-19 antibodies) as potential therapy for hospitalised COVID-19 patients in more critical conditions (see Annex 9). While initially it was considered that the therapy would be beneficial for all patients, including in intensive care, meta-analysis of large amounts of clinical data from multiple studies was needed to characterise the effect and to demonstrate that only donations with high concentrations of anti-bodies were useful and they had to be transfused into the recipient early in the development of the disease. Such insights make it possible to limit the use of therapies to where they are effective, and so avoid over-use, over-exposure of patients to risk, and over-spending of public healthcare budgets.

[199] With this, it needs to be noted that public and non-profit stakeholders offer valuable BTC therapies typically at a low, transparent cost-based price, with for example the price for a unit of red blood cells (for emergency transfusion, transfusion during surgery or cancer care) being typically below EUR 200.

[200] Examples and quantifications of such efficiencies are provided in section 8.

[201] See Annex 12.

through a clinical follow-up plan and be limited to EUR 60 000 and to EUR 25 000 for low levels of risk.

These savings for public health can be expected regardless of the policy option.

6.3.4 Employment

The impacts of the measures on employment were not quantified. But a streamlined, reliable and proportionate legal framework will increase the possibility to bring therapies with added value to patients. It allows growth in certain sub-sectors, e.g. the sub-sector of MAR, which is continuously expanding to address increasing societal needs.

Some increased needs for employment of digital staff can be expected, given the digital dimension of the proposal.

As eventual outcome, BTC therapies have the potential to fully restore health of citizens, and transform them from seriously ill patients (blood cancer, burn-wounds, and blindness) into ***active citizens.***

6.3.5 Competitiveness and trade

SoHO are not regulated under an internal market (Article 114 TFEU) legal basis, as described in sections 1 and 3. Beyond the facilitation of BTC supply within the EU, and the possible effect on the need for imports from 3rd countries (e.g., plasma), there is little direct evidence on the impact of the policy options on trade and competitiveness.

The improved environment for (open) innovation and research could strengthen the EU's competitiveness as a global ***location for research and innovation in BTC*** vis-a-vis third countries.

Several cases have been reported in the UK and Switzerland, where strengthening frameworks for hospital prepared therapies make it possible to offer more affordable therapies and to ***attract patients from abroad*** (EU) [202]. A stronger EU framework can allow EU centres of excellence to treat EU patients as well as non-EU patients with high quality therapies [203].

6.3.6 Cross-border exchanges (Internal market aspects)

Cross-border exchanges are important to ***match each patient to the best possible BTC graft*** (unit). Improving harmonisation (horizontal measures on oversight and consistent technical requirements in policy options 2 and 3), and increasing transparency where national more stringent measures are in place, will eventually reduce variations in national rules that create barriers to the exchange of BTC among Member States.

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[202] Swiss to Take On Big Pharma With Cheaper Cancer Treatment: NZZ – Bloomberg (https://www.bloomberg.com/news/articles/2019-07-28/swiss-to-take-on-big-pharma-with-cheaper-cancer-treatment-nzz)

[203] Leading tissue establishments, like the Centre for Reproductive Medicine of the Free University in Brussels, are known to attract patients from all over the world for treatments - UZ Brussel Fertility clinic CRG - Brussels (Jette) - Patients from abroad (http://www.brusselsivf.be/overseas-patients)

6.4 Digital impacts

A dedicated feasibility study on the implementation of a **common BTC IT platform (**SoHO-X) assessed different models for its implementation (see Annex 19). The use of interoperable standards, taxonomies and codes would enable linking or pooling with other datasets, applying advanced analytics based on artificial intelligence and reusing data across policy areas in full compliance with data privacy and security requirements. In particular, linking data on authorisation to the datasets of adjacent legal frameworks (EUDAMED for medical technologies; the Clinical Trials Database, DARWIN [204], EHDEN [205] and MINERVA [206] for pharmaceuticals) as well as the Data Portal of the Publication Office would improve regulatory consistency and give a more coherent view of complex innovations. Matching and triangulating records from multiple data sources, from multiple legal frameworks *can* create a richer, more accurate picture – this is particularly valuable for decision-makers.

A further developed single system for information management, in compliance with the General Data Protection Regulation (GDPR), has however important benefits in terms of flexibility, security and possibility for evolution. Such a system can host flexible solutions, allowing Member States and BE/TEs to maintain and connect with their own system or re-use existing components, through more secure (than currently) GDPR-compliant systems (federated approach). A single system on a European scale can exponentially increase the value of data and reduce certain costs (e.g. security, recurrent reporting). Such solutions would ensure the feasibility, accessibility, interoperability, and reuse of digital assets (FAIR principles), and could be used with the main European and global data standards and other initiatives. It could become an important node in the European Health Data Space and more broadly the EU digital ecosystem: in this case the work of sector experts is essential for the high quality, consistency, availability and use of data.

[204] Deciphering Antitumour Response and Resistance With Intratumour Heterogeneity.
[205] European Health Data & Evidence Network.
[206] Clinical Trial on novel CAR-T drug therapeutic.

