BSBMTCT Guidance on Storage and Discard of Cryopreserved Cellular Therapy Products

Background

This document is an update of previous guidance published on the BSBMTCT website and aims to give guidance to transplant programmes in England. It has been developed with input from legal advisers and the document has been approved by the BMT Clinical Reference Group.

Appendix 2 contains templates for letters that can be used to contact patients and GPs. Templates for patient information and patient consent have been developed and are on the BSBMTCT website. These are intended as guidance only.

Introduction

Cellular therapy products (CTPs) for Blood and Marrow Transplant (BMT) usually comprise haematopoietic progenitor cell-apheresis (HPC(A)), HPC-marrow (HPC(M)), T-Cells (TC), or cord blood (HPC(CB)). It is necessary to store HPC(A) and HPC(M) products routinely for patients having autologous haematopoietic progenitor cell (HPC) transplants as HPCs need to be collected from patients prior to conditioning therapy being completed. Most HPC products are returned to the patient within 6 months of donation but many donations contain sufficient HPCs for more than one transplant and so the remaining cells are kept for many years in cryogenic storage.

In the allogeneic setting prior to the COVID-19 pandemic, donated HPCs were not routinely cryopreserved unless excess cells had been collected, or if the transplant was delayed for some reason. Many BMT programmes moved to cryopreservation of allogeneic HPCs during the pandemic and although the majority have moved back to fresh issue, some cryopreservation continues. In addition, some transplant centres store a proportion of the HPCs collected in aliquots to be used for donor-derived lymphocyte doses (TCs). TCs can also be collected and stored in multiple doses at a later timepoint as needed should the recipient fail to achieve full donor chimerism or relapse.

Storage space is limited for frozen harvests and discarding cells that are no longer needed means that capacity for storing cells for current patients can be maintained.

This policy outlines the circumstances whereby stored HPCs and TCs can be discarded. Cord blood donations intended for family use (directed donations) are outside the scope of this document as are donations collected by unrelated donor registries. Such registries have their own policies around donor information, consent and CTP disposal.

Legal requirements vary across the devolved nations and this guidance is intended for use in England only.

1. Regulation of CTP storage and disposal

The storage of HPCs and TCs for a scheduled purpose (i.e. transplantation) is defined and governed by the Human Tissue (HT) Act 2004 and Human Tissue Authority (HTA)'s Codes of Practice.[1]

- The Act states that surplus tissue can be dealt with as waste if it has come from a person's body in the course of their receiving medical treatment, undergoing testing or participating in research. This material has to have ceased to be used or stored for use for a purpose specified in Schedule 1 of the Act.
- "Code A: Guiding principles and the fundamental principle of consent" states "It is not a legal requirement for consent to be obtained for the disposal of material. However, it is good practice for disposal options to be given, and for the wishes of the donor or their relatives obtained during the process of seeking consent to be respected, where possible."[1]

2. Consent for Storage and Disposal

Legal advice obtained as part of the review of this guidance has confirmed that it is considered best practice for there to be clarity about storage and disposal at the time of the initial consent and donation process. For example, how and when cells would be disposed of, including the actions to be taken when an intended recipient no longer requires the CTPs. Further guidance about the consent requirements is set out within the HTA's Code A[1] and their Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment.[2]

Discussions/documentation at the time of donation should explain the intended purpose of the cell collection and storage with the party providing the cells, whether a 'donor' (when providing the cells for someone else) or a 'patient' (when the individual is to receive their own cells). They shall be informed of the policy for CTP storage, discard, or disposal, including the actions to be taken when an intended recipient no longer requires the CTP[3]. There shall also be a pre-collection written agreement between the storage facility and the designated recipient or the donor defining the length of storage and the circumstances for the disposal of the CTPs.[3]

It is considered that a period of 5 years is a reasonable duration for storage of CTPs. CTPs can be stored beyond this period at the discretion of the transplant physician or transplant programme director (TPD). Conditions under which CTPs are considered unsuitable for clinical use should be explained to the person donating the CTP. A suggested template for a consent form is included in the appendix.

For related allogeneic donors, the consent process and the documentation signed by the donor should be clear that the purpose of the storage is for the treatment of a particular individual. For all allogeneic donors, the consent process should confirm their agreement that decisions around the discard of the CTPs stored will be between the patient and their clinical team without further input from the donor, as discussed below.

For registry (unrelated) allogeneic donors, the responsibility for the discussion about cell storage and discard lies with the donor's registry.

In all cases, a disposal must have approval by the Processing Facility Medical Director or delegate in consultation with the transplant physician or Transplant Programme Director.

