WHOLE BLOOD, LEUKOCYTE REDUCED RECOMMENDATIONS

LEUKOREDUCED WHOLE BLOOD SUBCOMMITTEE

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ACRONYMS

CQI	Continuous Quality Improvement
NAC	National Advisory Committee on Blood and Blood Products
RBC	Red Blood Cell
TRALI	Transfusion-Related Acute Lung Injury

PURPOSE

Using an ethics framework, considering stakeholder inputs, and considering pragmatic supply conditions, this document provides recommendations for the introduction of Whole Blood, Leukocytes Reduced for non-military use in Canada, to ensure equitable access and use to a finite resource.

BACKGROUND

Prior to 1999, whole blood was available as a licensed blood component in Canada. It has not been available since the introduction of universal leukoreduction because the filters used to remove white blood cells also significantly reduced the platelet concentration. Since that time, only component therapy (red blood cells, platelet, plasma) has been available from Canadian Blood Services. However, platelet-preserving leukoreduction filters for whole blood have been developed that now make it possible for Canadian Blood Services to manufacture a leukocyte-reduced whole blood component.

There has been renewed interest in the use of whole blood, particularly for the treatment of acutely bleeding trauma patients. This increased interest in whole blood (either leukoreduced or non-leukoreduced) as a resuscitation component or acutely bleeding trauma patients followed observational studies that found an association between improved hemostasis and fixed ratio transfusion of red cells, plasma, and platelets in trauma patients. Most of the recent use of whole blood has been in the military trauma setting but it has also been adopted by some civilian trauma centres outside Canada, and the use of whole blood has also begun to expand to the management of bleeding patients in non-trauma settings.

Despite the significant enthusiasm for whole blood in trauma and bleeding patients, the evidence regarding clinical effectiveness is limited. Four recent systematic reviews, which identified a total of 21 controlled studies (in which 1951 patients received whole blood), did not demonstrate a benefit for whole blood as compared to standard component therapy.[1-4] Importantly, there were no safety issues identified in the published studies of whole blood.

International studies to assess efficacy and safety in settings where component therapy is not readily available are ongoing (e.g., the pre-hospital setting).

In October 2022, Health Canada approved Whole Blood, Leukocytes Reduced to be manufactured and distributed by Canadian Blood Services. The use of Whole Blood, Leukocytes Reduced is indicated for treatment of patients with clinically significant bleeding and has a low anti-A and anti-B titres (less than a manual equivalent of 1:128).[1] The shelf life of Whole Blood, Leukocytes Reduced is 21 days and the component should be stored at 1-6^{o}C.[5] Whole Blood, Leukocytes Reduced will be collected primarily from group O (Rh positive and/or negative) male donors given the expected use for this component and to mitigate against TRALI risk.

The availability of Whole Blood, Leukocytes Reduced by Canadian Blood Services presents a unique situation with specific challenges. Donor and component requirements for Whole Blood, Leukocytes Reduced will increase pressure on the blood supply, particularly components from

Group O donors. Group O-negative donors are already in high demand; Group O-negative units represent 15% of all RBC units transfused in Canada, but only 3-4% of the potential donor population. The need for low anti-A and Anti-B titres also limits the number of potential donors for the manufacturing of Whole Blood, Leukocytes Reduced.