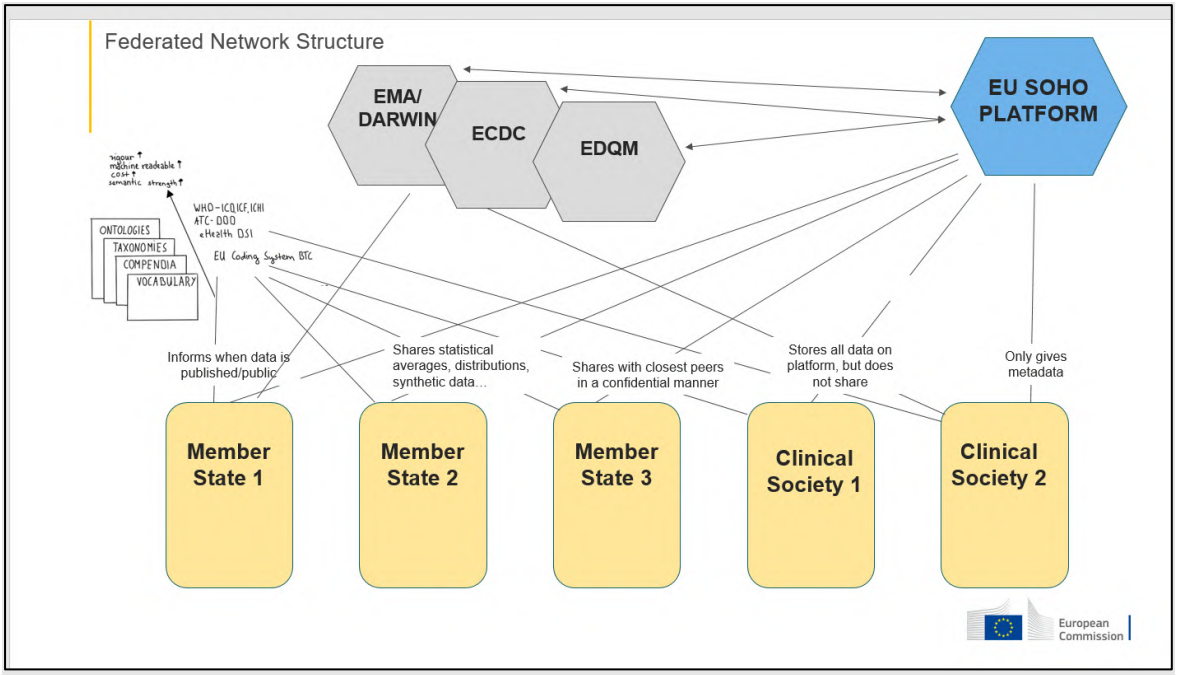

Figure 4: Federated network structure of the common EU SoHO platform

An overall EU budget of more than EUR 8 m is being foreseen to allow for the development of a federated SoHO-X platform to support the national authorities and (mainly public) professionals in the BTC sector.

6.5 Impacts on citizen fundamental rights

The measures that touch on some **fundamental rights** are the same across the three options (common elements); they are expected to have a positive impact (see Table 6). Though it needs to be underlined that most ethical points, in particular the ones related to access and organisation of healthcare, as well as the rights of children born from MAR (e.g. right to know their origin), are decisions taken by Member States at national level. The specific aspects of fundamental rights protection addressed are summarised in the table below, and cover reducing discrimination, privacy and non-commercialisation of the human body. In a workshop on ethical issues [207], most participants expressed agreement with the introduction of donor protection rules. While the general principles in legislation are the same across the three policy options, stakeholders had more confidence that option 2 and option 3 would improve fundamental rights, due to the stronger cooperation of experts.

[207] See summary of the workshop "Ethical Principles (Voluntary Unpaid Donation, Prohibition of Profit from the Human Body, and BTC Allocation)" in https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/icf_summarynotes_stakeholder-workshops_en.pdf.

Objective	Criterion	BL	PO1	PO2	PO3
Obj 1-2	Revising discriminatory terms and provisions (e.g. consistency in the term 'partner'; deferral from donation must be proportionate to risk) (Charter of Human rights article 21)	=	+	+	+
Horizontal	Consistent application of privacy provisions for personal data in the BTC framework. Offering secure infrastructure, technical assistance and GDPR advice will ensure that this data is secure and GDPR provisions are respected to ensure the protection of personal data (Charter of Human rights article 5)	=	+	+	+
Obj 2	Strengthening the fundamental rights of donors. Non-commercialisation of the human body. Donors should not pay for any costs associated with donations, nor be remunerated for their donations (Charter of Human Rights, article 3)	=	+	+	+
Obj 1-2	Stakeholder confidence that the measures would improve fundamental rights	=	+	++	++

Table 6: Main impacts on fundamental rights, per policy option (PO); = no difference, - negative impact, + some improvement, ++ significant improvement, +++ major improvement. See complete table in Annex 4 for details on scoring

6.6 Environmental Impacts

Research and consultations did not provide any information suggesting that the options would result in any specific and significant changes to natural resource use or environmental impacts. In particular, no changes in processing, no increase in waste or pollution is expected as a consequence of any of the policy options.

