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FACILITATING THE AUTHORISATION OF

PREPARATION PROCESS FOR BLOOD, TISSUES AND CELLS

Technical Annex 3 to overall guidance: assessing clinical data as part of Preparation Process Authorisation (PPA)

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Contents

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1. Introduction

Significant scientific and technological developments in the blood, tissue and cell (BTC) sector enable improved or novel processing and testing protocols, and novel and innovative applications of BTC. Such advancements, however, may pose a quality and safety risk and have a direct or indirect impact on the clinical outcome of the recipients, into which BTC are transfused, transferred, injected, grafted or implanted[1,2]. Furthermore, the wide distribution of these innovations can increase safety risks when their clinical efficacy is insubstantially claimed[2]. Therefore, it is of vital importance to evaluate the potential risk consequences and clinical efficacy applying to clinical use of BTC. Systematic collection and evaluation of clinical data validates the clinical safety and efficacy of novel BTC and provides valuable information for Competent Authorities (CAs) as part of the preparation process authorisation (PPA).

Serious Adverse Reaction (SAR) reporting is required by the European Blood, Tissues and Cells Directives (EUBTCDs)[3,4] for all BTC, not only for novelties. SARs are unintended responses associated with the procurement or human application of BTC that are fatal, life threatening, disabling, incapacitating or which result in, or prolong, hospitalisation or morbidity, such as the transmission of infectious agents (bacterial, fungal, viral or parasitical). However, apart from SAR reporting, the current EUBTCDs do not cover clinical assessment nor clinical follow-up before or after authorisation, nor the follow-up of offspring born as a result of Medically Assisted Reproductive (MAR) techniques using donor gametes or donated embryos. Even though Directive 2006/86/EC[5] Annex II B1 mentions the importance of retrospective evaluation of the clinical outcome for tissue and cells application, there is no explicit requirement in the EU Blood Directives (EUBDs)[3,6–8] or in the EU Tissue and Cell Directives (EUTCDs)[4,5,9] to demonstrate clinical efficacy of the BTC with respect to recipients. All the same, some CAs review detailed dossiers and require clinical outcome data as part of the PPA. However, other CAs only apply a minimal approach with less stringent national requirements. Moreover, data is collected and presented differently in the different Member States (MS). These divergent approaches to PPA occasionally lead to a lack of mutual acceptance of authorisations between MS and pose significant barriers for the exchange of BTC within the EU MS and patients' access to BTC[2]. As there is consensus that human applications of certain novel BTC require assessment of clinical efficacy/effectiveness[2,10], both Blood Establishments (BEs)/Tissue Establishments (TEs) and authorities agree that clinical data should be collated to support the PPA[1], and that it should also include requirements to confirm the clinical outcome data[2]. In order to fully support this purpose, guidance on evaluation of quality and safety as well as clinical efficacy of novel BTC is needed.

A standardised assessment of clinical data as part of PPA aims to facilitate:

- promotion of the evaluation of the clinical efficacy and safety of BTC applications;
- implementation of consistent requirements and the equal possibility for all stakeholders to distribute their BTC;
- comparison of data between different types of BTC for similar processes, stakeholders or MS;
- harmonisation of CAs evaluation and authorisation practices;
- mutual acceptance of authorisation amongst MS;
- inter-MS exchanges of BTC;
- access of patients to novel BTC therapies.

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Aim

This document aims to define *a methodological framework to evaluate clinical data requested for authorisation processes upon introduction of innovation to the current processing and testing protocols for human BTC therapeutics*, as defined in the GAPP Grant Agreement.

The aim of this document is to provide CAs with key principles as to:

- which factors should be considered by CAs when assessing the clinical component of a Preparation Process Dossier (PPD) for completeness and suitability;
- when a Clinical Follow-up Plan (CFUpP) or a Clinical Investigation Plan (CIP) should be requested in order to support the authorisation of a new BTC preparation process and/or therapeutic application;
- what elements should be included in the CFUpP or CIP;
- what type of clinical data would be required to determine the safety and efficacy of human BTC applications for therapeutic use in recipients.

Scope

The content of this document only applies to BTC and their applications as regulated by EUBTCDs[3–9], and all other novel BTC that are not currently covered by other regulations.

BTC that are subject to *substantial manipulation,* or those that *are not intended to be used for the same essential function or functions in the recipient as in the donor* (as defined in Advanced Therapy Medicinal Product Regulation 1394/2007/EC[11]), or products classified as medical devices or medicinal products (such as plasma-derived medicinal products), are not part of the scope of the GAPP Joint Action.

Furthermore, this annex focuses on BTC recipients (and their offspring in the case of MAR), not donors (except in the case of autologous donation). Another project called TRANSPOSE (TRANSfusion and transplantation: PrOtection and SElection of donors) has constructed risk-based guidelines for the selection and protection of donors.

The guidance provided does not consider additional requirements defined in relevant national/ regional/local regulations that should be taken into account by the CAs and the applicants.

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2. The extent of the plan for collecting clinical data should be based on risk assessment

The level of risk associated with the clinical use of BTC is determined by factors specific to the origin, collection/donation/procurement, processing, storage, handling and clinical application procedures of BTC. Therefore, an applicant/BE/TE should perform the risk assessment for any BTC intended for clinical use whenever a significant change in one of the aforementioned factors takes place. This assessment should identify the relevant risk factors, the potential risk consequences for recipients, and estimate the level of risk associated with the clinical use of the BTC. The risk assessment exercise should also consider all pre-clinical and clinical evaluations, and the possible risks and adverse reactions anticipated based on prior experiences. Other relevant data such as scientific literature or data generated by other BE/TEs or the clinical use of similar BTC, may also be considered during the risk assessment exercise. Examples of risk assessment methodologies available are described in the *Good practice guideline to authorisation on preparation processes in blood, tissues and cells*.