CONTEXT AND CONSIDERATIONS

- This document is subject to the National Advisory Committee on Blood and Blood Products (NAC) document review policy and is therefore expected to be reviewed three years after its publication date. As new evidence and information becomes available on the use of Whole Blood, Leukocytes Reduced, the NAC will review and adjust the recommendations, as needed, outside the typical review cycle.
- The ultimate aspiration is to have evidence-based clinical guidelines for the use of Whole Blood, Leukocytes Reduced. Should a guideline become available, through the NAC endorsement process, it will be evaluated for appropriateness in the Canadian context.
- Considering the rapid pace of emerging discoveries and insights, it is imperative to regularly reference reputable peer-reviewed sources and remain up to date with peer-reviewed literature in order to inform and enhance local clinical practices.
- When setting local policies, take into consideration the NAC position paper, *Utilization and Inventory Management of Group O RH(D) - Negative Red Cells*, specifically the recommendations for appropriate use of O-negative RBCs for emergency use for individuals of child-bearing potential (45 years of age and younger) when Rh type is unknown, indeterminate, discrepant or compatible units are not available.
- These recommendations should be read in conjunction with the *CAN/CSA-Z902 Blood and blood components* and applicable regulations in the Food and Drugs Act, and regulations promulgated thereunder.
- To achieve thorough reporting, it is advisable to assess the adequacy of local processes for adverse reaction reporting for Whole Blood, Leukocytes Reduced, particularly when its usage may extend to new environments, such as prehospital settings, beyond clinical study contexts. Another option worth considering is conducting audits to evaluate the effectiveness of these reporting processes.

RECOMMENDATIONS

The following recommendations were developed by consensus among NAC Leukoreduced Whole Blood Subcommittee members informed by the ethical framework (see Appendix A) and stakeholder inputs (see Appendix B). They are endorsed by the National Advisory Committee on Blood and Blood Products and the Canadian Blood Services-Provincial/Territorial Blood Liaison Committee.

1. It is recommended that the Canadian military-only restriction for use of Whole Blood, Leukocytes Reduced should be lifted.*
*Subsequent recommendations apply

Benefit may arise from increasing access to Whole Blood, Leukocytes Reduced in specific contexts. There is currently evidence supporting the safety of whole blood as a therapeutic intervention, although it falls short of establishing the superiority of Whole Blood, Leukocytes Reduced in terms of clinical efficacy compared to component therapy.

It is worth noting that access to this therapy may face restrictions imposed by Canadian Blood Services during times of shortage or increased demand.

Transfusion services that employ the use of Whole Blood, Leukocytes Reduced are expected to have specific local guidelines and protocols in place regarding clinical indications and monitoring practices. These measures ensure that the therapy is used appropriately and effectively in accordance with local healthcare standards and needs.

2. It is recommended that the demand for blood components shall be satisfied over Whole Blood, Leukocytes Reduced in the absence of clear evidence of benefit of Whole Blood, Leukocytes Reduced on patient outcomes.

In times of supply shortages, it is crucial for Canadian Blood Services to make prudent decisions regarding component manufacturing choices to ensure that supplies remain at acceptable levels.

It is essential to identify and prioritize the specific contexts in which the benefits of using Whole Blood, Leukocytes Reduced are applicable, all while giving due consideration to any potential risks that may arise. This comprehensive approach ensures that the clinical decision-making process is informed and cautious, especially in situations of supply constraints.

In the broader context of the national blood system, it becomes evident that achieving optimal utilization of blood components, including Whole Blood, Leukocytes Reduced, hinges on a collective commitment from all stakeholders. Solidarity among all involved parties is indispensable in ensuring the efficient and responsible utilization of these valuable resources.

3. It is recommended that the distribution of Whole Blood, Leukocytes Reduced in non-military settings be done through a formal process.

To ensure responsible stewardship and the efficient and equitable use of Whole Blood, Leukocytes Reduced, it is essential to establish transparent criteria that adapt to evolving evidence. This stewardship entails careful consideration of various factors, including the different contexts in which whole blood may be utilized and the potential for a high outdate rate.

System-level equity is a key consideration, particularly in terms of access to blood components across a spectrum of hospital-based and pre-hospital scenarios. Priority allocation for Whole Blood, Leukocytes Reduced, should be given to trials and studies in settings where limited or no access to other blood components exist. This approach prioritizes fairness and equal access across healthcare systems, considering diverse care settings.

Currently, the priority list for Whole Blood, Leukocytes Reduced use includes the Canadian Armed Forces, clinical trials or studies followed by other civilian uses. A formal process for the distribution approach will be developed. These priorities reflect an approach aimed at optimizing Whole Blood, Leukocytes Reduced utilization while maintaining fairness and transparency in the decision-making for allocation and distribution. Transparency is fundamental to fostering system-level accountability and trust.