7. HOW DO THE OPTIONS COMPARE?

7.1 Methodology of social multi-criteria assessment of European policies

The identified impacts of the proposed policy measures were subjected to a **multi-criteria decision analysis to compare the effectiveness and efficiency of the options.** To that end, this IA has piloted the tool of the JRC called SOCRATES [208] (SOcial multi-CRiteria AssessmenT of European policieS – see Annex 4), using it to compare the different options based on the criteria described in the previous section. SOCRATES applies a mathematical aggregation rule to the information collected during the assessment and compiled in the impact matrix (Table 4.1, Annex 4).

The impacts were assessed against the baseline for each of the policy options (the common measures are part of all policy options).

[208] https://knowledge4policy.ec.europa.eu/modelling/topic/social-multi-criteria-evaluation-policy-options_en

7.2 Effectiveness

The performance of the three options on the various dimensions is summarised below. The multi-criteria decision analysis shows a clear ranking: option 2 is the best choice followed by option 3. The set composed by options 1 and the baseline is clearly the worst one. More information can be obtained by checking the pairwise comparisons, which allow one to be fully aware of the mutual weaknesses and strengths on each single evaluation criterion. This information is summarised graphically in the figures (pairwise comparison) in Annex 4, which illustrates the degrees of credibility with which any option is preferred or indifferent with respect to another one on each single criterion. From these figures it is possible to deduce that options 2 and 3 are indeed very similar, although there is a distinct stakeholder preference towards option 2. In fact, if one looks at the performance on each of the single criteria, it is possible to see immediately that only the digital criteria are slightly in favour of option 3, while all the other criteria evaluate these two options as indifferent or are strongly in favour of option 2. On the contrary, when comparing one of these two top options with the other options the preference relation is very clear.

For **patient protection** (objective 1), options were assessed in relation to the time needed to update the rules for safety and quality, the quality of the rules and their consistency among Member States. Option 2 performed best on these criteria, followed by option 3 and then option 1 (with option 1, the timing for update can be short for those establishments having sufficient capacity for conducting risk assessments of their procedures, but this will be cumbersome for small establishments; in addition, this could lead to more divergence among Member States, and even within Member States. With option 3 the consistency can be higher but the timelines are significantly longer to come to updated safety and quality rules).

The common measures for objective 1 were also considered, in particular the possibility of filling legal gaps and ensure safety and quality for currently unregulated therapies.

For **donor and offspring protection** (objective 2), the same criteria of time needed for update, quality and consistency among Member States of safety and quality rules were used. The scoring of the options is the same as for objective 1.

All common measures to **strengthen national oversight** systems (objective 3) are expected to reduce barriers to exchange of BTC across the EU. Measures setting principles and guidelines are necessary first steps to achieve transparency and convergence. Further measures, mainly at EU level, support Member States in the consistent implementation of inspections by improving the capacity of Member States to inspect, and through measures to facilitate cooperation and trust between them (EU audit, joint inspections…). Still, option 1 with possibly more divergence in the practices of establishments would mean more need for oversight work and more difficulties to oversee the sector for the NCAs, where option 2, and option 3, would be more effective.

The common measures to **facilitate innovation** (objective 4) are synergistic in providing a clear regulatory pathway for innovators - one that allows public and private health providers, academia, as well as industrial manufacturers (using BTC as starting materials) to develop innovations under clear and transparent provisions.

The three options foresee different technical solutions for assessing the risks of novel processes, where the use of expert bodies is expected to be most efficient (option 2). Measures to facilitate the development of safe and effective innovative BTC therapies were assessed in relation to criteria of how best to assess safety, quality and efficacy of those therapies across the EU, impact on R&D (open innovation, transparency), as well as what are the impacts on finances (affordability) and patients' access: options 2 3 score higher than option 1, due to their possibility to have harmonised rules for the assessment of novel preparation processes will be more efficient (possibility for Member States to refer to an authorisation already given, so less data needs to be collected and provided by an establishment requesting for the authorisation).

The common measures to improve **resilience of the BTC sector** (objective 5) are expected to improve crisis preparedness by ensuring that supply can be monitored and possible interruptions can be prevented by early action.

The options were assessed on their potential to improve the resilience of the sector, mitigating risk of shortage (objective 5), using criteria related to preparedness and predictability. Options 2 and 3 score equally, and higher than option 1, as they facilitate the application of common technical rules on sufficiency data reporting and on the building of emergency preparedness plans. All Member States would have information on the supply situation in their country, and in the EU, and could use this information to take appropriate actions. For small establishments, this would also spare them the burden of defining their own emergency plans.

7.3 Efficiency - The benefits versus the costs

Efficiency considers the extent to which the options incur costs and other resource implications for the sector, National Competent Authorities, the EU and other stakeholders. It also takes into account the allocation of the costs across the actors: one-off and compliance costs for NCAs and BE/TE with particular attention to the smaller organisations.

