

December 2020

Dear Valued Customer:

Terumo Blood and Cell Technologies is issuing this letter in response to reports of adverse events related to performing a custom prime with an insufficient number of red blood cells (e.g., diluted RBC units) on low-TBV patients. This letter has two purposes:

1. To inform customers performing a custom prime using red blood cells of the importance of ensuring that the custom prime unit contains enough red blood cells (RBC) or RBC volume (RCV) to adequately fill the extracorporeal circuit of the tubing set. An insufficient RCV may lead to an unintended decrease in patient hematocrit (Hct). This issue may occur due to the use of low-volume and/or diluted custom prime RBC units.
2. To provide additional information to mitigate the risk of using diluted and/or low-volume RBC custom prime units.

The function of a custom prime is to displace the prime saline in the tubing set with donor RBC, plasma, or albumin prior to connecting a patient so that the patient remains isovolemic throughout a procedure. In addition, a certain extracorporeal circuit volume (ECV) and RCV are required in the tubing set to establish and maintain the interface during the procedure. The ECV and RCV required vary and depend on the tubing set, the type of filler used, whether a blood warmer is used on the return line, and the entered patient total blood volume (TBV) and hematocrit (Hct). At the start of a procedure, the system draws in the ECV and RCV necessary, first from the custom prime unit and then from the patient, if necessary, to fill the tubing set and establish the interface. If the custom prime unit used does not contain enough RBC to adequately fill the set (e.g., if it is diluted or low-volume), the additional RCV the system needs will be pulled from the patient. As a result, the patient will experience a decrease in Hct and may be unable to tolerate the procedure.

REASON FOR THE ALERT

Terumo Blood and Cell Technologies has received complaints from three customers of adverse events during continuous mononuclear cell collection (CMNC) procedures when the RBC unit used for the custom prime was diluted to a Hct of less than 30%. These adverse events occurred because of a reduction in the patient's RBC that included exacerbation of anemia.

You are being notified because all Spectra Optia protocols performing a custom prime with RBC can result in RBC loss when the custom prime unit contains an insufficient number of RBC/RCV. IDL protocols present higher risk due to the greater number of RBC required to fill the IDL filler and establish the interface.

Terumo BCT, Inc.

10811 West Collins Ave.
Lakewood, Colorado 80215-4440
USA
USA Phone: 1.877.339.4228
Phone: +1.303.231.4357
Fax: +1.303.542.5215

Terumo BCT Europe N.V.

Europe, Middle East and Africa
Ikaroslaan 41
1930 Zaventem
Belgium
Phone: +32.2.715.0590
Fax: +32.2.721.0770

Terumo BCT Asia Pte. Ltd.

89 Science Park Drive
#04-25 (Lobby B)
The Rutherford
Singapore 118261
Phone: +65.6715.3778
Fax: +65.6774.1419

Terumo BCT Latin America S.A

La Pampa 1517-12th Floor
C1428DZE
Buenos Aires
Argentina
Phone: +54.11.5530.5200
Fax: +54.11.5530.5201

Terumo BCT Japan, Inc.

Tokyo Opera City Tower 49F,
3-20-2, Nishi-Shinjuku,
Shinjuku-ku, Tokyo 163-1450,
Japan
Phone: +81.3.6743.7890
Fax: +81.3.6743.9800

RISK TO THE PATIENT/DONOR

If the operator performs a custom prime with a diluted RBC unit that results in insufficient RBC in the system prior to connecting the patient, an unintended decrease in patient Hct may occur. It is the responsibility of the treating physician to assess the patient's condition and determine the tolerance of the patient to ECV and RCV shifts.

PROCEDURAL CONSIDERATIONS

Terumo Blood and Cell Technologies does not recommend using diluted RBC units to perform a custom prime. The importance of using standard packed RBC units with sufficient volume is highlighted in the examples in Attachment 1.

Consult the treating physician when the custom prime recommendation screen is displayed to determine the appropriate custom prime unit for the patient undergoing treatment.

