TABLE OF CONTENTS

Application for Inclusion of Whole Blood/Red Blood Cells as a Medicine in the WHO Model List of Essential Medicines

1. Summary Statement of the proposal for inclusion

Applicants propose that Whole Blood and Red Blood Cells be included in the WHO Model List of Essential Medicines (WHO EML and WHO EMLc). The applicants believe that the addition of Whole Blood and Red Blood Cells to the EML will serve as an important tool to support the sixty-third World Health Assembly (WHA 63) resolution on Availability, safety and quality of blood products (WHA63.12) Geneva, 17-21 May 2010).

WHO has defined "medicine" as "any substance or pharmaceutical product for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient." (http://www.who.int/medicines/areas/quality_safety/regulation_legislation/blue_book/en/index.html) Blood meets the generic definition of a substance used to treat, mitigate, or prevent disease. Whole Blood and Red Blood Cells differ from the small molecule medicines in their inherent biological variability unit to unit. Blood components are biologicals that share many attributes with those medicines.

Although blood transfusion evolved initially as a medical practice or service, transfused literally from the vein of the donor to the vein of the patient, two important developments significantly changed the nature of blood transfusion. First, the identification by Karl Landsteiner in 1901 of the major blood groups and the subsequent introduction of compatibility testing by agglutination facilitated the characterization of blood units. Second, the introduction of anticoagulant solutions that enabled storage (that is, banking) of blood in lieu of donor to patient transfusion, made it possible to think of whole blood and its labile components as products that must meet defined standards. Today, the anticoagulant solutions and the process and quality controls inherent in blood collection, processing and distribution, render blood transfusion less like a "transplant," and more like the administration of a medicine.

Technical and regulatory developments during the past half century have also led to the "manufacture" of blood to ensure purity, potency and safety. The blood donor is qualified as the source of raw material by rigorous selection and testing standards. Units undergo in-process quarantine, quality control to ensure that reagents, equipment and methods perform as expected, temperature monitoring, batch release after suitability determination, and labeling for identity, content, expiration date and intended use. Once issued, blood components are subject to standards for traceability. Like other medicines, blood has defined medical indications, recognized adverse effects, and may be administered only by a doctor's order or prescription.

Today, the anticoagulant and preservative solutions and the process and quality controls inherent in blood collection, processing and distribution, render blood transfusion less like a "transplant," and more like the administration of a medicine. Moreover, the units of whole blood and red blood cells transfused contain, in addition to the blood itself, pharmaceuticals that require licensure, specifically anticoagulants (e.g., citrate), nutrients (e.g., dextrose), buffers (e.g., phosphate), and preservatives (e.g., adenine).

Many countries regulate blood and its components as a "medicine." As an example, in the United States, blood has been regulated as a medicine under the Food and Drug Cosmetic Act since 1938 and in 1972 became subject to the regulations applicable to the manufacturing of pharmaceutical drugs. In Canada, blood components are subject to the Food and Drugs Act and drugs are defined as "any substance or mixture of substances... (a) for use in the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms...or (b) restoring, correcting or modifying functions in human beings...." Additional information on existing national regulations is included in Section 13.

Whole Blood and Red Blood Cells cannot be characterized by an exact chemical formula or a purified bulk substance, as they are biologic materials that can vary due to the inherent biological variations among individual blood donors. However, the development and adoption of internationally recognized standards for whole blood and blood components have evolved over time and these products now share fundamental features with medicines. Specifically, although the composition of units cannot be uniform, maximal standardization is achieved through process controls that are comparable to medicine preparation processes. Raw material qualification through the application of donor selection criteria and testing, in-process quarantine, batch release of each blood unit to ensure that all donor and product requirements are met before release, quality control procedures to ensure that reagents, equipment and methods perform as expected, expiration dating and traceability requirements are all part of blood and medicine preparation. Like most medicines, blood can only be administered on a physician's order or prescription. Blood components also have well defined medical indications and contraindications. And each unit is specifically labeled for identity, content (including additive medicines such as anticoagulants, nutrients, buffers and preservative solutions) and intended use. Examples of Whole Blood and Red Blood Cell standards are included in the references section of the application.