Costs of implementation. NVP annual 1000 EUR	**Costs**	**Additional costs**		
	BL	**PO1**	**PO2**	**PO3**
Costs of implementation for the BTC sector - BE-TE and healthcare providers	38.700	+45.000	+32.200	+32.300
Costs of implementation for the BTC sector -Public Administrations	9.500	+3.100	+2.900	+2.900
Cost of implementation EU budget	1.500	+5.400	+6.900	+8.400

Table 7: Costs for implementation – baseline costs and additional costs per Policy Option

The cost calculation shows that compared to the baseline, option 1 increases the annual costs for the sector by EUR 45 m – a significant change, considering the size and largely public nature of the sector. This would disproportionately affect establishments that are smaller in size and have not yet implemented the proposed measures. Considering that option 1 underperformed in terms of the benefits compared to option 2 and option 3, this is clearly a suboptimal option.

Options 2 and 3 are estimated to add significantly less cost for the sector (EUR 32.2 m). The costs of options 2 and 3 are similar for the sector. The main costs are driven by the monitoring and reporting costs - for (hospital) entities processing BTC (M1A), for establishments monitoring certain categories of donor [209] and offspring born from donated BTC (M2A), and for establishments monitoring critical BTC supplies (M5A). However, due to initial one-off costs for digitalisation, the annual administrative costs can remain rather limited per entity/establishment – below EUR 500 to report BTC processing in hospital/entity (M1A), just above EUR 5000 to monitor donors/offspring (M2A) and around EUR 1250 for monitoring supplies (M5A).

It needs to be noted that the baseline values are zero for the new measures. Moreover, the calculations do not take into consideration the cost of all activities in the sector (e.g. the cost of tests or processing required by the technical guidance; or the costs of the internal accounting and supply management systems – such costs could not be retrieved in the public settings of most BE/TEs). Comparisons to the baseline should take this into account, and might rather consider a comparison to the overall sector value which is around EUR 8-12 b (see Annex 8, Table 8.3). An implementation cost of EUR 32.2 m for the sector corresponds to 0.3-0.4% of this sector value.

EU level investments to support development of technical standards, oversight, coordination as well as a data platform to exchange data flows in the sector can facilitate uptake by the sector and thus be a key success factor.

Option 3 entails higher costs for the EU budget (NPV: EUR 6.9 m for option 2 and EUR 8.4 m for option 3). Given the better benefit and impact profile of option 2 and the lower costs for EU budget, option 2 is the most efficient option.

Not all saving effects from digitalisation have been quantified in this comparison, but it can be expected that the policy options that allow for more harmonized regulation (joint under option2 and centralised under option 3) will allow to capture these benefits better. Besides the benefits on monitoring/reporting for professionals (see above), digitalisation efforts will in particular allow to build a shared digital space for the SoHO sector, to support the use of best available evidence and data from the professionals, health providers (including innovators) towards and between public authorities and other stakeholders (M3B and M4A).

7.4 Coherence

The policy options mainly relate to technical aspects within the BTC sector, and therefore make little difference in terms of coherence with most initiatives outside the BTC sector. Nevertheless, some important elements of coherence need to be mentioned with the following EU priorities and initiatives:

[209] Those donors that are exposed to some risk for the purposes of donation, including hormone treatment, an invasive procedure or frequent and repeated donation.

EU initiatives/ regulatory framework	Key considerations
Organs Directive [210]	Provisions for vigilance reporting can be more aligned, and closer collaboration can be planned between organ and BTC competent authorities (for cases of donation of tissues and cells, and organs, by the same donors). The intensified use of expert bodies like the ECDC and the EDQM (option 2) can also be of benefit for the EU organs legal framework.
Medical Device Regulation	Strategic alignment on safety and quality. The two sectors are alike in their diversity and innovation dynamics: both frameworks use a risk-based approach to define proportionate requirements on safety, quality and efficacy (performances in the MD sector). Similar structure of ad hoc working groups. Technical integration on standards, nomenclature, interoperability with EUDAMED. – No impact of policy options. A BTC advisory mechanism will facilitate coordination with the MD sector, in particular to correspond to its working group on classification, its procedure to authorise combination products (MD/BTC) and the provision for the Commission to coordinate different sector authorities at EU level. The BTC advisory mechanism will allow, regardless the delineation, to improve regulatory coherence by clarifying appropriate safety and quality rules and oversight at the borderline. This is in particular important where the classification of BTC is unclear, where BTC become starting materials for medicinal products MD or where BTC are combined with products under the MP (or MD) framework.
Pharmaceutical Legislation Structured dialogue	Strategic alignment on access, safety and quality, resilience of supply, autonomy and innovation. The EDQM as expert body under option 2 plays a (similar) technical role in the pharmaceutical framework (Pharmacopeia). The delineation between the BTC and pharma sectors, set by definitions in the pharma framework, will not be altered by the BTC revision. (However possible developments might occur under the pharma revision, which will have to be assessed there for their impact on BTC and will be closely followed and coordinated with). The BTC advisory mechanism will allow, regardless the delineation, to improve regulatory coherence by clarifying appropriate safety and quality rules and oversight at the borderline. This is in particular important where the classification of BTC is unclear, where BTC become starting materials for medicinal products (PDMP and ATMP) or where BTC are combined with products under the MP (or MD) framework. Improved supply of plasma for manufacturing PDMP is a key element to ensure supply continuity of these therapies (also subject to the structured dialogue and to a BTC/Blood Working Party collaboration).
EU Health Union	Strategic alignment on crisis preparedness; improving available data to manage crises; coordination mechanisms, improving resilience of supply to life-saving treatments. The European Health Emergency Preparedness and Response Authority (HERA) can play a role for such crisis preparedness measures in the BTC sector, once HERA is fully deployed.
ECDC strengthened mandate proposal	Option 2 would bring more coherence with the ECDC proposed strengthened mandate, which is planning to further expand the role and tasks of the ECDC regarding epidemiological diseases/risks in substances of human origin. Therefore, option 2 would allow further synergies with the ECDC tasks.
The EU's Beating Cancer Plan	Facilitated and reliable availability of blood units for transfusion during cancer care, of units of bone marrow transplants for blood cancer patients, and of fertility preservation for cancer patients.