- For custom prime, Terumo Blood and Cell Technologies recommends using a 300-mL standard packed RBC unit for IDL procedures and a 200-mL standard packed RBC unit for Exchange/Collect procedures. These units should contain a sufficient number of RBC for the respective procedures.
- If you choose to use a diluted RBC unit, refer to Tables 1 and 2 of Attachment 1 to understand the potential RBC loss.

System Operation Summary

The Spectra Optia system prompts operators to consider performing custom prime of the tubing set based on the patient's entered total blood volume (TBV) and Hct when:

- The patient's extracorporeal volume (ECV) is greater than 10% or 15% of their TBV, as configured by the operator.
- The patient's extracorporeal red blood cell volume (ERCV) is greater than 10% or 15% of their red blood cell volume (RCV), as configured by the operator.

The system calculates the patient TBV and RCV required to fill the tubing set and displays the volumes on the custom prime recommendation screen. An example custom prime recommendation screen for a CMNC procedure is shown in Figure 1 below.

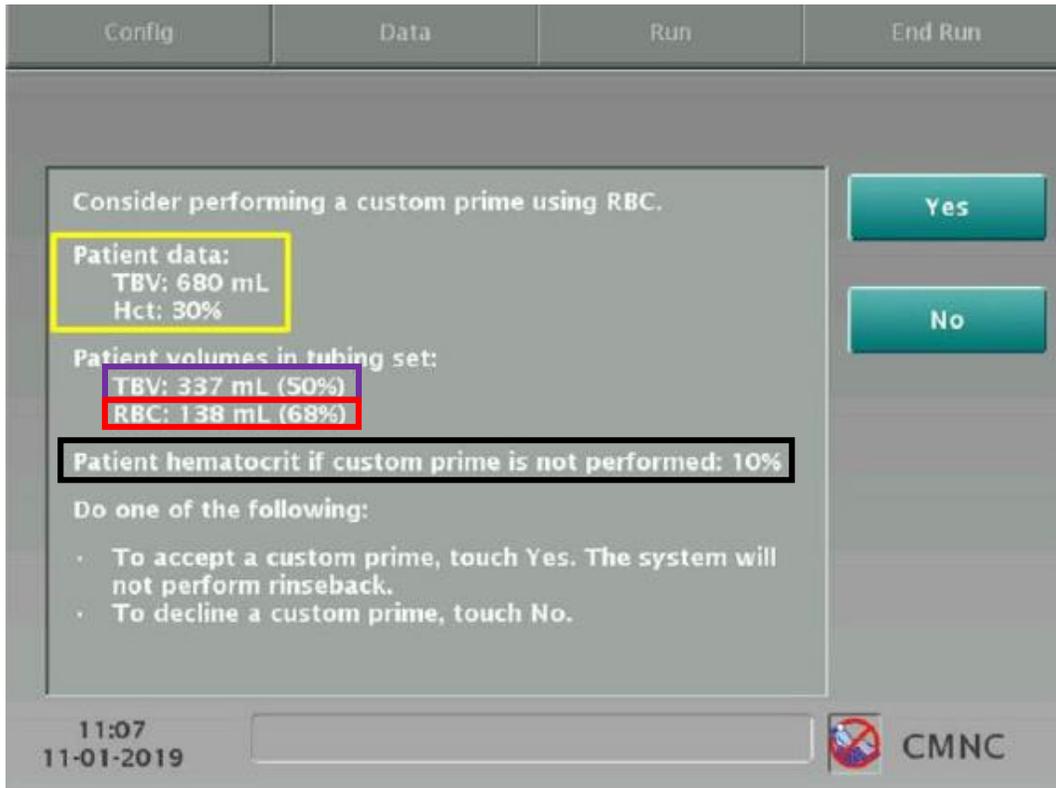


Figure 1: Example custom prime recommendation screen for a CMNC procedure

The screen in this example shows a patient with a TBV of 680 mL and a Hct of 30% (yellow box). Note that the information displayed is specific to the TBV and Hct entered for this patient and will vary for each patient.