The inclusion of Whole Blood and Red Blood Cells on the WHO EML accomplishes a number of critical objectives in blood safety and efficacy, in furtherance of WHA Resolution 63.12.

- Placement on the WHO EML brings heightened awareness of the need for blood in every country and of the role of blood in protecting the public health.

- Placement on the WHO EML underscores the government's responsibility for ensuring financially sustainable funding and support for a safe and adequate supply of blood that is accessible to patients in need and creates a favorable environment for governments to support a National Regulatory Authority specifically pertinent to blood, and to invest in infrastructure, systems and governance for blood establishments.

- Placement on the WHO EML underscores the need for effective and efficient procurement systems to provide equipment, supplies and reagents to collect, process, test, store and transport blood.

- Placement on the WHO EML emphasizes the need to ensure that blood is cost-effective, affordable AND available.

- Placement on the WHO EML underscores the importance of, and enables appropriate regulatory oversight of, blood collection, processing, testing, storage and distribution to ensure the safety and quality of blood and the safety and efficacy of blood transfusion.

  Assessment criteria for national blood regulatory systems. World Health Organization, 2012. Website link: http://www.who.int/entity/bloodproducts/NationalBloodRegSystems.pdf

  Recommendations of the 15th International Conference of Drug Regulatory Authorities (ICDRA), Tallinn, 21 – 26 October 2012. In press, WHO Drug Information 2013 (http://www.who.int/medicines/publications/druginformation/en/index.html). http://www.who.int/entity/bloodproducts/publications/GMP_Bloodestablishments.pdf

- Placement on the EML brings visibility to the need for adherence to universally accepted and evidence-based clinical guidelines.

2. The focal point in WHO supporting the application is the Expert Committee on Biological Standardization.

The concept of Whole Blood and Red Blood Cells as essential medicines has been endorsed by the WHO Expert Committee on Biological Standardization—blood products and in vitro diagnostics track, the WHO Blood Regulators Network and the International Conference of Drug Regulatory Authorities at their respective meetings in October 2012. The WHO Department serving as secretariat for the above Committees, network and forum is the Department of Essential Medicines and Health Products. The focal person is Dr. Ana Padilla, Programme Manager Blood Products and Related Biologicals.

3. The organizations supporting the application include the following:

AABB (formerly the American Association of Blood Banks), the American Red Cross, Canadian Blood Services and the International Society of Blood Transfusion.

4. The International Nonproprietary Name (INN, generic name) of the medicine

The generic names are Whole Blood and Red Blood Cells. No international nonproprietary name (INN) is assigned to natural human blood products (http://www.who.int/entity/medicines/services/inn/BioRev2011.pdf).

5. Formulation proposed for inclusion; including adult and pediatric doses.

Adults:

Whole Blood (from which Red Blood Cells can be derived) can be collected in containers of different sizes, ranging from 300 to 500 mL for adults.

Each container is considered to be a unit. A single dose of Whole Blood is generally considered to be one unit of Whole Blood and, with respect to Red Blood Cells, the Red Blood Cells that are separated from one unit of Whole Blood. Each unit of Whole Blood and each unit of Red Blood Cells holds approximately 147-278 mg of iron, most in the form of hemoglobin. The number of doses (units) required is dependent on the underlying condition of the patient.

Requirements relating to blood donor qualifications, approved containers and approved preservatives and anticoagulants vary from country to country, although product formulations generally conform to the characteristiscs stated above. This is because composition of the product is standardized through control of donor screening, blood collection, testing, processing (product manufacture), storage and administration processes.

Pediatrics:

Whole Blood and Red Blood Cells derived from a single collection in one plastic container (300-500mL) can be separated in a closed system into multiple pediatric packs of approximately 50-80mL each. For neonates and infants, Whole Blood and Red Blood Cells can also be removed from the single collection set or a pediatric-sized container by syringe for transfusion.