[210] Directive 2010/53/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation.

EU health data space	The proposed structure is fully aligned to the proposed European Health Dataspace (EHDS), and the SoHO-X Platform is considered to be a domain-specific use case (node) in EHDS. It is designed to facilitate exchanges and reuse of data with adjacent legal frameworks. Protection of citizens' health data; developing a federated, networked data system based on technical and semantic interoperability and the FAIR principles. The BTC sector can be seen as one domain – the central data system being a node in the EHDS network.
Shaping Europe's Digital Future	Strategic alignment on digital transformation, the integrity and resilience of our data infrastructure, networks and communications. Respect of personal data and fundamental rights. The SoHO-X initiative is also aligned to on-going work in the frame of the Regulatory Reporting Community on interoperability and on re-using existing digital components (such as eIDAS REGULATION (EU) No 910/2014 or the regulation proposal for a European Digital Identity). It follows clear principles set out in ongoing EU digital initiatives and digital principles (including the European Strategy for data and the Data Governance Act). It enhances the 'once-only' principle as stated in the REGULATION (EU) 2018/1724 of a Single Digital Gateway.
Food framework	The policy options are not different in terms of coherence with the food framework. Including breast milk banks in the scope of the BTC framework would not have an impact on EU food legislation. When breast milk is used as a starting material for the manufacture of breast milk fortifiers placed on the market. Under that framework, the BTC framework would apply to the donation, testing and collection steps and Food legislation would apply for subsequent steps.

Table 8: Key considerations on EU priorities and initiatives

7.5 Proportionality

The measures proposed are limited to actions that need to be taken at EU level in order to reach the objectives, in an effective, efficient and coherent manner. The overall initiative is limited to aspects that Member States cannot achieve satisfactorily on their own, and where there is an EU added value. For example, very few Member States can harness significant and wide-ranging expertise for every technical aspect of ensuring the safety and quality of BTC for donors and patients in their own Member State. The added value of the EU approach in this proposal is to ensure access to a high level of scientific and technical expertise. However, the analysis also shows that a fully centralised system does not perform better and that the most proportionate solution is to rely on expertise already available in the ECDC and the EDQM (Option 2).

The principle of proportionality is strongly reflected also in the new provisions for oversight of operators working on BTC.

- Although the scope of the proposal will affect operators and activities not previously within the scope of the BTC framework, a graded approach to oversight has been defined, with lighter requirements for registration only or for preparation process authorisation only for those entities carrying out BTC activities with lower risk levels. Some entities previously inspected and authorised as BTC establishments can be moved to a simpler registration regime with limited reporting requirements.
- Furthermore, planning of inspections will be adapted to the inherent risk of the establishments, allowing for more frequent inspections for those with high volumes, complex activities or with a poor safety-record.
- Similarly, although the proposal includes new requirements for demonstrating efficacy for novel ways of processing or using BTC, these requirements are graded according to

the degree of risk or novelty and the most demanding clinical studies will be required only for those (rare, less than 5%) novel processes that imply higher risk for patients.

The proposal balances the need for clear and high standards to protect donors and patients equally while ensuring that Member State competences for health care organisation are not compromised. To achieve this need, the two current basic Directives will be replaced by a Regulation and the existing implementing legislation will also be repealed. This instrument will provide a significantly higher level of clarity and conformity to common safety and quality principles.

The proposed legal basis (Article 168(4) of the TFEU) allows Member States to maintain and introduce more stringent measures when they consider them necessary. The proposal does not interfere with that right but does increase the level of safety and quality to be achieved in all Member States, thus reducing the need in most cases for more stringent measures that can create barriers to exchange and to patient access. In addition, the proposal will ensure the adoption of more stringent measures is made more visible so that exchanges can be more easily organised in full respect of those measures. Given that rules relating to ethical aspects of this field, or to healthcare organisation, are not included in the proposal, no special circumstances in individual Member States were identified that required a particular territorial variation in the measures to be applied.