The risk assessment results should be presented to the CA as a part of the PPD (Figure 1). The CA should assess whether the risk assessment takes into account all relevant and up-to-date information regarding the BTC in question and whether the final estimated risk level has been determined correctly.

VISTART Joint Action has defined the "*Principles for Competent Authorities for the evaluation and approval of Clinical Follow-up Protocols for BTC prepared with newly developed and validated processing methods*"[1], which determine the correlation between risk level and the extent of clinical data to be required for the clinical component of PPD. According to VISTART, if the application of the BTC does not pose any risk for recipients (or offspring in the case of MAR), only the Serious Adverse Reactions and Events (SARE) reporting that is mandatory for all BTC would be required[1]. With regard to novel BTC preparation processes, a minimum information part of the PPD, including the results of the risk assessment performed, should always be provided for the CA. However, when the human application of the BTC poses any risk (low, moderate or high), a plan for collecting clinical data should be requested to support the PPA. The extent of the plan for collecting clinical data required as part of PPD should be proportional to the risk level[1,10] (see Figure 1). In the case of low risk, in addition to the mandatory continuous SARE reporting, the applicant should develop a clinical follow-up plan (CFUpP; see section 5). For moderate risk, in addition to the SARE reporting and CFUpP, the applicant should develop a clinical investigation plan (CIP; see section 6). In the case of high risk, in addition to the SARE reporting and CFUpP, the CIP should be designed so as in order to compare the novel BTC to a standard/conventional therapy, if available (see section 7).

EuroGTP II project has defined the "*Good Practices for evaluating quality, safety and efficacy of novel tissue and cellular therapies and products*"[10] (EuroGTP II Guide), including some of the requirements for Clinical Evaluation Protocol. In the context of this current guidance, these procedures were further specified and defined as CFUpP and CIP.

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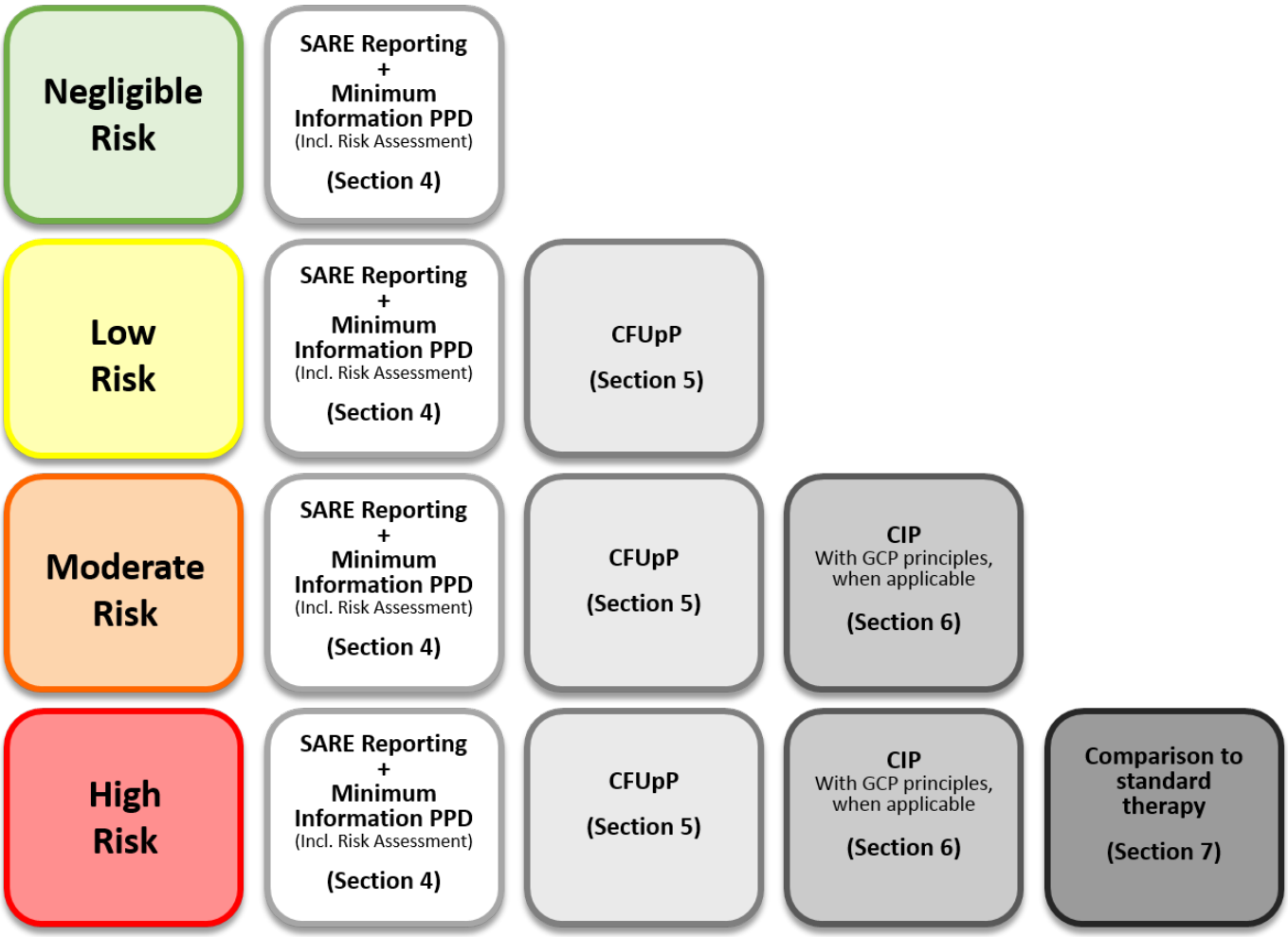

Figure 1. The extent of plan for collecting clinical data included in the clinical component of the PPD is based on the risk level.