3. Discard of CTPs

Clinicians may consider discarding HPC and TC products in the following circumstances:

a) The patient dies.

b) The patient relapses or their disease progresses so that it is clear further treatment with the stored HPC or TC will be ineffective.

c) If the patient becomes ineligible for further treatment using the stored cells by way of poor performance status or developing significant comorbidities.

d) The patient has engrafted and cells were stored as back-up for an allogeneic transplant (for use if the allogeneic cells failed to engraft).

e) Five years have elapsed and multiple TC doses remain in storage such that a number of these are never likely to be used.

f) If the total cell dose of HPCs remaining for the respective patient is less than 0.5 x10^6/kg or viability is below acceptable level required for successful engraftment.*

g) If the HPC or TC are no longer considered suitable for clinical use eg they can no longer be clearly identified, loss of product integrity in storage, or contamination.*

h) If the storage period was discussed and agreed with the person providing the cells and that storage period has ended.**

Where the patient is alive it is recommended that clinicians perform a review of HPC and TC products stored at the end of the period of storage discussed with the patient, followed by an annual review thereafter if products remain in storage.

*In scenarios f and g, a risk assessment must be done and documented in the patient's notes prior to disposal.

**In scenario h, the consent documentation should be checked to confirm the agreement of the person providing the cells.

In all cases, the time, place and method of disposal should be recorded and all documentation relating to storage and discard of stem cells must be kept for a minimum of 30 years from use or disposal as documentation of traceability from donor to recipient[2].

For the avoidance of doubt, CTPs must be disposed of if the person who provided the necessary consent to store the CTPs withdraws their consent for storage. Consent may be withdrawn at any time, whether it is generic or specific. The rights of withdrawal should be discussed at the outset when consent is being sought. The practicalities of withdrawing consent and the implications of doing so should be made clear.[1]

4. Consent and Disposal Scenarios

For all the below sections, if the transplant physician who was looking after the patient at the time of CTP collection is no longer in the same role, the communication about the disposal should instead be with the transplant physician currently responsible for the patient's care or the Transplant Programme Director.

4.1. Where the patient has died

Written permission of the transplant physician should be obtained by the Processing Facility (PF) prior to discard and the Processing Facility Medical Director is responsible for authorisation of discard. Unless a patient dies whilst an inpatient within the transplant physician's hospital, best practice is for two independent sources to be used to verify a patient's death. For example, confirmation of death should be obtained from local records and the national patient database, or local records and the patient's GP.

4.2. Where the patient is alive

The consent process should include the documentation of the wishes of the individual providing the CTPs in relation to their storage, discard, or disposal, including the actions to be taken when an intended recipient no longer requires the CTPs. This includes the option to transfer the CTPs to another storage facility prior to discard if the patient is still alive (as per JACIE standards[3]). However, it is acknowledged that there may be some (historic) situations where there is a lack of clarity and therefore it may be appropriate to subsequently take further steps to clarify the patient's wishes.

Within the following situations (4.2.1 and 4.2.2), contact with the patient is ONLY REQUIRED if their agreement to the disposal has not already been obtained (e.g. during the initial consent process) or it is unknown whether they would want to be given the option to transfer the CTPs to another storage facility

4.2.1. Where Patient is Alive and CTPs are Considered Suitable for Clinical Use

The transplant physician currently responsible for the patient's care or the Transplant Programme Director and the Processing Facility Medical Director are responsible for deciding when CTPs are suitable for clinical use or not.

4.2.1.1. Where a patient can be contacted

Subject to the below, written consent from the patient and the transplant physician must be obtained by the CPF prior to discarding their CTPs. This may be in the form of a letter or signature on a form designed for this purpose, and may have been provided at an earlier time such as at the time of donation. The CPF may accept written permission from the transplant physician alone if they are able to verify in writing that the patient has provided them with written consent.

(See Appendix 1: Pathway for Trying to Obtain Consent for Discard of Cellular Therapy Product and Appendix 3: Template Form Agreement For Disposal)

If the patient does not consent to the proposed disposal, consideration should be given to the reasons for their position by the Processing Facility Medical Director and transplant physician. If, having considered their reasons, the Processing Facility Medical Director and transplant physician are of the view that the CTPs should be disposed of, despite the wishes of the patient, then the decision should be confirmed to the patient, who should be advised that, if they want their CTPs to be retained, they will need to transfer their CTPs to another facility, to be stored at their own expense.