4. It is recommended that Whole Blood, Leukocytes Reduced should not be limited to group O RhD negative.

In the ethical framework, considerations of benefit, safety, and evidence-informed practice are paramount. It is anticipated that whole blood will be most frequently used in high acuity clinical scenarios (out-of-hospital care, trauma) where the recipient ABO/Rh is unknown and for which group O whole blood will be most appropriate. Manufacturing capability for both Whole Blood, Leukocytes Reduced of RhD positive and negative is recommended to ensure flexibility in the supply to meet demands. Additionally, non-group O blood groups, may be more appropriate for non-acute situations, such as planned procedures like cardiovascular surgery.

To make informed decisions about the appropriate use of blood components, healthcare professionals can refer to the circular of information for Whole Blood, Leukoreduced which provides essential details regarding component characteristics.

5. Transfusion services should not issue Whole Blood, Leukocytes Reduced only to prevent outdating.

Transfusion services are advised against the practice of issuing Whole Blood, Leukocytes Reduced solely for the purpose of preventing outdating. This recommendation stems from the limited evidence on the use of whole blood as a treatment in the absence of active bleeding. The recommendation is in line with the NAC position paper, *Utilization and Inventory Management of Group O RH(D)- Negative Red Cells*.

While data on the utilization of whole blood outside of scenarios involving active bleeding is limited, it is deemed unacceptable to employ it solely to avoid expiration when an ABO/Rh identical red blood cell unit is readily available in the local inventory.

This practice distorts the data on the actual demand for whole blood, making it challenging to accurately assess and allocate resources based on genuine clinical needs. It is imperative that transfusion services prioritize the ethical principles of patient safety and evidence-informed decision-making when considering the use of Whole Blood, Leukocytes Reduced, ensuring that these valuable resources are employed judiciously and in line with established clinical guidelines.

6. Transfusion services shall report on Whole Blood, Leukocytes Reduced disposition to Canadian Blood Services.

Reporting on the disposition of Whole Blood, Leukocytes Reduced is in alignment with ethical principles of accountability, responsiveness, and transparency. Consistent with existing reporting on other blood components, transfusion services shall report on the disposition of Whole Blood, Leukocytes Reduced, including transfused, in-date discards, and outdates. Regular reviews of the demand for and disposition of Whole Blood, Leukocytes Reduced are expected to be in place with consideration of continuous improvement measures.

Sharing comprehensive information regarding component disposition is fundamental. Such transparency contributes to a better understanding of the system's operations and enhances public trust, ensuring that ethical principles and efficient practices are upheld in the utilization of Whole Blood, Leukocytes Reduced.

7. It is recommended that any further processing, aliquoting and transformation of Whole Blood, Leukocytes Reduced shall be in accordance with the *Blood Regulations*.

Any further manipulation of Whole Blood, Leukocytes Reduced should be performed in accordance with the *Blood Regulations*. It is recommended that clarification be sought from Health Canada regarding the definition of “processing” in relation to separating out components from Whole Blood, Leukocyte Reduced (e.g., RBCs, plasma) post-distribution by Canadian Blood Services.

8. The clinical community is strongly encouraged to share information on the outcomes of using Whole Blood, Leukocytes Reduced.

It is imperative that the clinical community actively share information regarding the outcomes of using Whole Blood, Leukocyte Reduced thereby contributing to the scientific literature, and fostering evidence-informed practice. This holds especially true in critical areas such as cardiovascular surgery, obstetrics, care for premature and/or neonatal patients, vascular surgery, trauma, and pre-hospital care.

Moreover, beyond formal studies clinical teams could embark on post-implementation reviews, continuous monitoring, and sharing of data on outcomes. Such information enhances the collective understanding of real-world uses, reinforcing accountability and transparency while demonstrating commitment to optimizing the use of Whole Blood, Leukocytes Reduced for the benefit of patients and the healthcare system.

