Chapter 11
Adverse Events and Corrective and Preventive Actions

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A very important part of the quality programme is the development of a robust system for reporting, investigating, and resolving errors, accidents, adverse events, biological product deviations, and complaints. Reporting and reviewing adverse events (AE) should not be about "blaming" individuals but about assessing if the process which may be at fault can be improved. All personnel should be encouraged to report anything which affects transplant safety [1].

Centres often used a hospital-based incident reporting system, but it may not be adequate to meet the needs of the HSCT programme. Often, not all AEs were reviewed by the programme director and/or a report was issued to the patient's physician. Other significant problems included those related to donor selection and testing, labelling and process control [2]. The HSCT programme should have a system in place which allows the team to follow the management of any occurrences, to propose preventive actions to avoid the occurrences that will happen in the future and to assess the efficacy of those actions.

Prevention of errors is one of the most important aspects of safety in transplantation. Analysis of potential risk factors associated with the entire range of procedures should be part of the overall transplant programme development. Every procedure should be analysed and potential risk factors identified BEFORE they are implemented. Documentation is important to support the investigation of errors, accidents and adverse events, biological product deviations and complaints because these investigations are frequently retrospective [1]. Fundamentally, one should know *where* errors occur in the processes, *why* they occur and *how* to manage them, e.g.

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does quality system include a near-miss reporting system (prevention of errors) and a corrective actions system when incidents have happened?

Definitions of What to Report

- *Adverse Events*/Serious Adverse Events (SAE): any untoward occurrence associated with the procurement, testing, processing, storage, distribution and application of tissues and cells which might lead to transmission of communicable disease, death or life-threatening, disabling or incapacitating conditions for patients or which might result in or prolong hospitalisation or morbidity[1]
- *Near Miss*: an event which, if not identified in time, would have led to an error, accident or adverse reaction or SAE.
- *Biological Product Deviation (BPD)* [3]: any event associated with the manufacturing of a cellular therapy product, including testing, processing, packing, labelling, or storage, or with the holding for distribution, of a licensed biological product, if that event meets the following criteria:
- Either represents a deviation from current good manufacturing practice (or current good tissue practices), applicable regulations, applicable standards or established specifications that may affect the safety, purity or potency of that product
- Or represents an unexpected or unforeseeable event that may affect the safety, purity or potency of that product:
- Occurs in your facility or another facility under contract with you
- Involves a distributed biological product
- *Complaints*: many institutions have an institution-wide complaints policy in place and the transplant facility will be expected to follow institutional requirements. If there is not a policy in place, then one should be developed and implemented. See Example 5 SOP Adverse.

Investigation, Analysis

While there is no set timeline for investigation, review, and analysis, this should be undertaken quickly so that a potential repeat of the issue is avoided. This aspect should be included in internal specific SOP.

Investigation and analysis in some centres are done through formal review of the entire process to identify where the error has occurred. Collection and processing facilities will have quality incident reporting mechanisms in place and these are shared with the clinical programme where an incident occurred across the linked process, e.g. transportation of the product from collection/processing facility to clinical facility: all parties receive the quality incident report analysis and close the incident. The investigation itself might involve looking at all documentation,

Table 11.1 List of examples templates provided for this section

Number	Title
1.	Types of incident reported
2.	Form to report deviations and near-misses
3.	Registration form for recording complaints, adverse events and near misses
4.	Example of an allogeneic day case inpatient pro forma
5.	SOP adverse event and near-miss reporting

NOTE: This is not a exhaustive list

Example 1 Types of incident reported	
Category	Details
Medication errors	
ABO incompatible blood products	
Malfunction/misuse of equipment	
Contaminated drugs, devices or products provided by facilities	
Labelling of products	
Samples missing or delivered to wrong laboratory	
Results not provided in adequate time	
Signing of drug charts	
Verification of cytotoxic drugs	
Bag damage during thawing of cellular product	
Deviations from policy or procedure if unplanned	
Severe reaction during infusion of cellular product	
Transport issues	
Product found to have positive microbial culture	
Failed engraftment	

training record, having discussions with staff involved and observing the process as it happens.