3. Clinical data sources and types

Clinical data that the applicant uses in the clinical evaluation and provides to support the clinical component of PPD can be obtained from various sources and in different forms. Relevant data may include clinical investigation(s) of the BTC concerned, or it may be available from scientific literature or from Real-World Data (RWD)[1,12]. Factors to be considered when assessing clinical data for completeness and suitability will be presented in the sections below.

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3.1. Clinical data generated and held by the BE/TE and clinicians

Clinical data may have been generated by collaborating BE/TE(s) and clinicians, also in other MS(s) or in third country(ies). Data may include unpublished data by the applicant and some clinical investigations carried out on behalf of BE/TE.

All data generated and held by the BE/TE, whatever their trends, should be identified and made available for CA evaluation. Documentation related to results and conclusions of the investigation needed for the clinical evaluation (as well as the independent ethics committee opinions and CA approvals) should be provided by the applicant.

3.2. Clinical data in scientific publications

Clinical data derived from scientific literature can be used to augment data not held by the applicant that are needed for the clinical evaluation. For some BTC, clinical data generated using literature searches will represent the greater part (if not all) of the clinical evidence available. Clinical data may not necessarily relate only to the BTC under evaluation, but also to similar BTC.

There are different sources of scientific literature that can be utilised for clinical evaluation. Important sources include scientific literature databases, internet searches and citation referenced in scientific literature. A comprehensive search strategy is recommended, generally involving multiple databases. The search strategy should be thorough and objective, i.e. it should identify all relevant favourable and unfavourable data. Therefore, the search strategy should be documented and justified. The literature search protocol and the literature search report form a key part of the clinical evidence and should be included in the clinical component of the PPD. (Adapted with modifications from MEDDEV[12])

It is important to consider the quality and reliability of the data. For example a large scale clinical investigation published in a high impact, peer-reviewed journal would be considered of high quality and reliability, whereas unpublished clinical data with limited follow up in a small number of recipients less so.[10]

3.3. Real-World Data

The CIP or the CFUpP should be supplemented where possible by Real-World Data (RWD) either at national level or, if possible, at international level[1]. So-called RWD are data related to recipient health status and/or the delivery of health care collected from a variety of sources. Examples of RWD include data derived from electronic health records (EHRs), data from registries, and recipient-generated data, including from in-home-use settings.

Electronic health record (EHR) systems, which are electronic platforms containing individual patient health records, are generally maintained by health care providers, health care organisations, and health care institutions, and are used to deliver care. A typical individual EHR may include for example a patient's medical history, diagnoses, treatment plans, pharmacy records, and laboratory and test results[13].

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The large European registries in the field of BTC - maintained for example by ESHRE, EBMT, and ECCTR - gather the most relevant clinical indicators which have been agreed upon by experts of the sector in question. The registries collect clinical indicators in order to promote scientific knowledge and to assess the efficacy of the different therapies amongst the stakeholders. In addition to BTC registries, there are also disease specific registries, which contain data of clinical care and outcome of a defined patient population. These include rare disease registries initiated by many organisations, such as patients' advocacy groups, private foundations, clinicians and national health systems. Most disease registries are used to support care management for groups of patients with one or more diseases.

The fitness for using registry data requires sufficient processes, such as the ability to gather recipient follow-up information when needed, to ensure data quality, and to minimise missing or incomplete data.

Registries may not capture all data elements needed to answer every question of interest. They generally collect major events and as such, other changes in medical status may not be reliably and consistently documented, if at all. Additionally, data related with the quality of the BTC is very limited or inexistent in the majority of the registries.

Registries and the clinical information of the recipients are not currently available for all BTC, and applicants may need to establish alternative methodologies to provide and structure the required data.

Quality of life measures and patient reported outcome measures (PROM) are increasingly being used to understand patient experiences and preferences. These may be particularly important when well-defined widely accepted clinical outcomes are not available. The use of PROM is justified when the number of affected patients is small and therefore often results in limited clinical experience.

With regard to registry and EHR data quality, CA should consider that:

- Information collected in BTC registries is typically based on voluntary submissions by the stakeholders. Therefore retrieval of information about outcomes may be incomplete and unreliable. For instance, they may offer limited coverage of a MS and all recipients are not considered;
- The registry or EHR may also lose contact with recipients if they change healthcare providers or residence[13];
- The way the data elements are entered in the EHR may limit their accessibility. For example, recipient's symptoms may be documented in unstructured data in the clinician's note without the use of standardised language or a standard symptom scale.

There are several potential advantages of the use of RWD in clinical evaluations that CAs should consider:

- Registries and EHRs may facilitate clinical investigators and study personnel to have access to many types of data that can be combined, aggregated, and analysed;
- PROM may have the potential to provide clinical investigators access to real-time data;
- Registries and EHRs can facilitate follow-up on recipients to assess long-term safety and efficacy of BTC;
- There are opportunities for long-term follow-up of large numbers of recipients, which may be of particular importance in studies where the outcome of interest occurs rarely[13].