TABLE 1. SUMMARY OF RECOMMENDATIONS FOR USE OF WHOLE BLOOD, LEUKOREDUCED

1. It is recommended that the Canadian military-only restriction for use of Whole Blood, Leukocytes Reduced should be lifted. **Subsequent recommendations apply*
2. It is recommended that the demand for blood components shall be satisfied over Whole Blood, Leukocytes Reduced in the absence of clear evidence of benefit of Whole Blood, Leukocytes Reduced on patient outcomes.
3. It is recommended that the distribution of Whole Blood, Leukocytes Reduced in non-military settings be done through a formal process.
4. It is recommended that Whole Blood, Leukocytes Reduced should not be limited to group O RhD negative.
5. Transfusion services should not issue Whole Blood, Leukocytes Reduced only to prevent outdating.
6. Transfusion services shall report on Whole Blood, Leukocytes Reduced disposition to Canadian Blood Services.
7. It is recommended that any further processing, aliquoting and transformation of Whole Blood, Leukocytes Reduced shall be in accordance with the *Blood Regulations*.
8. The clinical community is strongly encouraged to share information on the outcomes of using Whole Blood, Leukocytes Reduced.

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APPENDIX A: ETHICAL FRAMEWORK

Relevant values and principles:

The values and principles described below in alphabetical order are meant to: a) facilitate the process of making recommendations about the use of Whole Blood, Leukocytes Reduced (at the outset and ongoing); and b) serve as a basis for determining whether and when these recommendations may need to be revised or updated in relation to the anticipated or desired goals for the use of Whole Blood, Leukocytes Reduced. While each value and principle are described separately, all are employed together to weigh and balance the assessment of different options for recommendations related to the use of Whole Blood, Leukocytes Reduced.

Substantive:

Benefit (beneficence, "do good") – no conclusive superior benefit(s) have been demonstrated in the summation of current literature (as of April 2023) for the use Whole Blood, Leukocytes Reduced. Accordingly, for the purposes of this framework, benefit can be understood as that which arises from having access to Whole Blood, Leukocytes Reduced for use in specific contexts.

- The contexts within which this understanding of benefit applies need to be identified and ranked with due consideration, as appropriate, of any possible negative consequences of using Whole Blood, Leukocytes Reduced (to the extent that this evidence is available).
- Over time, as new evidence emerges about the use of Whole Blood, Leukocytes Reduced and other blood components or alternatives are developed, this may mean that the definition of benefit and recommendations about the use of Whole Blood, Leukocytes Reduced may need to be revised (see "Responsiveness" below).

Evidence-informed – in considering use in different contexts, evidence (current and future) will contribute to identifying which patient conditions and care-settings are most appropriate for its use.

Safety – Whole Blood, Leukocytes Reduced should not be used indiscriminately nor without regard to safety and the other identified relevant considerations.

Security of supply – The availability and use of Whole Blood, Leukocytes Reduced should not materially impact the supply of other blood components. This is particularly important to ensure when the main benefits of Whole Blood, Leukocytes Reduced may be setting-specific (i.e., about access) rather than outcome-specific.

Solidarity – highlights that "we're all in this together". With respect to the national blood system, making the best use of blood components, including Whole Blood, Leukocytes Reduced, entails that we each do our part (at the highest level of governance and oversight through to patient care) to ensure that this happens.

Stewardship – to make the most efficient and fair use of Whole Blood, Leukocytes Reduced. This includes due consideration of factors such as different contexts for the use of Whole Blood, Leukocytes Reduced and the possible high outdate rate for this component. It is also important to consider the use of Whole Blood, Leukocytes Reduced within the larger context of the overall use of different blood components as part of making any recommendations.

System-level equity – for the purposes of Whole Blood, Leukocytes Reduced, equity is understood here in relation to considerations of **access** to blood components in and across a range of hospital-based and pre-hospital circumstances. Priority for the use of Whole Blood, Leukocytes Reduced will be given to circumstances in which there is (more) limited or no access to other blood components. This focus on system-level equity is meant to support consideration of overall access to blood components in different care settings and whether/when the use of Whole Blood, Leukocytes Reduced may be appropriate to recommend in light of this broader context.