The forms and reports can be categorised by type, e.g. procedure (e.g. cell reinfusion) and equipment used and then evaluated. This evaluation can be done by specific groups or as part of one of the regular meetings, e.g. quality group. The more frequent events should be prioritised and then resolved (Table 11.1); this can be done by amending policies and procedures, implementing revised worksheets or retraining staff. By doing this, the quality programme is continuously being improved.

Corrective, Preventive Action

Action taken to eliminate the root causes of an existing discrepancy or other undesirable situation to prevent recurrence. As an example, weekly meeting to review with relevant director, quality manager, chief nurse and/or medical

Table 11.2 Example form to report deviations and near-misses; adverse events; occurrences

EXAMPLE TEMPLATE 2 **FORM TO REPORT DEVIATIONS AND NEAR MISSES**
LESSONS FOR IMPROVED CARE SYSTEM Clinical Area: Category: Time: Date: Was there a Deviation from any Policy and/or Standard Operating Procedure : YES/NO What is the Title of the Policy and/or Standard Operating Procedure Deviated from : _____ Job/Role of person completing form: _____
What Happened?
What Immediate Action Was Taken?
What Could Be Changed to Prevent Reoccurrence?
Complete on reverse of form or separate sheet if necessary Was any other type of Incident Form Completed? Reference No.

director and area where incidents occurred. Some centre quality group meetings have errors, accidents and adverse events as part of the standing agenda; group members should include all related facilities. Some centres have separate risk management groups.

The investigation and reporting system is a means of quickly recording near-misses as they occur (Table 11.2). All staff are responsible for completing the forms which ask three simple questions – what happened, what immediate action was taken and what might be done to prevent recurrence of the problem. Each near-miss is categorised, e.g. products, sampling, transport, labelling, infusion, nursing, medical, drugs, pharmacy, result processing. Every day, reports are collected and on a weekly basis, the relevant director, quality manager, head nurse and pharmacy or

other services as required review the documents and discuss corrective actions. Sometimes, thorough investigation is needed and this will involve observations, interviews and complete review of the procedures linked to the near-miss which took place. The results and outcomes are reported back to all departments within the programme and monthly "*Trend*" reports are written to establish whether improvements have been made and are working. Whatever corrective action is taken, e.g. amending an SOP or re-training staff, must be documented, and assessed whether it has achieved the desired impact.

Biological Product Deviations (BPD)

The most common BPDs encountered by clinical programmes involve products with positive microbial cultures or products from ineligible donors. Such products are only used by clinical programmes when evaluation shows that the benefits outweigh the risk to patient if no alternative is available.

In some cases, the relevant information is not known until after the infusion has occurred. Centres are responsible for deciding on whether they will use these products and, if so, under what circumstances. There must be a detailed plan and procedures in place which describe the following:

- Whether a product with positive microbial culture can be used
- In what circumstances its use would be permitted
- How the recipient is protected
- How full record about all aspects of the process is filed

For methods for investigation and review where the BPD was unknown until AFTER the cellular product was infused, centres can also follow the processes above.

Investigation and analysis in some centres are done by reviewing the entire procedure to identify where the contamination might have come from. Collection and processing facilities have quality incident reporting mechanisms in place and these are shared with the clinical programme where an incident occurred across the linked process. All parties receive the quality incident report and meet to analyse and close the incident – the investigation itself might involve looking at all documentation, training records, having discussions with staff involved and observing the process as it happens.