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In the future, there will probably be increasing interest in using RWD to generate evidence to support CA decisions about the efficacy of novel BTC. If such data will be provided for CA for assessment, the CA should consider whether the RWD are fit for use, and whether the RWD can provide adequate scientific evidence to answer or help answer the regulatory question.

Examples from other sectors include the European Medicines Agency's (EMA) *Regulatory Science to 2025*[14] strategy which includes consideration of how to use RWD in decision-making while the EUnetHTA Joint Action is developing standards for the use of patient registry data for health technology assessment (HTA) purposes.[15]

4. Minimum information of the clinical component of the PPD

4.1. General information

In the context of the authorisation request for the clinical application of a novel BTC or preparation process, applicants should always provide CAs with a minimum set of information, including at least the following:

- A clear characterisation and definition of the BTC under evaluation (defined in *Good practice guideline to authorisation on preparation processes in blood, tissues and cells* and *Technical Annex 1 to overall guidance: authorisation of changes in donation, procurement and collection, processing, preservation, storage and distribution*);
- Risk assessment results (section 2);
- Justification of the change or the innovation, including the key benefits;
- Alternative therapies or BTC, if any;
- Relevant bibliography used as clinical evidence including a description of literature search protocol (names of databases, search terms etc.) and the literature search report (section 3.2.).

4.2. Clinical indications

The disease(s)/condition(s) and/or population that a clinical use of BTC is intended to treat should be clearly described, for example:

- Pathologies/conditions that can be treated or prevented with the novel BTC;
- The scientific rationale behind the proposition of a new clinical indication (if applicable);
- Potential contra-indications.

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4.3. Application/administration methods

Application methods and procedures, as well as any particular requirement associated with the novel BTC therapy/BTC resulting from novel preparation process should be described, namely:

- Administration form(s), concentration(s) and dosage(s) of the BTC (if applicable);
- Immediate pre-implantation preparation procedures (e.g. adding solutions/reconstitution procedures, cutting, thawing, auxiliary devices required, if any);
- Application/implant methods (e.g. infusion, surgery, laparoscopy, insemination, etc.);
- Special skills or training required (depending on the level of novelty and/or complexity of the clinical application procedure(s)).

5. Assessment of Clinical Follow-Up Plan (CFUpP)

Clinical follow-up of BTC recipients should be required whenever clinical application of a BTC, resulting from a novel preparation process, poses any risk (low, moderate or high) to recipients or to MAR offspring. Even so, the clinical follow-up should be proportionate in terms of scale, complexity and duration to the level of residual/unknown risk[1]. The extent of the clinical follow-up could also be adjusted in the light of previous clinical experience with a similar BTC[1,10].

To confirm the adequacy of the clinical follow-up of recipients or MAR offspring, the CA should request the applicant to present a CFUpP[1]. The CFUpP should be planned in close cooperation with the BE/TE and the clinicians responsible for the clinical application of the BTC. The CFUpP should include at least:

- the number of BTC applications/recipients for follow-up;
- the type and duration of clinical follow-up, including information on follow-up procedures (for example samples, imaging);
- the methodology for clinical follow-up data collection (examples in section 6.7);
- the parameters identified to prove safety and/or efficacy of the specific BTC (sections 5.1 and 5.2);
- data consistency assessment and/or data analysis including biometrics, statistics.

(Adapted from Vistart[1] and EuroGTP II[10])

According to the risk level, the CFUpP may differ from the standard follow-up in clinical practice to a more structured plan for active collection of a specific set of data related to the safety and efficacy of the BTC[1,10]. Moreover, in case of moderate or high risk level, CFUpP should be sent for CA assessment once clinical investigation according to the CIP is concluded (sections 6 and 7), and may be updated or amended according to its results (section 8). More specific examples of aspects which could be considered when assessing the CFUpP provided by an applicant are presented the following sections.

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5.1. Clinical safety data

Clinical safety data to be collected should be based on risk factors related to the process (donation, procurement, processing, storing, transport, product or clinical application) identified during the risk assessment that cannot be mitigated to negligible risk level by *in vitro* or pre-clinical studies and therefore may have consequences once BTC is applied to recipients. In particular, the collection of data on the potential risk consequences associated with the clinical application of the BTC (see Table 1) should be considered.

TABLE 1: Examples of potential risk consequences of the clinical use of BTC[1,10]
- Unexpected immunogenicity - Implant failure/engraftment failure/pregnancy loss - Disease transmission (incl. disease transmission to offspring in case of MAR) - Toxicity/carcinogenicity - Other potential risks (associated with specific BTC)

While the safety concerns are closely linked to the specific characteristics of the BTC, the critical assessment of safety should consider the following issues (non-exhaustive list):

- findings from pre-clinical studies and/or results from clinical investigations that affect, or could affect, the evaluation of safety in clinical use;
- the nature of the recipient population (e.g. demographics) and the number of recipients required to obtain statistically significant data[16–19], where applicable. If the number needed is too high because the disease concerned is a rare disease, then alternative solutions could be proposed;
- detection of common and non-serious adverse events, focusing on events of relatively high frequency and those that are known to occur with similar BTC (for example, adverse events possibly related to the BTC administration process, surgical procedures or other).

5.2. Clinical efficacy data

Clinical efficacy data should be collected to determine the therapeutic effect of any BTC resulting from novelty in the preparation process. As with clinical safety data, the applicant should propose the plan for collection of efficacy data.

Clinical efficacy data should be adequate to demonstrate efficacy in the recipient population after a predefined period of time, to demonstrate results of the optimal therapeutic effect, to evaluate the duration of the therapeutic effect of the administered BTC and to allow for a benefit – risk assessment that takes into account the existing therapeutic alternatives for the target population.