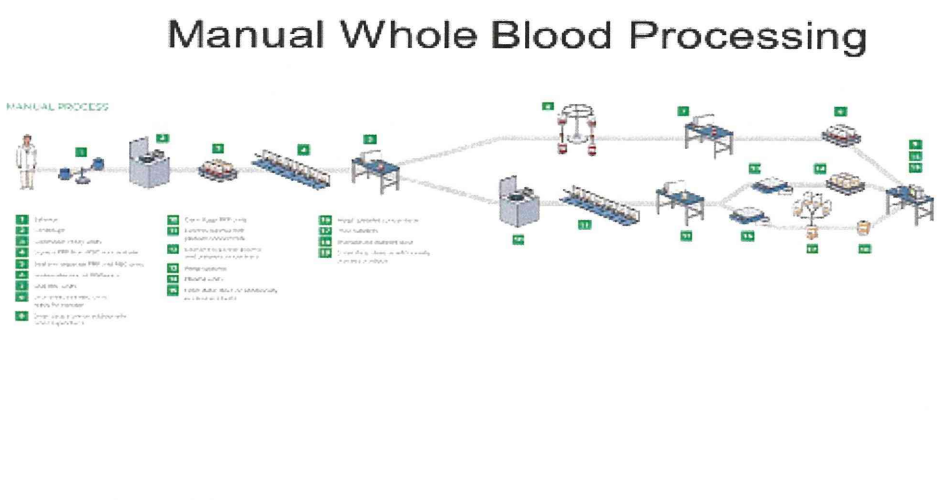
A pediatric dose can be either administered as one pediatric unit or alternatively 10-15 mLs per Kilogram, depending on the practice in the country and/or the availability of pediatric collection sets. (Roseff 2006)

6. International availability –sources of possible manufacturers.

First, a review of what is involved in "manufacture" of Whole Blood and Red Blood Cells may be in order. Whole blood is collected by venipuncture from a suitable volunteer. Suitability determination involves two aspects: safety of the volunteer in donating and safety to the patient to be transfused. This is determined by assessing the volunteer's vital signs, and by questioning the individual regarding past and current health, as well as behaviors associated with risk of infections that can be transmitted

by transfusion. Along with several tubes of blood for testing, a pre-determined volume of whole blood is collected into a sterile, single-use, plastic collection set already containing anticoagulant and preservatives, buffer and nutrients. For Whole Blood and Red Blood Cells production, the collected blood is then cooled and refrigerated, and initially kept in quarantine. For Red Blood Cells production, the Whole Blood is placed in a refrigerated centrifuge, to sediment the red blood cells to the bottom of the collection set. The centrifuged whole blood is then placed in a plasma expressor, which expresses the supernatant plasma (or platelet-rich plasma (PRP) if a platelet component is to also be produced) through integrally connected tubing into a separate container. This separated plasma must then be frozen promptly; it can either be used later for direct transfusion, or used as starting material for further manufacture into plasma derivatives, e.g., immunoglobulin or anti-hemophilic factor. (Note that these two plasma derivatives are already on WHO's EML, and that they can also use whole blood as the source material.)

The Whole Blood, or Red Blood Cells and Plasma, must remain in quarantine, until results of testing of the associated tubes of blood has been completed and found acceptable. These tests include, at least, ABO and Rh type, hepatitis B, hepatitis C and HIV. Records of processing must be reviewed to ensure all procedures have been followed correctly and that test results are acceptable, before the Whole Blood or Red Cell Unit can be released from quarantine and labeled as acceptable for distribution. Temperature during storage and transport (distribution to the transfusion facility) must be maintained within a strict cold range. One example of manual whole blood processing is depicted in the following schematic:



Used with permission of Terumo BCT

All of these activities must be performed in conformance with Good Manufacturing Practices, which include quality control, quality assurance, and traceability. Adherence to GMPs is much more likely to occur where there is strict, pertinent regulation by a National Regulatory Authority. This lesson has been learned the hard way in developing countries, as awareness of HIV transmission by transfusion became apparent in the 1980's. This development precipitated government regulators in developed countries, most notably in the US, to apply more strict regulations initially developed solely for the medical pharmaceutical industry, to blood establishments, inspecting these facilities more frequently, and even imposing enforcement actions including product seizures, plant closures, fines and prison sentences for responsible employees. These measures have resulted in a much better practices in blood establishments, a safer blood supply, and have helped decrease the potential risk for subsequent other transfusion risks (e.g., HCV WNV, vCJD).