8. PREFERRED OPTION

The comparative assessment of options based on the SOCRATES tool using an equal weight of all the criteria resulted in the following ranking: Option ***2*** is the best choice followed by option ***3.*** The set composed by option ***1*** and the ***baseline*** is clearly the worst (see figure 4.5 Annex 4).

To test the robustness of results a *sensitivity analysis* was performed. We looked first at the influence of the exclusion of the various criteria and dimensions, one at a time, and at the effect of using the subset of criteria belonging to one dimension only (i.e. first one criterion at a time is eliminated and the corresponding ranking is obtained, later a whole dimension with all its criteria is eliminated and the effect on the final ranking is checked). Proceeding in this way, it became clearer and clearer that option ***2*** is the most desirable, in fact it occupies the first position in ***93 per cent*** of all the rankings obtained.

Finally, since we have computed the rankings according to the equal criterion weighting assumption, we then looked at what happens if *all possible combinations of criterion weights* are considered. This exercise is carried out by means of a global sensitivity analysis. The results are very stable: in fact, whatever weight set we use, ***option 2 is always the top-ranked option.***

The Feasibility study identified the single digital system (measure M6C) as the most efficient approach (Annex 19) – **digitalisation is the only area where a centralised solution scored the best on the criteria**. The requirements for the set-up of the SoHO-X platform are currently being defined by the Feasibility study. To allow re-use of data, federated networks was identified as the most efficient approach (by copying and mirroring data they reap the benefits of sharing and analysing data – while allowing the data to remain local in existing structures and ownerships.). As all three sub-options for digital implementation are horizontal, this digital architecture is compatible with the overall preferred option 2.

Finally, an equity analysis has been performed too. This analysis starts from a social impact matrix in which the position of the various stakeholders towards the set of policy options being considered is summarised using qualitative scores. Based on this, SOCRATES then generates the following information: 1) indications of the distance between the positions of the various social groups; 2) ranking of the policy options according to actors' impacts or preferences; 3) vetoed options, the main idea here being that it is not prudent to implement policy options which would create too high a degree of conflict (and thus the decision taken might be very vulnerable). The SOCRATES equity analysis shows that ***option 2*** is also the least conflictual option, as no stakeholder is against its implementation. This is not true for any of the other options considered. All the data and technical details on the results summarised here can be found in Annex 4.

In the legislative proposal, an efficient implementation, adding flexibility and proportionality, will be followed. All stakeholder consultation activities showed a broad support in general for option 2 to define the technical standards and guidance, although the need to ensure that higher level principles on safety, quality and efficacy are defined in EU legislation was also highlighted. However, it was pointed out that, to be successful, appropriate representation in the drafting of technical standards by expert bodies will need to be ensured, including EU Member States' authorities, professionals from the BTC sub-sectors [211], and industry, to ensure transparent and evidence-based working methods [212]. Those concerns can be addressed through agreements between the Commission and those expert bodies.

The conclusion of the IA is that the optimal approach to setting technical standards is to establish a 'hierarchy of standards' approach in the legal drafting, a concept which emerged from the IA process. The legislative proposal will therefore be based on option 2, with joint requirements for technical standards and guidance developed by the EDQM/ECDC, but still with the possibility to have fully centralised requirements (option 3) in a limited number of cases where considered necessary, and with the possibility for local/decentralised requirements where these are not developed under options 2 nor 3 [213]. This 'hierarchy of standards' will only apply on the technical elements, other elements (like principles) will still be set in EU law.

The choice of legal instrument, a Regulation instead of Directives, will minimise divergence due to national transpositions and interpretations. In any case, Member States have the right, as set out in Article 168(4)(a) of the TFEU, to set more stringent standards, which might for example be required to fit to national healthcare settings. This proposal will respect this but

[211] See ESHRE position paper "*F2332684-ESHRE_comments_for_TD_2021*" available at 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.

[212] See Annex 2, Section 3.2.

[213] Thus, at the highest level of the hierarchy, technical standards are set in the legislation. When such technical standards are not in legislation, then technical standards published by expert bodies, the ECDC and the EDQM, must be followed (option 2). In the absence of technical standards from expert bodies, establishments will set their own technical standards taking into account internationally recognised standards, scientific evidence and a documented risk assessment (option 1). The approach will facilitate an efficient and responsive updating of technical standards whenever risks and technologies change and is proportionate in that it ensures EU legislation would be adopted for technical rules only when necessary and when it adds EU value (option 3).

will bring more transparency on such more stringent national standards in order to facilitate cross-border exchange and optimal access to BTC for patients across the EU.

It should be noted that some stakeholders, through the consultation process, asked for specific legal frameworks for certain particular substances (plasma, cord blood [214], FMT [215], human milk [216], allogeneic bone grafts), arguing that the specificities of those substances require a 'separate' legal framework (for example, an implementing act of the basic act). Two stakeholder organisations [217] also expressed that the Blood and the Tissues and Cells Directives should remain separate. By setting strong common principles to protect citizens and then making reference to technical standards of expert bodies for technical rules, it is possible to respect the specificities of these different substances within one single new act covering all SoHO. These specificities will be recognised in these technical standards, and the proposed risk-based approach to oversight allows all of the SoHO 'sub-sectors' to be regulated appropriately without increasing complexity or time needed for implementation. For example, for breast milk and FMT, the legal act will bring them within the scope of this legislation while the substance-specific technical standards of the expert bodies [218], will take into account the specificities of those substances. For plasma, introducing better definitions in the legal act, to reflect the intended use (transfusion or manufacturing of PDMP), can allow for further specifications at technical level by expert bodies, and address concerns raised regarding undue burdens (see section 2.1.6).