The CA should be provided with a plan that proposes to collect all relevant data, whether positive or negative, and the applicant should explain how the data is intended to support the application of BTC for the proposed indications.

While assessing the plan to collect clinical efficacy data the CA might consider the following issues:

- relevant features of the recipient populations, including demographic features, disease stage, and any other potentially important covariates;

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- the nature and scale of expected clinical benefit and the basis for these expectations;
- statistical methods and any issues that could affect the interpretation of the results;
- summary of patient reported outcome measures, if collected by the applicant.

5.3. Duration of the clinical follow-up

The length of clinical follow-up will depend on the expected shelf-life and characteristics of the BTC in question, as well as on the clinical indication. The use of a previously validated or generally accepted follow-up period is possible, provided that a correlation between the duration of clinical follow-up and safety and efficacy can be established[20]. If the efficacy is dependent on the long-term persistence of the BTC, a long-term clinical follow-up of the BTC recipients (and/or offspring) should be requested. However, if the follow-up period is very long then alternative solutions, e.g. at shorter follow-up period, might be acceptable, if suitably justified[14]. The duration of the clinical follow-up should always be justified and scientifically sound.

6. Assessment of Clinical Investigation Plan (CIP)

If the end result of the risk assessment performed by the applicant is moderate or high risk level, the applicant should plan for a clinical investigation for evaluating the novel BTC. Clinical investigation should be the primary way for evaluating if a novel BTC is safe and effective in recipients. A Clinical Investigation Plan (CIP) is a document that describes how the clinical investigation will be conducted (the objective(s), design, methodology, statistical considerations and organisation of a clinical investigation) and ensures the safety of the novel BTC recipients and integrity of the data collected.

The depth and extent of CIP should be adaptable and appropriate to the nature, intended purpose, and risks of the BTC in question. It should be presented to the relevant CA for assessment and approval before starting clinical application of the novel BTC.

The CIP provided to CA should define (at least):

- Objectives and purpose of the clinical investigation;
- Recipient inclusion and exclusion criteria;
- Number of BTC recipients planned to be included in the clinical investigation;
- Alternative therapies or BTC, if any;
- Control treatment (if applicable);
- Recruitment procedures and informed consent protocol for the recipients;
- Planned follow-up visits and procedures (incl. tests, samples, imaging etc.) and duration of the clinical investigation;
- Data collection methodology;
- Safety and efficacy parameters;
- Endpoints defined by the applicant and end users to assess safety and efficacy;
- Statistical protocols, data handling, record keeping and methodology for data analysis;

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- Discontinuation/termination criteria (safety signals defined; if these were reached, the clinical application of the BTC were to be discontinued/terminated);
- Predicted timing for periodic or final reports of the CIP.

The type of clinical investigation selected depends on a number of considerations and should be justified according to:

- Remaining level of risk;
- The availability of a suitable control treatment, if applicable (section 7);
- The length of time that recipients need to be monitored will depend on the BTC in question and its indication. If a long term follow-up is required, a controlled investigation may not be practical, and a registry approach may be considered[10].

The CIP design, and the eventual execution of the clinical investigation, should take into consideration and follow the principles of Good Clinical Practices (GCP)[21], where applicable (Appendix I).

After completion of the clinical investigation, the applicant should report the results of parameters assessed, as well as the conclusions.

Specific aspects of CIP are described in sections below.

6.1. GCP principles

For CIPs with moderate or high levels of risk, the principles of GCP[21] should be adhered to, when applicable (see Appendix I - Good practices of clinical setting for BTC [adapted from GCP principles]).

In addition to a conclusive statement on compliance with GCP principles, the information provided in the PPD should allow the assessment of the adhesion and implementation to GCP principles. Where the nature of the BTC does not permit full compliance with GCP principles, applicants should justify the reasons for non-compliance and describe the alternative practices adopted.

6.2. Independent Ethics Committee (IEC) decisions/opinions

Local/regional/national Independent Ethics Committees (IECs) are bodies designated to review and approve biomedical research involving human subjects. IECs should safeguard the rights, safety, and well-being of the participants under clinical investigation. In particular, special attention needs to be paid to clinical investigations that may include vulnerable subjects.[16] In some MS, the IEC's favourable decision/opinion of the CIP could be mandatory before commencing the clinical investigation on humans. The IEC may review informed consent forms (ICF; section 6.3), including the information provided for the possible recipients of the novel BTC, participant recruitment procedures, available safety information, and investigator's qualifications (section 6.14.2) and any other documents that the IEC may need to fulfil its responsibilities.[21] If IEC opinions/decisions are given, these should be included in the application and reviewed by the assessor.

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6.3. Recruitment procedures and informed consent process of the recipients

The role of informed consent is crucial in maintaining the trust of the general public in health professionals. Therefore, it is important that the limits of the consent are clearly established (and subsequently, accurately respected). As a result, the informed consent form (ICF) should be as clear and concise as possible and written in simple and easy to understand terms comprehensible to the intended clinical investigation participant.

Clinical investigation of a novel BTC can be carried out only after the person concerned (BTC recipient) has given informed consent to it.[22] This person should make a free choice as participation to CIP is voluntary. Beforehand, participants need to be given appropriate information of certain aspects of the CIP, see examples listed below. In some MS, the IEC assesses the contents of the ICF and the information given to the novel BTC recipients, in some other MS the CA assessor needs to assess the those. The ICF should give information on:

- the therapy, as well as its consequences and risks;
- alternative therapies available;
- how long the participation in the clinical investigation is likely to last, and what type of follow-up procedures are involved;
- approximately how many other recipients are taking part, and the probability for random assignment to each group (if applicable);
- compensation or treatment available in case something goes wrong;
- the circumstances under which their participation (or the investigation in its entirety) may be terminated;
- the right of the person concerned to refuse to participate or withdraw their consent, at any time, without penalty or loss of standard treatment to which they are otherwise entitled to.