- The calculated TBV required in the tubing set is 337 mL, which equals 50% of the patient’s TBV (purple box).
- The calculated RBC volume required in the tubing set is 138 mL, which equals 68% of the patient’s RBC volume (red box). This is also the minimum number of RBC required in the custom prime unit to minimize any change to the patient’s Hct.
- If a custom prime is not performed, the patient’s estimated Hct will be 10% (black box).

For an IDL set, Terumo Blood and Cell Technologies recommends the use of a 300-mL RBC unit with a Hct of 60% to perform a custom prime. If the recommended unit is used, no additional RBC from the patient will be drawn into the tubing set to establish the interface because there is an adequate RCV from the unit (refer to Figure 2 below).

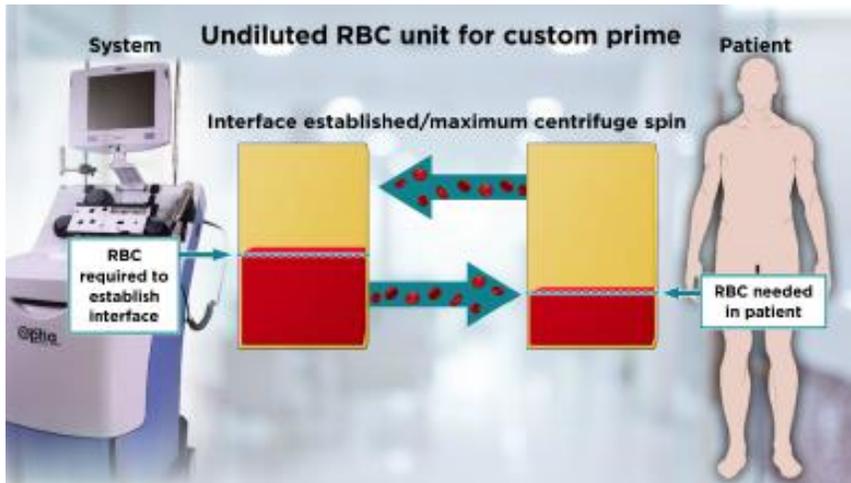


Figure 2: Diagram showing the RBC needed in patient when the interface is established for an undiluted RBC unit

Note: To determine the number of RBC (RCV, also known as RBC volume) in the unit you are using for the custom prime, multiply the unit volume by the unit hematocrit (see Attachment 2).

When a custom prime is completed using a diluted RBC unit, the system retains some of the patient’s RBC in the tubing set, as illustrated in Figure 3 below. As a result, the patient may experience a decrease in Hct and may be unable to tolerate the procedure.

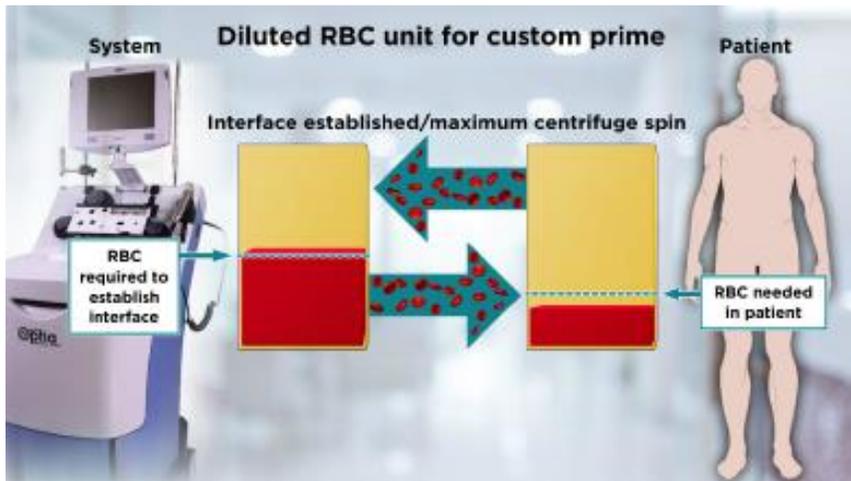


Figure 3: Diagram showing the RBC needed in patient when the interface is established for a diluted RBC unit.