For the protection of donors and offspring, donor registries will play a key role, while complying with the GDPR. EU-level donor registries will, for instance, allow centres to apply agreed maximum numbers of donations by a single donor [219]. In the workshops organised as part of the impact assessment, there was a consensus on the need for donor follow-up

[214] Cord Blood Association 2019 (see Annex 20).

[215] See responses given by pharmaceutical stakeholders on FMT in the public consultation: "Such fragility constrains the collection procedure and preservation conditions, and may dramatically impact the therapeutic potential of the collected faeces to be used as appropriate starting material of microbiome-derived medicinal products. In a clinical setting, donor screening, as well as collection and preservation conditions may have to be defined on a "case by case basis", taking into consideration the target patient population and the medical condition of interest. (…) Nevertheless, minimum requirements for safety in all types of indications need to be in place. Therefore, this would require a specific sub-category for faeces within SoHO."

[216] See for example EFCNI Working Group on Human Milk Regulation. Making Human Milk Matter - The need for regulation in the European Union. Policy Recommendations. EFCNI; 2020: "We request European policy makers to ensure that any revision of the Tissues and Cells Directive (…) Includes a delegated act on donor human milk to be developed in close cooperation with key stakeholders in infant care and human milk safety." (EFCNI, 2020)

[217] Expressed by the German Authorities in their submission to the public consultation, ("*F2225402-2021-04-09_DKG-Stellungnahme_Oeffentliche_Konsultation_Revision_Blut_Zellen_Gewebe"* available at 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), as well as by the Bulgarian Authorities in their response to the Inception Impact Assessment (available at https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12734-Blood-tissues-and-cells-for-medical-treatments-&-therapies-revised-EU-rules/F1307595_en).

[218] EDQM guide: Chapters 33 and 34 in part C of the current edition of the Tissues and Cells Guide.

[219] Position paper of the Sociedad Espanola de Fertilidad (SEF) submitted to the Targeted Public Consultation (see Annex 18).

proportionate to the level of intervention or risk associated with the donation. A registry for children born from MAR was discussed but the efforts this would require were not seen to be justified considering its limited expected benefit to individual children and the potentially misleading association it might foster between certain conditions and children born from MAR [220].

The revision of the BTC legislation, with an approach proportionate to risks in different areas (authorisation or registration of establishments/entities, authorisation of new preparation processes, health monitoring of certain donors and offspring [221]) also brings opportunities for savings in the sector, and for carrying out some activities more efficiently within the same resources (e.g. risk-based inspections), though these opportunities have not always been fully quantified. The table below gives an overview of the main opportunities under the preferred option. Several of these do address some of the undue burdens flagged under section 2.

REFIT Cost Savings – Preferred Option		
Description	***Amount***	***Comments***
Graded oversight approach allows to oversee some establishments with lighter approach and less resources than today	EUR 4 m	750 establishments eligible [222], mainly saving on inspection costs for authorities and for themselves
Common IT-platform to share assessments of new BTC technologies reduces duplications	>EUR 2 m	Conservative estimate; Requests to authorise same new technologies are introduced and assessed in parallel across EU; Sensitive to unit cost of assessments and authorisations
Risk-based schedule allows to inspect same activities/establishments more efficiently (targeting high-risk activities)	Not quantified	Model has rather assumed this to be a cost-neutral measure as the same number of resources (inspectors) allow for more oversight on most complex activities
Recognition of authorisations of importing tissue establishments in other Member States, reduces need for ad-hoc import authorisations in different Member States	EUR 0.5 m	Applicable for almost 1 000 imports per year of blood stem cells (from bone marrow or peripheral blood) through a central registry (World Marrow Donor Association registry, subject to one joint authorisation)
Removing obsolete tests and systematic screening measures from the legislation	EUR 2 m (example – West Nile Virus NAT tests [223])	Very high potential, given that every saving is multiplied by number of donations. Other examples could be the screening for

[220] For a summary of the workshop "Better Protection of MAR Donors and Children Born from MAR", see https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/icf_summarynotes_stakeholder-workshops_en.pdf .

[221] Those donors that are exposed to some risk for the purposes of donation, including hormone treatment, an invasive procedure or frequent and repeated donation and offspring born from donated BTC.

[222] This concerns establishments that only do procurement of haematopoietic stem cells, lab testing, import or distribution, and are currently authorised as standard tissue/blood establishment.

		tattoos/piercings or testing for syphilis.
Digitalisation allows for more efficient administrative processes in authorities and establishments	To be further quantified	The SOHO IT platform, financed by the Commission, will facilitate local administration including registration and reporting by professionals as well as authorisations and oversight by authorities. E.g., annual reporting costs are estimated to go down from current EUR 5 000-15 000 to EUR 200-2 000 with an automated reporting tool.