4.2.1.2. Where the patient can no longer be contacted

Reasonable methods to contact the patient should be used by the clinician with responsibility for the patient's transplant treatment or Transplant Programme Director. The national patient database must be accessed to check the patient's address. If registered with a GP, the GP should be contacted to ask if they have contact with the patient, if the patient has moved and if they have any forwarding address. (Appendix 2: template letter C to GP). Clinicians should consider sending at least one letter to the patient by recorded delivery with proof of postage or receipt. If considering using e-mail communication, refer to section 5 below. (See Appendix 1: Pathway for Trying to Obtain Consent for Discard of Cellular Therapy Product, Appendix 2: Template Letters and Appendix 3: Template Form Agreement For Disposal)).

If, despite this, a patient cannot be contacted, their case should be discussed at the transplant centre. This decision about discard should be passed on to the CPF with documentation of the attempts made to contact the patient and reasons for discard. The evidence should be reviewed by the Processing Facility Medical Director before discard.

4.2.2. Where Patient is Alive and CTPs are No Longer Considered Suitable for Clinical Use

Stored cells are considered unsuitable for use if they can no longer be clearly identified. If it is possible to identify the relevant Transplant Programme Director, the Processing Facility Medical Director should discuss the case with them and may authorise the discard of those CTPs.

In some other cases, the Transplant Programme Director or Processing Facility Medical Director may consider the CTPs are not suitable for clinical use. For example:

a) If the total cell dose of HPCs remaining for the respective patient is less than 0.5 x10^6/kg or viability is below acceptable level required for successful engraftment
b) The product integrity has been compromised in storage or the product contaminated

The Processing Facility Medical Director should discuss the case with the Transplant Programme Director. If there is agreement that the CTPs are not suitable for clinical use, the Processing Facility Medical Director and/or Transplant Programme Director should write to the patient informing them of the plan for disposal and the reasons for this. Subject to the following, written permission from the patient and the transplant physician must be obtained by the CPF prior to discarding their CTPs. (Template letter D).

If the patient responds but does not consent to the proposed disposal, consideration should be given to the reasons for their position by the Processing Facility Medical Director and transplant physician. If, having considered the patient's reasons, the Processing Facility Medical Director and transplant physician are of their view that the CTPs should be disposed of, despite the wishes of the patient, then the decision should be confirmed to the patient, who should be asked advised that, if they want their CTPs to be retained, they will need to transfer their CTPs to another facility, to be stored at their own expense.

If the patient does not respond, or cannot be contacted, then the approach discussed within 4.2.1.2 should be used.

4.3 Paediatrics

A child is defined as being under 18 years old and, when a child is competent to reach a decision and give consent, their consent is sufficient to make lawful the removal, storage or use of tissue for the specified scheduled purpose(s) under the Human Tissue (HT) Act[1]. The principle of 'Gillick competence' applies to the assessment of a child's competence to consent in these circumstances. In the Gillick case, the court held that a child was considered competent to give valid consent to a proposed intervention if they had sufficient intelligence and understanding to enable them to fully understand what was involved. Therefore, if a competent child consents to an activity, or activities, covered by the HT Act, that consent carries over into adulthood unless it is withdrawn.

Where a child is either not competent to make a decision, or is unwilling to make a decision, a person who has parental responsibility for the child may consent on their behalf. A person who has parental responsibility will usually, but not always, be the child's parent. The Children Act 1989 is the relevant legislation for establishing who has parental responsibility.

Where there is any dispute between people with parental responsibility, or any doubt as to the child's best interests, advice should be obtained from a trust's legal department or ethical committee. The matter may need to be referred to the court, and subsequently to the HTA.

Where a child has capacity to consent, and agrees to the sharing of their information, it is good practice to consult the person (or people) who have parental responsibility for the child and to involve them in the process of the child making the decision. However, it should be emphasised

that, if the child has capacity to consent, the decision to consent and to share their information must be the child's. It is also essential to make sure that a child has consented voluntarily and has not been unduly influenced by anyone else. If a child does have the maturity or understanding to make a decision about whether to disclose their information to those with parental responsibility for them, you may only disclose information where it is in the best interests of the child.

4.4 Allogeneic stem cell and T-cell donations

As above, the intended purpose of CTPs donated should be explained to the donor at the time of donation. There should be a written agreement defining the length of storage and the circumstances for the disposal of CTPs. The consent process should confirm the donor's agreement that decisions around the discard of the CTPs will be between the patient and their clinical team without further input from the donor.