If the clinical investigation involves children or adults who lack the capacity to consent, there should be more than one ICF – each tailored to the sub-group in question. For example, one aimed at children and the other for the parent/guardian(s).

CIP should describe the BTC recipient recruitment process. For example, the following details should be given:

- How will potential clinical investigation participants be identified (e.g. advertising the clinical investigation or via existing recipient lists);
- What resources will be used for recruitment (description of the format of the resources, e.g. letters to possible participants, in the clinic, through social media or through newspapers);
- Who will be approaching potential participants and who will be obtaining informed consent (description of the professionals' role and whether there is a prior clinical relationship with potential participants);
- How will it be assured that potential participants (or their legal representative) have understood the information and that their consent is informed.

(Adapted from Recruitment and Informed consent procedure template of European Commission[23])

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6.4. Insurance

It must be ensured that there is an adequate insurance coverage for the recipients of novel BTC, in accordance with applicable regulatory requirements. Proof of insurance should be requested when this is stipulated by national legislation.

6.5. Inclusion and exclusion criteria

The target population needs to be described in the CIP, specifying the inclusion and exclusion criteria for participating in the clinical investigation. Inclusion criteria are characteristics that the prospective participants must have if they are to be included in the clinical investigation. Exclusion criteria are those characteristics that disqualify prospective participants from inclusion in the clinical investigation. Inclusion and exclusion criteria may include factors such as age, gender, type and stage of disease, the participant's previous treatment history, and the presence or absence of other medical conditions. Defining clear-cut inclusion and exclusion criteria increases the likelihood of producing reliable and reproducible results, minimises the likelihood of harm to the participants, and guards against exploitation of vulnerable persons.

6.6. Clinical endpoints

An endpoint is the primary outcome that is being measured by clinical investigation. A clinical endpoint is an outcome that represents clinical benefit (such as survival), the absence of disease or onset of symptoms. Endpoints can also be subjective, as for example improving symptom score or health-related quality of life score.

Endpoints should be selected to address the objectives of the clinical investigation and should be clinically relevant, practical and affordable to obtain, and measurable in an unbiased manner.

6.7. Planned follow-up procedures, samples and/or visits of the recipients

The CIP should contain all the details relevant for the clinical investigation, for example:

- The expected duration of BTC recipient participation;
- A description of the sequence and details of all investigative procedures (including tests, samples, imaging etc.);
- The methods and timing for assessing, recording, and analysing safety and efficacy parameters;
- The type and duration of the follow-up of participants after (serious) adverse reactions.

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6.8. Methods for data collecting

The CIP should be designed to collect high-quality, reliable and meaningful data. Methods for data collecting should be specified and justified, including for example:

- Patient reported outcome measures (PROM) (for example questionnaire surveys and participant diaries; in paper or electronic format) should use standardised instruments, where possible, to promote the collection of uniform high-quality data and allow for meaningful comparisons. If standardised instruments are not available, investigator-invented scales can be used but should be carefully designed and piloted before using in clinical investigation. Electronic PROM systems provide better quality of data and could allow for immediate intervention if problems or deviations occur.
- Review of EHRs may be used either as the sole source of data, or complementary to other methods used to collect information. EHRs can be important sources of information that can document participants' medical history, clinical or laboratory profile at varying time points in a cost-efficient manner.
- Investigation report forms (paper or electronic) can be designed specifically for data collection regarding the clinical investigation in question so that all the data needed to answer the research question will be captured. All the data on each individual taking part in a clinical investigation will be held in the investigation report forms.
- Collection of biological material/samples and various imaging technologies can be used to obtain information on anatomical, pathological and biological mechanisms involved in the development of disease, its prognosis, or response to treatment. Biological data can serve as clinical endpoints but obtaining samples can burden participants. Biological data need to be collected under standardised conditions with considerable attention to detail.

6.9. Multicentre investigations

A multicentre investigation is an investigation conducted by more than one organisation responsible for human application (ORHA). Multicentre investigations can be conducted in one MS, at multiple MS, or they can include centres from third countries. Multicentre investigations benefit from a larger number of participating recipients, the possibility of including a wider range of population groups, and the ability to compare results among centres. Multicentre research promotes networking by bringing together different groups of investigators who can also share resources, expertise and ideas. Multicentre investigations are recommended, whenever possible, in order to reduce any potential bias.

In multicentre investigations, the ORHAs (incl. countries), as well as numbers of recipients planned for each centre should be specified in the PPA application.

6.10. Data protection and data integrity

All data handling must comply with the international and national data protection requirements[24]. There should be organisational and technical arrangements in place to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and personal data processed. There should be measures in place to ensure confidentiality of records and personal data of the BTC recipients

(including data gathered in the context of CFUpP and SARE reporting). All these arrangements and measures should be described in the CIP.

All data regarding the clinical investigation should aim to be complete and accurate, and consistent between recipients and different ORHAs (in multicentre investigations). Achieving high-quality data can usually only be proven via audits, inspections or assessment of the results.