Process:

Accountability – as Whole Blood, Leukocytes Reduced is expanded beyond military use, it is appropriate in making any recommendations to consider whether and what continuous quality improvement (CQI) systems will be in place to help ensure timely identification of any issues, concerns, or need for adjustment to the parameters defined for its use.

Collaboration – working well together includes respecting and listening to different perspectives, being open to revising one's perspective, and jointly sharing in developing recommendations.

Responsiveness – in accordance with input from partners in the blood system (e.g., hospital and pre-hospital), CQI systems, and/or new evidence regarding the use of Whole Blood, Leukocytes Reduced, this information will be used to determine whether there is a need to adjust the parameters for its use as well as the definition of benefit above. This includes possible changes within the broader context of blood components, and their use, across the country.

Transparency – contributing to accountability, transparency focuses on the sharing of information about how recommendations and decisions are made and implemented. Sharing this type of information can contribute to understanding and trust.

APPENDIX B: STAKEHOLDER ENGAGEMENT APPROACH

The NAC LRWB Subcommittee gathered stakeholder feedback and perspectives on the civilian utilization of whole blood through the following activities:

- 1:1 interviews with nominated representatives from organizations that have been identified by the NAC LRWB Subcommittee Working Group;
- NAC LRWB Subcommittee membership from organizations identified by the Subcommittee; and,
- Online survey on the CBS Stakeholder Engagement website (Engage+).

Engagement will be facilitated through the use of a structured questionnaire that determines respondents':

- Role of the respondent and their associated medical organization in the medical system;
- Current opinions on appropriate, acceptable and inappropriate applications of whole blood for identified applications;
- Views on the presence, absence, or anticipated publication of clinical evidence; and,
- Anticipated usage of whole blood if available.

Responses gathered through 1:1 interviews will be recorded electronically using the survey Word document or similar means while online engagement was automatically recorded, summarized and electronically submitted to the CBS Portfolio Management and Stakeholder Engagement teams for review. Subcommittee members providing LRWB engagement were encouraged to utilize the survey Word document to ensure all relevant information was captured and responses could be compared. Following the completion of the engagement process, all responses were collected, analysed, and presented to the NAC LRWB Subcommittee through a sub-team consisting of Drs. Andrew Shih, Susan Nahirniak, Johnathan Mack and Cyrus Eduljee.

Societies and Associations for Contact

- Canadian Prehospital and Transport Transfusion Network
- Canadian Association of Emergency Physicians
- Trauma Association of Canada
- Canadian Association of General Surgeons
- Canadian Anesthesiologists' Society
- Canadian Critical Care Society
- Canadian Cardiovascular Society
- Canadian Society of Cardiac Surgeons
- Society of Obstetricians and Gynecologists of Canada
- Canadian Pediatric Society
- Canadian Pediatric Anesthesia Association
- Society of Rural Physicians of Canada

All groups were contacted by the sub-team noted above for a 1:1 interview. The online survey was leveraged for groups unable to participate in the interviews or for sharing with their membership for additional engagement.

Engage+ Website and 1:1 Interviews

To obtain the perspectives of healthcare professionals practicing in settings that may benefit from leukoreduced whole blood, a webpage on Engage+ was developed specifically to host the whole blood questionnaire for stakeholders that wish to respond electronically and to broaden engagement beyond those contacted directly. The survey was open to all users, and respondents were encouraged, but not required, to pre-register on the site.

Between February and April 2023, 13 interviews were completed, and three respondents completed the online survey. One-on-one interviews sorted by organization are summarized in Table 1 below.

Trauma (9), Massive Hemorrhage Protocol use (8), out-of-hospital care (8), cardiovascular surgery (8), and research (7) were most commonly listed as the most appropriate clinical circumstances for LRWB use. Five respondents indicated that the most appropriate circumstance was not established. When asked which clinical circumstance should be prioritized, responses were divided equally between Trauma (6) and out-of-hospital (6), followed by Research (3), and one respondent feeling that a single clinical circumstance for priority had not been established.