Many transplant physicians may want to store allogeneic CTP donations including T-cells whilst the recipient remains alive. However, cell discard may be requested in circumstances identified above, or in the case of a second allogeneic transplant using a different donor for the patient. In the latter scenario, the discard of any HPCs or TCs remaining from the first donor may be a sensible precaution to avoid inadvertent infusion of cells from the wrong donor.

As per the above, it is regarded as good practice to seek the consent of the recipient, where possible, before discarding CTPs. Written consent by the transplant physician will generally be required for discard and the transplant physician should verify that the patient has agreed.

5.0 Use of e-mail for Communication with Patients About Discard

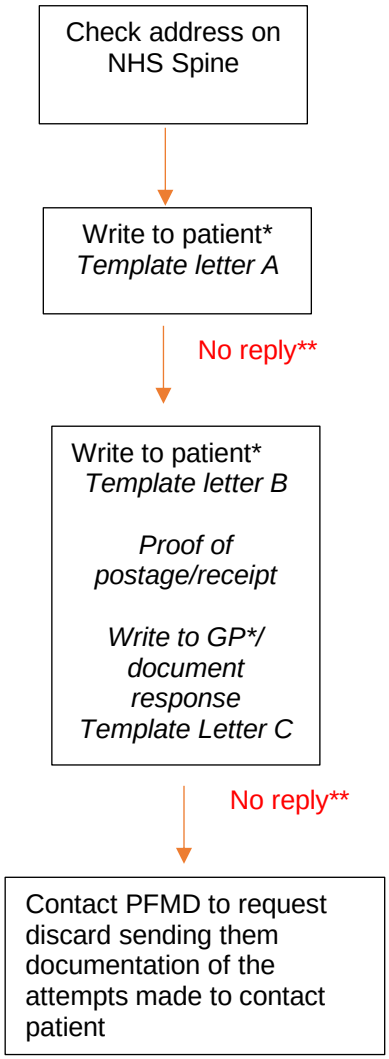
If an e-mail address has been provided, consideration should be given to whether there is clarity about when the email address could be used and whether the use of an email for this purpose is permitted under the trust's own data protection and communication policies. Where the use of e-mail is permitted, the message should be sent by the method approved by the trust with strict regard to patient confidentiality.

6.0 Records and Traceability

In all cases, the time, place and method of disposal should be recorded and all documentation relating to storage and discard of stem cells must be kept for a minimum of 30 years from use or disposal as documentation of traceability from donor to recipient.[2]

APPENDIX 1

Pathway for Trying to Obtain Consent for Discard of Cellular Therapy Products



* Contact must be in writing but sending by post and/or e-mail is acceptable. Clinicians should consider sending at least one letter to the patient by recorded delivery with proof of postage or receipt.
If using e-mail, see section 5 above.
**No reply - suggested minimum period of 4 weeks before progress to next step.

PFMD - Processing Facility Medical Director

APPENDIX 2

TEMPLATE LETTERS

Haematology Department
Address
Phone number
Email

FIRST LETTER – LETTER A

STRICTLY PRIVATE AND CONFIDENTIAL – TO BE OPENED BY ADDRESSEE ONLY
(TO BE MARKED ON ENVELOPE AND IN LETTER)

Date

Dear [Name],

Re: Disposal of stored cells.

As you will recall, you had some of your stem cells or white blood cells such as lymphocytes harvested and stored as part of your previous treatment. The conditions of storage and disposal were discussed with you at the time.

I am writing to inform you of our intention to dispose of these cells. Discarding cells that are no longer needed means that we will maintain our capacity for storing cells for our current patients.

Please can you sign and return the attached form by post or e-mail within 14 days, to confirm that you have received this letter and do not object to the disposal taking place.

Should you wish to arrange for the continued storage of your cells, they will need to be transferred to be stored in a private facility at your own expense.

Please contact us by return to let us know your intention, and then within 28 days confirm the arrangements you have made, as otherwise your cells may be disposed of.

Naturally, if you have any questions regarding this letter please contact us as soon as possible.

Thank you.
Yours sincerely

Blood and Marrow Transplant Physician/Programme Director
BMT e-mail address

Haematology Department
Address
Phone number
Email

SECOND LETTER (LETTER B) Date:

STRICTLY PRIVATE AND CONFIDENTIAL – TO BE OPENED BY ADDRESSEE ONLY
(TO BE MARKED ON ENVELOPE AND IN LETTER)

Dear [Name],

Re: Disposal of stored cells

We wrote to you recently on this matter and have not received a reply. Our apologies if our letters have crossed in the post

As you will recall, you had some of your stem cells or white blood cells such as lymphocytes harvested and stored as part of your previous treatment. The conditions of storage and disposal were discussed with you at the time.