Attachment 1 shows examples of the calculated approximate change in the patient’s Hct immediately after a custom prime using RBC and also shows the calculated approximate change if no custom prime is performed.

ACTIONS BEING TAKEN BY TERUMO BLOOD AND CELL TECHNOLOGIES

1. This safety alert serves to inform you of the potential risk of using a diluted or low-volume RBC unit when performing a custom prime with red blood cells.
2. In addition to this alert, Attachment 2 provides enhanced operator instructions. Please review the attachment and keep a copy with each Spectra Optia operator's manual at your facility.
3. Additional supplemental training specific to performing a custom prime has also been released. This training is currently available in eLearning format in English at www.terumobct.com/elearning under Spectra Optia Apheresis System titled "Spectra Optia Custom Prime eLearning Course."

ACTIONS REQUIRED BY HEALTHCARE PROVIDERS AND DISTRIBUTORS

1. Distribute this notification to all Spectra Optia system users within your organization.
2. Continue to use your Spectra Optia system(s) in accordance with the operator's manual and the operator training materials.
3. Refer to the information provided in the attachments to this letter. When performing a custom prime, consider the information on the Spectra Optia custom prime recommendation screen for the custom prime fluid recommended and the patient's TBV and RBC in the tubing set. When performing a custom prime using RBC, ensure the unit contains a sufficient number of RBC or RBC volume (RCV) to adequately fill the extracorporeal circuit of the tubing set. An insufficient RCV may lead to an unintended decrease in patient Hct.
4. **IMPORTANT:** Complete and fax or email the customer reply form to Terumo Blood and Cell Technologies by **December 31, 2020**. **Your return of the acknowledgement is critical so we can confirm that you have received the Safety Alert.**

CONTACT INFORMATION

Terumo Blood and Cell Technologies is dedicated to providing you with the highest quality support and communicating information regarding our products. If you have any questions, please contact your Terumo Blood and Cell Technologies representative or your regional Customer Support Center:

Sincerely,

Allie Piccoli

Quality Manager

Attachment 1

Examples of the Calculated Approximate Change in the Patient/Donor's Hct Immediately After a Custom Prime Using RBC

Table 1: Approximate, calculated change in patient/donor hematocrit (Hct) immediately after a custom prime of an IDL set using a unit with a 60% Hct vs. a unit with a 30% Hct

Custom Prime With RBC for IDL Set ⁱ				
Patient/Donor		Calculated Approximate Change in Patient/Donor Hct Immediately After Custom Prime		
		300 mL RBC (Undiluted)	300 mL RBC (Diluted)	No Custom Prime
TBV	Hct	<u>Hct 60%ⁱⁱ</u>	<u>Hct 30%ⁱⁱ</u>	
300 mL	15%	+13%	-5%	-13%
	20%	+12%	-6%	-17%
	25%	+11%	-7%	-22%
	30%	+10%	-8%	-26%
	35%	+9%	-9%	-27%
	40%	+8%	-10%	-28%
600 mL	15%	+7%	-3%	-10%
	20%	+7%	-3%	-13%
	25%	+6%	-4%	-14%
	30%	+5%	-5%	-14%
	35%	+5%	-5%	-15%
	40%	+4%	-6%	-15%
1000 mL	15%	4%	-2%	-7%
	20%	+4%	-2%	-8%
	25%	+4%	-3%	-9%
	30%	+3%	-3%	-9%
	35%	+3%	-3%	-9%
	40%	+3%	-4%	-10%
1500 mL	15%	+3%	-1%	-5%
	20%	3%	-1%	-6%
	25%	+3%	-2%	-6%
	30%	+2%	-2%	-6%
	35%	+2%	-2%	-6%
	40%	+2%	-2%	-7%