Clinical situations that would be considered acceptable for LRWB use to avoid component expiration (but not necessarily a priority situation) included trauma (8), cardiovascular surgery (4), obstetrics (3), vascular surgery (3), and GI bleeding (1).

Transfusion of unnecessary blood components (compared with component therapy) and component waste were the most commonly stated drawbacks to LRWB in Canada (7), followed by about the potential impact on conventional component inventory (6), possibility for adverse reactions (5), need for broad education on the component (5), and concerns about ABO/Rh incompatibility (5).

A need for additional evidence regarding the potential benefits and risks of LRWB was emphasized by a majority of respondents during the one-on-one interviews. A need for a structured plan to monitor and evaluate the use and clinical benefits of LRWB was also commonly mentioned.

Organization	Interviews
Trauma Association of Canada*	0
Canadian Cardiovascular Society	0
Canadian Anesthesiologists' Society	3
Canadian Pediatric Society*	0
Canadian Association of Emergency Physicians*	0
Canadian Prehospital and Transport Transfusion Network	4
Canadian Critical Care Society	1
Society of Obstetricians and Gynecologists of Canada	0
Canadian Society of Cardiac Surgeons	0
Canadian Association of General Surgeons	1
Canadian Pediatric Anesthesia Association	4
Society of Rural Physicians of Canada	0

Table 1: Organizations contacted for one-on-one interviews and number of completed interviews.
*Representation on NAC LRWB Subcommittee.

In the province of Québec, a Google Forms survey was developed using the same questions as the ROC whole blood questionnaire designed for stakeholders.

The survey was distributed to the various associations through their newsletters, which are sent to all their members, as well as to all blood bank medical directors in Québec. Associations are listed in table 2 below.

Between July and September 2023, a total of 51 respondents completed the online survey. However, 6 responses were excluded from the analysis as they addressed leucodepletion instead of whole blood. In total, 45 answers were further analysed.

Trauma and Massive Haemorrhage Protocol use (33 / 73%) were most commonly listed as the most appropriate clinical circumstances for LRWB (leukoreduced Whole Blood) use. Six respondents indicated that the most appropriate circumstance was not established, and six respondents stated that they didn't have an answer to the question. When asked which clinical circumstance should be prioritized, the majority responded Trauma/ Massive Haemorrhage Trauma (14), followed by Massive Haemorrhage (13). Surgical bleeding (1) and post-partum haemorrhage (1) were also mentioned.

Respondents also identified various clinical situations in which LRWB use would be acceptable to prevent blood component expiration. These included trauma (24), cardiovascular surgery (5), obstetrics (9), post-surgery (5), and GI bleeding (1). Additionally, some respondents mentioned that whole blood should be used in high-volume transfusion centres to decrease/minimize the risk of wastage.

The most mentioned drawback of LRWB in Québec was component waste (16), followed by transfusion of unnecessary blood components (9) when compared to component therapy. Eight respondents were unable to provide a drawback. Other drawbacks mentioned were pressure on O donors (4) and the cost of manufacturing whole blood (4).

Finally, the most frequent comment received from participants was the lack of general information on LRWB to enable them to make a recommendation.

Association	Response
Québec Association of Emergency Physicians	9
Québec Association of Anesthesiologists	4
Québec Association of General Surgeons	1
Association des spécialistes en médecine interne du Québec	22
L'Association des Obstétriciens et Gynécologues de Québec	3
L'Association des médecins hématologues et oncologues du Québec	6

Table 2: Associations contacted to promote the online survey and number of responses.

Public Review of final draft

For a two-week period in mid-October 2023, the final draft of the recommendations was published on the Engage+ Website. It was also disseminated to the initial stakeholders and broadly circulated across all jurisdictions via the NAC members' network. Minor suggested changes were integrated into the final recommendations.