6.11. Analysis of the clinical data

The plan for analysing the clinical data should be specified in the PPA application, should use sound methods and should include:

- a description of the statistical methods to be used, including timing of any planned interim analysis/analyses;
- the number of recipients planned;
- reason for choice of sample size;
- the level of significance to be used.

In general, data that are not methodologically sound (such as single recipient reports) should not be accepted for demonstration of adequate clinical safety and efficacy of a BTC (adapted from MEDDEV[12]).

The assessor should identify if additional clinical follow-up or other measures are necessary in order to generate any missing data.

6.12. Discontinuation/termination criteria

The CIP should outline the discontinuation and termination criteria for the clinical investigation. For example, individual participant(s) must have the possibility to discontinue the clinical investigation in the event of:

- withdrawal of consent at any time;
- circumstances that would endanger the health of the participant;
- non-compliance with clinical investigation procedures.

Premature termination of the clinical investigation might be necessary, for example for safety reasons, if the IEC terminates its approval/favourable opinion of the clinical investigation, or if the clinical investigation proves to be impossible or difficult to conduct in practice. Applicants should inform the CA of premature termination.

6.13. Periodic and final reports

When clinical investigations are very large or long in duration, when the interventions have associated serious safety concerns, or when the disease being studied is very serious, then interim data monitoring and periodic reporting should be considered.

The CIP should determine the time point, or number of treated recipients reached, when the periodic and final reporting should be conducted. The periodic and final analysis process can be described in a separate document.

6.14. Appendices required to support PPA

The CA should also consider some additional aspects when performing the PPA. These are reviewed in the following sections.

6.14.1. Agreements

A written and signed agreement should be formulated between:

- the clinician(s) performing the recipients' clinical investigation (also institution/ORHA, if applicable)
- and the BE or TE that is responsible for the novel BTC therapy/BTC resulting from novel preparation process.

The agreement should:

- take into account relevant national/local requirements for these agreements
- list responsibilities of the participants, for example regarding
    - data collection and data analysis;
    - communication with relevant CAs;
- detail who owns, has access to, has the right and the responsibility to process, has the right to publish, and stores the generated data;
- define the period of validity of the collaboration;
- refer to data protection requirements (for example EU's General Data Protection Regulation[24]);
- be signed by all relevant parties.

6.14.2. Experience of investigators

The clinicians responsible for performing the clinical investigation of BTC recipients (investigators) must collect and report investigation-related data in addition to the standard clinical practice.

Investigators should:

- be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation;
- meet all the competences specified by the applicable regulatory requirement(s);
- provide evidence of such competences through an up-to-date curriculum vitae (CV) and/or other relevant documentation as required by the BE/TE, the IEC, and/or the CA;
- be thoroughly familiar with the appropriate application of the BTC;
- be aware of, and comply with, relevant national/local regulatory requirements, and principles of GCP;
- permit inspection by appropriate CAs, as and when applicable.
  (Adapted from GCP[16])

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It is recommended to appoint one of the investigators in a Principal Investigator (PI) role. The Principal Investigator will be the lead investigator with responsibility for following the CIP and for the proper conduct of the data collection and reporting. The PI should have the required competence according to relevant legislation.

7. Control treatments for BTC with high risk level

Details related to the definition, performance and evaluation of control treatment(s) should be included as part of the CIP, at least for those BTC with high levels of risk.

In most cases, the standard/conventional BTC is recommended to be used as control, if available. If ethical considerations prevent using established BTC in parallel with the novelty or if the effect of the novelty is expected to be major, based on preliminary data, already existing comparison data of standard/conventional BTC could be used. Reasons for not using a control group should be justified in the CIP.

When applicable, alternative therapies/procedures, other than standard/conventional BTC can also be considered as control treatment(s).

Randomisation into novelty and control treatment groupings should always be considered as a good practice. Randomisation is used to prevent allocation bias into the treatments groups by creating balanced investigation division. Known and unknown recipient characteristics that may influence the investigated outcome parameters should be balanced, as ideally the treatment intervention is the only difference between the investigation groups. Randomisation is considered a critical element in establishing a causal relationship between treatment and clinical outcomes. Treatment assignment based upon investigator's judgment, rather than randomisation, creates a challenge for proving treatment efficacy that must be addressed. However, for several reasons (including ethical and practical considerations), the administration of BTC can in many cases not be subjected to a randomised, controlled investigation. In this case, the reason for not using randomisation should be justified in the CIP.

8. Updates and amendments

The CFUpP and CIP resultant from the risk assessment should be updated by the applicant throughout the BTC life cycle, as and when necessary[20].

Applicants should inform the CA, in a timely fashion, when there is a need to change and/or update the initial CIP and/or CFUpP, based on:

- New clinical data available for the BTC under evaluation;
- Identification of potential new risks and risk consequences;

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- Changes concerning current knowledge/the state of the art, such as changes to applicable standards and guidance documents, new information relating to the medical condition managed with the BTC and its natural course, or therapeutic alternatives available to the target population;
- Other aspects identified during clinical follow-up/post authorisation.

9. Final considerations

These guidelines indicate that a common framework and harmonised approach can be suitable to assess the clinical component of the PPD for the different BTC.

The good practices proposed in this document are aligned with the views of CAs and stakeholders, and reflect the contents of preceding EU initiatives. Nevertheless, appropriate levels of flexibility should be considered during the implementation of these guidelines as the assessment of clinical data (beyond the reporting of serious adverse reactions) is not included in the scope of the current EUBTCDs, and at present clinicians/end users are not obliged to provide clinical data to BE/TE. Additional challenges may arise considering the structure and limited resources of many CAs and BE/TEs, the anticipated number of recipients lost to follow-up due to the nature of the BTC therapies, and the absence of formal registries for all BTC.