Custom Prime With RBC for IDL Set ⁱ				
Patient/Donor		Calculated Approximate Change in Patient/Donor Hct Immediately After Custom Prime		
		300 mL RBC (Undiluted)	300 mL RBC (Diluted)	No Custom Prime
TBV	Hct	<u>Hct 60%ⁱⁱ</u>	<u>Hct 30%ⁱⁱ</u>	
2000 mL	15%	+2%	-1%	-4%
	20%	+2%	-1%	-4%
	25%	+2%	-1%	-5%
	30%	+2%	-1%	-5%
	35%	+2%	-2%	-5%
	40%	+1%	-2%	-5%

Table 2: Calculated approximate change in patient/donor Hct immediately after a custom prime of an exchange/collect set using a unit with a 60% Hct vs. a unit with a 30% Hct.

Custom Prime With RBC for Exchange/Collect Set ⁱ				
Patient/Donor		Calculated Approximate Change in Patient/Donor Hct Immediately After Custom Prime		
		200 mL RBC (Undiluted)	200 mL RBC (Diluted)	No Custom Prime
TBV	Hct	<u>Hct 60%ⁱⁱ</u>	<u>Hct 30%ⁱⁱ</u>	
300 mL	15%	+7%	+1%	-11%
	20%	+6%	0%	-12%
	25%	+5%	-1%	-13%
	30%	+4%	-2%	-14%
	35%	+3%	-3%	-15%
	40%	+2%	-4%	-16%
600 mL	15%	+4%	+1%	-6%
	20%	+4%	0%	-7%
	25%	+3%	0%	-7%
	30%	+2%	-1%	-8%
	35%	+2%	-1%	-8%
	40%	+1%	-2%	-9%

Custom Prime With RBC for Exchange/Collect Set ⁱ				
Patient/Donor		Calculated Approximate Change in Patient/Donor Hct Immediately After Custom Prime		
		200 mL RBC (Undiluted)	200 mL RBC (Diluted)	No Custom Prime
TBV	Hct	<u>Hct 60%ⁱⁱ</u>	<u>Hct 30%ⁱⁱ</u>	
1000 mL	15%	+3%	+1%	-4%
	20%	+2%	0%	-4%
	25%	+2%	0%	-5%
	30%	+2%	-1%	-5%
	35%	+1%	-1%	-5%
	40%	+1%	-1%	-6%
1500 mL	15%	+2%	0%	-3%
	20%	+2%	0%	-3%
	25%	+1%	0%	-3%
	30%	+1%	-1%	-3%
	35%	+1%	-1%	-4%
	40%	+1%	-1%	-4%

ⁱThis custom prime table provides a general estimate of the patient hematocrit immediately after a custom prime is performed and the target flow rate has been reached for the procedure selected. This table was generated using a theoretical model which was then tested utilizing laboratory techniques to confirm that the estimates generated were accurate.

The table assumes a unit with a Hct of 60% or 30% and with a large enough volume to completely displace the saline within the channel, cassette, and inlet and return lines. Some additional assumptions include a fixed total blood volume for the patient, a fixed Hct within the channel, and a fixed RBC volume within the cassette and tubing lines based on the patient Hct. Steady state is assumed to occur once the patient's blood has completely filled the set; this occurs after approximately 200 to 300 mL of inlet volume has been processed. The model considers the expansion of the channel and the sequestration of RBC within the channel as the target inlet flow rate is reached at the beginning of the procedure. Because the centrifuge speed begins to increase during the initial "establishing interface" phase, the RBC concentration within the channel may be different than the RBC concentration within the patient. The combination of empirical data and the theoretical model helps to establish the estimates.

ⁱⁱThe Hct of individual CPD-A and AS1 units may vary. An undiluted unit should contain enough RBC despite the differences in Hct.

Attachment 2

Spectra Optia® Apheresis System Custom Prime – Operator’s Manual Addendum

Keep a copy of this attachment with each Spectra Optia operator’s manual at your facility.