I am writing to inform you of our intention to dispose of these cells. Discarding cells that are no longer needed means that we will maintain our capacity for storing cells for our current patients.

Please sign and return the attached form by post or email to confirm that you have received this letter and do not object to the disposal taking place.

As previously advised, should you wish to arrange for the continued storage of your cells, they will need to be transferred to be stored in a private facility at your own expense. Please contact us within 28 days to inform us of the arrangements you have made.

Please note that **your cells will be disposed of by [date x] if we do not hear from you**, so please ensure you contact us before that date if you would like to arrange a private transfer and continued storage.

Naturally, if you have any questions regarding this letter please contact us by return.

Thank you.
Yours sincerely

Blood and Marrow Transplant Physician/ Programme Director
BMT e-mail address

Haematology Department
Address
Phone number
Email

LETTER TO GP (LETTER C) Date:

STRICTLY PRIVATE AND CONFIDENTIAL – TO BE OPENED BY ADDRESSEE ONLY
(TO BE MARKED ON ENVELOPE AND IN LETTER)

Dear Colleague,

Re: Disposal of stored cells – request for notification of any reasons for lack of patient reply

Patient:
NHS number:
Address:

Some years ago a patient listed at your practice had some of their stem cells or white blood cells harvested and stored as part of their treatment. Conditions of storage and disposal were discussed with them at the time.

The cells are no longer required for their intended purpose and we have written to the patient twice to seek their consent for cell disposal. We have written to them informing them that the cells will be discarded on *** unless we hear that they wish to transfer them into a private storage facility at their own expense.

We have not received a reply from the patient and, before we dispose of the cells, we would like to check with you that there are no circumstances that you are aware of that could affect the patient's ability to reply to us such as:

- the patient having moved: if so, please notify us of a forwarding address if you have one;
- current mental health issues or serious illness.

Please contact me on the e-mail address below should you be aware of any such issues. The cells will be discarded soon after the date above if we do not hear from you or the patient.

Thank you for your help.

Yours sincerely

Blood and Marrow Transplant Physician/Transplant Programme Director
BMT e-mail address

Haematology Department
Address
Phone number
Email

(LETTER D) CELLS NOT SUITABLE FOR CLINICAL USE

Date:

STRICTLY PRIVATE AND CONFIDENTIAL – TO BE OPENED BY ADDRESSEE ONLY
(TO BE MARKED ON ENVELOPE AND IN LETTER)

Dear [Name],

Re: Disposal of stored cells

As you will recall, you had some of your stem cells or white blood cells such as lymphocytes harvested and stored as part of your previous treatment.

I am writing to inform you of our intention to dispose of these cells. Your cells are unsuitable for clinical use because

[Insert reason - give details and explanation]

Discarding cells that are no longer needed or suitable for transplants means that we will maintain our capacity for storing cells for our current patients.

Please sign and return the attached form by post or e-mail, within 14 days, to confirm that you have received this letter and do not object to the disposal taking place.

Should you wish to arrange for the continued storage of your cells, they will need to be transferred to be stored in a private facility at your own expense. Please contact us by return to let us know your intension, and then, within 28 days, confirm the arrangements you have made, as otherwise the cells may be disposed of.

Naturally, if you have any questions regarding this letter please contact us by return.

Thank you.
Yours sincerely

Blood and Marrow Transplant Physician/ Programme Director and/or Processing Facility Medical Director
BMT e-mail address

APPENDIX 3 Template Form - Agreement for Cell Disposal

Agreement for cell disposal

Please complete the following or contact us via details on the accompanying letter if you have any queries:

I agree to my stem cells, bone marrow or white cells such as lymphocytes being removed from the current storage facility and disposed of		
Patient Name & Address (Please print)	**Signature**	**Date**
This section to be completed by transplant physician/programme director once form has been returned.		
Consultant	**Signed**	**Date**

AUTHORS: Rachel Pawson,[1] Sue Davey[2], Jon Smythe[3], Deborah Richardson[4] with advice from Weightmans LLP.[5]

[1]Consultant Haematologist NHSBT; [2]National Operations Manager Cellular and Molecular Therapy NHSBT; [3] National Head of Cellular and Molecular Therapies NHSBT; [4]Consultant Haematologist and Director Wessex Blood and Marrow Transplant & Cellular Therapy, President Elect BSBMTCT. [5]Weightmans LLP Solicitors.

REFERENCES

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