Despite the foreseen challenges, this document should be considered an integral part of the generic guidance produced by the GAPP technical WPs, and interpreted as an important milestone for the improvement of practices and the safety of BTC recipients in Europe.

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Acronyms

BE	Blood Establishment
BTC	Blood, Tissues and Cells
CA	Competent Authority
CFUpP	Clinical Follow-Up Plan
CIP	Clinical Investigation Plan
CV	Curriculum vitae
EBMT	European Society for Blood and Marrow Transplantation
ECCTR	European Cornea and Cell Transplantation Registry
EHR	Electronic health record
EMA	European Medicines Agency
ESHRE	European Society of Human Reproduction and Embryology
EUBD	European Blood Directives
EUBTCD	European Blood, Tissues and Cells Directives
EUnetHTA	European Network for Health Technology Assessment
EuroGTP II	Good Practices for evaluating quality, safety and efficacy of novel tissue and cellular therapies and products (EuroGTP II Guide)
EUTCD	European Tissues and Cells Directives
GAPP	Facilitating the Authorisation of Preparation Process for blood, tissues and cells
GCP	Good Clinical Practice
GvHD	Graft versus Host Disease
ICF	Informed Consent Form
IEC	Independent Ethics Committee
JA	Joint Action
MAR	Medically Assisted Reproduction
MS	Member State
ORHA	Organisation Responsible for Human Application
PI	Principal Investigator
PPA	Preparation Process Authorisation
PPD	Preparation Process Dossier
PROM	Patient Reported Outcome Measures
RWD	Real-World Data
SAR	Serious Adverse Reaction
SARE	Serious Adverse Reactions and Events
TE	Tissue Establishment
VISTART	Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction and Transplantation
WP	Work Package

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Definitions

Applicants – European Blood/Tissue Establishments (BE/TE) that request Competent Authorities for authorisation for the clinical application of blood, tissues or cells (BTC).

Blood, Tissues and Cells – Substances of Human Origin included in the scope of the European Directives 2002/98/EC[3] and 2004/23/EC[6].

Clinical benefit - The positive impact of (a) BTC therapy(ies) on the health and quality of life of an individual, expressed in terms of a meaningful, measurable, recipient-relevant clinical outcome(s), including outcome(s) related to diagnosis. (adapted from [25])

Clinical data - Information concerning safety or efficacy that is generated from the use of a BTC and is sourced from the following: clinical investigation(s) of the BTC concerned; clinical investigation(s) or other studies reported in scientific literature of the BTC in question; reports published in peer reviewed scientific literature on other clinical experience of the BTC in question; clinically relevant information coming from post authorisation surveillance. (adapted from [25])

Clinical Investigation Plan (CIP) - A document that describes the rationale, objectives, design, methodology, monitoring, statistical considerations, organisation and conduct of a clinical investigation[25], prepared by the applicant(s) in the context of the authorisation request for clinical use of novel BTC therapies/BTC resulting from novel preparation process.

Clinical Follow-up Plan (CFUpP) – The plan for monitoring the novel BTC recipient for a given time after clinical application/administration; may comprise of medical visits, tests, diagnostic procedures, samples etc. (adapted from [1])

Efficacy - Presence of desired (clinical) effects/patient outcomes depending on the mode of action of the BTC[1,26].

Follow-up - Subsequent evaluation of the health of a recipient for the purpose of monitoring the results of the BTC application, maintaining care and initiating post-application interventions. (adapted from [26])

Informed consent - A person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to donate, to participate in research or to undergo a diagnostic, therapeutic or preventive procedure.[26]

Randomised controlled study - A study in which subjects are allocated at random into groups, called the "investigation" and "control" groups, to receive or not receive an experimental therapeutic intervention. (adapted from [26])

Recipient - Person to whom human BTC are applied. (adapted from [26])

Third countries - Countries that are not members of the EU.

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Appendix I - Good practices of clinical setting for BTC

(Adapted from GCP principles[16])

1.	Clinical investigation should be conducted in accordance with the ethical principles in the Declaration of Helsinki and the applicable regulatory requirement(s).
2.	Before clinical investigation is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual novel BTC recipient and society. A clinical investigation in recipients should be initiated and continued only if the anticipated benefits justify the risks.
3.	The rights, safety, and well-being of the BTC recipients involved in the clinical investigation are the most important considerations and should prevail over interests of science and society.
4.	The available nonclinical and clinical information on an investigational BTC should be adequate to support the proposed clinical investigation.
5.	Clinical investigation should be scientifically sound, and described in a clear, detailed plan.
6.	Clinical investigation should be conducted in compliance with the plan that has received prior independent ethics committee (IEC) approval/favourable opinion.
7.	The medical care given to, and medical decisions made on behalf of, BTC recipients should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8.	Each individual involved in conducting a clinical investigation should be qualified by education, training, and experience to perform his or her respective task(s).
9.	Freely given informed consent should be obtained from every BTC recipient prior to participation in the clinical investigation.
10.	All information associated with the clinical investigation should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11.	The confidentiality of records that could identify BTC recipients should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12.	Investigational BTC should be donated, analysed, processed/prepared, handled, stored and distributed in accordance with good practices described in current versions of the Guide to the quality and safety of Tissues and Cells for human application[26] and Guide to the preparation, use and quality assurance of blood components[27] of the Council of Europe. They should be applied/transplanted/transfused in accordance with the approved plan(s).
13.	Systems with procedures that assure the quality of every aspect of the clinical investigation should be implemented.

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