Methods for investigation and review where the BPD was known BEFORE cellular product was infused followed the systems described above. As an example, we present a case whereby a product from an unrelated donor was potentially contaminated due to infection of the donor with a tropical disease. The collection centre advised the transplant centre only on the morning of the collection. In the meantime, at the transplant centre, the recipient was fully conditioned using full intensity conditioning regimens. The reasons behind the potential contamination

were fully investigated and revised processes put into place at the collection facility following close liaison with the clinical facility. The centre had no alternative but to use the product as no other donor was available in time. The centre quickly liaised with specialists at their own centre and external specialists in tropical diseases, and several different samples were sent to different laboratories and results returned within hours prior to cell infusion. All steps were taken to safeguard the recipient (prophylaxis), and the recipient was informed prior to, during and after infusion. Records of the entire process were documented and filed in patient case notes, incident reports, deviations and near-miss reporting with corrective actions clearly shown.

The centre where the BPD occurred BEFORE infusion should investigate the process of collection and infusion with relevant staff and report to medical director of corresponding service, and BPD incidents and reports should be audited regularly. Some centres have separate risk management groups working with all related facilities to develop procedures on how products are managed and reported in accordance with applicable regulations. Policies are in place which cover criteria for release, labelling, notification of recipient, investigation of cause, disposal and timely notification of transplant physician and other related facilities involved. Procedures are in place for dealing with BPD if unknown until infusion has occurred as per JACIE standards [4].

Example 3

Registration form for reporting complaints errors and adverse events		
	Date reported: ……	Quality manager: ……
	Employee ……	Number ……
Informant		
Name:		
Department/address:		
Postcode/place:		
Phone number:		
Nature of complaint or adverse event		
Corrective actions		
Suggestions		
Program director:		
Incident closed: Date:		

Example 4

EXAMPLE TEMPLATE FROM AN ALLOGENEIC INPATIENT DAILY REPORTING PRO-FORMA (PART OF)

SHOWING HOW DEVIATIONS MIGHT BE DOCUMENTED

ALLOGENEIC TRANSPLANT DAILY PRO-FORMA
TO BE COMPLETED IN FULL BY PHYSICIAN ATTENDING AT ALL TIMES OF REVIEW

PATIENT DETAILS

TODAY'S Date :_____ Days Post-Transplant : _____

WEIGHT : _____Kg Performance Status : _____
[Good-ECOG 0-1; Poor - ECOG 2-3]

COMPLETE ON DAY 0 ONLY

Source of Stem Cells : *Bone Marrow / Peripheral Blood / Cord Blood / Other

Ex-Vivo Manipulation : *Yes/No _____ If "Yes": *Negative/Positive Selection

Cells actually infused: $TNC = \frac{\qquad}{\qquad} \times 10^8/Kg\ CD34 = \frac{\qquad}{\qquad} \times 10^6/Kg$

Adverse Events/Reaction to Infusion of Cells: *Yes/No

If "Yes", has an IR1 been completed: *Yes/No

Conditioning Regimen Used

Timetable in Notes YES NO

Was there a Deviation from Planned Timetable YES NO *

If Yes, please give details

_____
_____

WBC x 10^9/L :-	NC x 10^9/L :-	Hb g/dl :-	Platelets x 10^9/L :-
G-CSF	Yes	No	Date Started:
Platelets Needed Today	Yes	No	

Example Template 5

ADVERSE EVENT AND NEAR-MISS REPORTING PROCEDURE HEADINGS
STEM CELL TRANSPLANT PROGRAMME
STANDARD OPERATING PROCEDURE

TITLE: ADVERSE INCIDENT AND NEAR-MISS REPORTING

Code		Issue	No:		No. Of Pages:		Copy No:	

Replaces: Revision :

INDICATIONS FOR PRACTICE
AUTHORISED PERSONNEL/TRAINING REQUIRED (Who is responsible for Reporting and what level of training is required)
PROCEDURE FOLLOWING INCIDENT/NEAR MISS:
What Actions MUST be taken and how is safety assured following an Incident or Near Miss?

WHEN PRINTED
This SOP is for single use only. Please destroy following use.

Effective Date:		Review Date:		Obsolete Date:	
STEM CELL TRANSPLANT PROGRAMME STANDARD OPERATING PROCEDURE					

References

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4. FACT-JACIE international standards for hematopoietic cellular therapy product collection, processing, and administration. 7th ed. FACT-JACIE; 2018.