Table 9: Refit cost savings

9. HOW WILL ACTUAL IMPACTS BE MONITORED AND EVALUATED?

A series of monitoring parameters have been identified to evaluate impact of the proposed measures on each of the objectives:

Objectives	***Measures of success* and monitoring indicators**
1. Safety and quality for patients	*Consistently used technical guidance on safety and quality that is based on the latest scientific evidence and available in a timely manner.*
	- Availability of technical standards that achieve a high level of safety and quality in a timely manner ; Data on activities and SARE available for decision-makers - # of updated standards, including frequency of updates of standards and time required for issuing revision - Involvement of experts - # of serious adverse reactions and events reported for each BTC activity
2. Safety and quality for donors and for children born from donated eggs, sperm or embryos	*Improved monitoring and reporting of adverse events for donors and offspring.*
	- Data on donor and offspring protection is available for decision-makers - # of donor serious adverse reactions reported per all donations - # of adverse outcomes for offspring reported
3. Strengthen and allow for harmonisation of oversight practices among Member States	*Trusted oversight that ensures a minimum standard of control and is proportionate to the risk.*
	- Improved and reinforced oversight - # of establishments in the scope (including new ones FMT, breast milk) - # of risk-based inspections - # of joint inspections - # of EU audits + findings
4. Facilitate the development of safe and effective innovative BTC therapies	*Improved regulatory coherence in the adjacent life science legal frameworks: clarity of regulatory pathways and comparable requirements for products of similar risk profile.* *National authorisation process requiring proportionate data on quality, safety and efficacy for novel processing; data shared across MS.* *Level playing field for the public sector throughout the entire innovation cycle.*

[223] Individual NAT test for West Nile Virus can be replaced by pooled NAT test, which is EUR 7 cheaper per test. Applicable to ~300 000 blood donations per year in countries affected by West Nile Virus, saving estimated based on 2016 calculation by NHSBT (UK blood service), see table 1 of the Evaluation {SWD (2019) 376 final}, section 5.3.1.2, p. 59.

	- Clarity of regulatory pathways and comparable requirements for products of similar risk profile: # of questions answered at EU level on BTC (and of those, # of questions answered in coordination with pharma/MD initiatives - # National authorisation process for novel processing; data shared across MS; # assessments recycled between authorities - # Patients treated with these authorised BTC used or processed in new ways
5. Improve the resilience of the sector, mitigating risk of shortages	*Crisis prevention/crisis;* *Centrally available information on activity/supply/shortages.*
	- # emergency plans verified by NCAs - # critical BE/TE participating in monitoring system - # establishments reporting shortages - # reports of low stock
Horizontal and process indicators	- # working group meetings and specific output (e.g. guidance) - # indicators on the development of the data platform (e.g. connections of databases established, including more composite indicators on the resilience of the networks; registered entities) - Technical assistance to the sector (uptake of funding allocated, project specific indicators of success)

Table 10: Measures of success for each specific objective, and monitoring indicators

The monitoring will be possible thanks to the data from reporting obligations on Member States and SoHO entities. The SOHO-X data platform will enable the collection of all elements of the continuous monitoring plan as it automates the extraction of relevant indicators without additional input from stakeholders. It also provides an important perspective on the number of serious adverse reactions and events, which cannot be well interpreted in the absence of a denominator – the activity data. The platform also keeps track of the different pace of implementation across the EU. For the evaluation, additional data will be collected, in particular on the costs, the usability and the integration across systems. The data platform will be used to publish transparently aggregated indicators of general interest, such as SARE related to BTC, insufficiencies of supply or authorised processes. Some of these data collections will allow for synergies, such as cost savings for the annual reporting of SARE data (currently, an extensive annual exercise for the authorities and Commission).

The data quality, processing and semantic interoperability have to be assured during the implementation (implementing acts as well as the development of the IT platform) in line with the Digital Europe principles. The feasibility study also establishes the technical and semantic interoperability with other legal frameworks and allowing re-use across these systems in line with the once only principle.

Optimal monitoring will depend on common reporting standards and the interoperability of the data systems with other initiatives that involve European collaboration across Health Authorities in Member States in particular with the medical devices regulation, the regulation on health technology assessment, the new mandate and roles of the ECDC and the EMA, the upcoming revision of the pharmaceutical legislation, and the European Health Data Space as well as the crisis preparedness and Recovery initiatives [224]. While stand-alone monitoring is possible within the BTC-framework, it would be desirable to develop a joint monitoring and

[224] Many BTC therapies are prepared and supplied by national blood and transplant services, or NGO's with similar functions, and as such are part of the overall national healthcare systems, subject to their organisational aspects and resilience. These systems have been significantly impacted by COVID and fall under the scope of the EU Recovery and Resilience Facility.

evaluation plan (with some/all of these initiatives) so as to capitalise on synergies and achieve cost-savings.