The warning statements shown in Figure 1 below will be added to the “Warnings for Use” section in Chapter 1 of the operator’s manual.

- 39 To avoid potential side effects and complications for patients that have a low blood volume (LBV) or a low hematocrit (Hct), the Spectra Optia Apheresis System recommends performing a custom prime of the tubing set for patients whose extracorporeal volume (ECV) is greater than 10% or 15% of their total blood volume (TBV), or if their extracorporeal red blood cell volume (ERCV) is greater than 10% or 15% of their red blood cell volume (RCV). The attending physician should prescribe the appropriate procedural settings for the patient.
- 40 When performing a custom prime using red blood cells (RBC), ensure the unit contains a sufficient number of RBC or RBC volume (RCV) to adequately fill the extracorporeal circuit of the tubing set. An insufficient RCV may lead to an unintended decrease in patient hematocrit. The system will calculate the necessary extracorporeal RCV based on the patient data entered and the procedure being performed.
- 41 Terumo BCT does not recommend the use of a diluted RBC unit to perform a custom prime. A diluted unit may not contain a sufficient number of RBC or RBC volume (RCV) to compensate the patient for the RCV required to adequately fill the extracorporeal circuit of the tubing set. If a diluted unit is used, the patient may experience a decrease in hematocrit and may be unable to tolerate the procedure. The attending physician should assess the patient’s condition and determine the appropriate RCV of the unit used.

Figure Error! Main Document Only.: New warning statements

The new warning statements in Figure 1 and a new Note will be added to the “Selecting and Performing a Custom Prime” section in Chapter 6 of the operator’s manual, as shown in Figure 2 and 3 below.

Selecting the custom prime option

To select the custom prime option, touch the custom prime button until **Yes** appears on the button.

Accepting a custom prime recommendation

After you enter the patient data, the system displays a screen recommending that you consider performing a custom prime. Perform the following steps:

- 1 Review the information on the screen, and confirm that it is correct. The screen also shows the recommended fluid to use, the patient's TBV and RBC volume that is in the tubing set, and what the system predicts the patient's Hct to be if a custom prime is not performed.



Warning: When performing a custom prime using red blood cells (RBC), ensure the unit contains a sufficient number of RBC or RBC volume (RCV) to adequately fill the extracorporeal circuit of the tubing set. An insufficient RCV may lead to an unintended decrease in patient hematocrit. The system will calculate the necessary extracorporeal RCV based on the patient data entered and the procedure being performed.



Warning: Terumo BCT does not recommend the use of a diluted RBC unit to perform a custom prime. A diluted unit may not contain a sufficient number of RBC or RBC volume (RCV) to compensate the patient for the RCV required to adequately fill the extracorporeal circuit of the tubing set. If a diluted unit is used, the patient may experience a decrease in hematocrit and may be unable to tolerate the procedure. The attending physician should assess the patient's condition and determine the appropriate RCV of the unit used.



Note: To determine the number of RBC or RBC volume (RCV) in the unit you are using for the custom prime, multiply the unit volume by the unit hematocrit. For example, a unit of 240 mL with a hematocrit of 60% contains 144 mL of RCV ($240 \times 0.6 = 144$).

- 2 To accept the recommendation, touch **Yes**. To decline the recommendation, touch **No**.

Figure Error! Main Document Only.: New warning statements and new note

Entering data for the custom prime

If you select the custom prime option or accept a custom prime recommendation, the system prompts you to enter data for the custom prime. Perform the following steps:

- 1 Choose one of the following fluid types to use for the custom prime by touching the corresponding button on the screen:

- RBC



Note: To determine the number of RBC or RBC volume (RCV) in the unit you are using for the custom prime, multiply the unit volume by the unit hematocrit. For example, a unit of 240 mL with a hematocrit of 60% contains 144 mL of RCV ($240 \times 0.6 = 144$).

- Plasma
- Albumin

Figure 3: New note for calculating the RBC volume of the RBC custom prime unit