WHO has developed guidelines in this regard:

WHO requirements for the collection, processing and quality control of blood, blood components and plasma derivatives. In: WHO Expert Committee on Biological Standardization (1994) http://www.who.int/entity/bloodproducts/publications/WHO_TRS_840A2.pdf; and

WHO good manufacturing practices for blood establishments. In WHO Expert Committee on Specifications for Pharmacetucial Preparations. 2011. http://www.who.int/entity/blood_products/ppublications/GMP_Bloodestablishments.pdf.

Whole Blood and Red Blood Cells can be and are manufactured in virtually every country in the world and are generally available, although the safety, quality and availability of these products is currently variable. Blood components are manufactured by blood establishments in their respective countries, generally under the coordination of a national programme. The World Health Assembly Resolution 63.12 on availability, safety and quality of blood products, adopted in May 2012 (http://apps.who.int/gb/ebwha/pdf_files/WHA63-REC1/WHA63_REC1-en.pdf), urged Member States to "update their national regulations ...in order to ensure that regulatory control in the area of Quality and safety of blood products across the entire transfusion chain meets internationally recognized standards." WHO is requested to guide Member States to meet these standards.

The WHO Global Database on Blood Safety (based on 2008 data) establishes that about 8000 centers in 159 countries reported that they collect blood. A total of 164 countries, representing 92% of the world's population, responded to the survey. Whole Blood and all blood components, including Red Blood Cells, are not generally shipped cross national borders, with the exception of rare units and in cases of emergency. This application is not intended to, and does not contemplate, a change in that practice.

This application to include Whole Blood and Red Blood Cells in the WHO Model Lists of Essential Medicines is also not intended to change, and will not require that any country change, its reliance on volunteer non remunerated blood donors.

7. **Listing is requested as an individual medicine or as an example of a therapeutic group.**

Not applicable.

8. **Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)**

While there are not good validated data on the uses of Whole Blood and Red Blood Cells in developed and developing countries, the ninety countries (20 high-income, 45 middle-income and 25 low income) contributing data to the 2011 WHO Global Database on Blood Safety reported that more than 9 million patients received blood transfusions during the reported year (based on 2008 data or the latest data available since 2006 if 2008 data were not available.) The same database revealed that there is significant variation in the age distribution of transfused patients between developed and developing countries, as there are different underlying disease burdens. Specifically, in high-income countries, transfusion was reported as most commonly used for supportive care in cardiovascular and transplant surgery, massive trauma and therapy for solid and hematological malignancies. In low-and middle-income countries transfusion was reported as used more often in pregnancy-related complications and severe childhood anemia.

Several smaller studies in both developed and developing countries reinforce the vailidity of these conclusions. In the United States, the National Blood Collection and Utilization Survey, funded by the U.S. Department of Health and Human Services and conducted by AABB, concluded that more that 15 million units of Red Blood Cells were transfused in the U.S. in 2008. The two highest uses of Red Blood Cells were attributed to General Medicine (28.2% of all Red Blood Cells transfused in the U.S.) and Surgery, including general, orthopedic and cardiac surgeries, combined (23.6%), although these calculations could have been confounded by the use of self-defined categories by reporting hospitals. Whole Blood transfusions in the U.S., as a percentage of total transfusions, are significantly fewer in the U.S. than in the developing world (0.03% of total transfusions, or approximately 5,000 units). (NBCUS 2010)

In the developing world, there are few studies to validate the uses of Red Blood Cells reported in the 2011 WHO Global Database on Blood Safety Summary report, although there are ongoing efforts to estimate blood needs.

The Pan American Health Organization (PAHO) has proposed a methodology and instrument to assess the underlying needs for blood in the region. Both the methodology and the instrument were validated by 20 professionals in 9 hospitals in Nicaragua. The proposed methodology recommended that patients who receive transfusions be assigned to one of the following four groups:

- Clinical conditions, such as anemias and diseases of the blood; leukemias and lymphomas; non-hematologic malignant tumors , and anemia associated with gastrointestinal bleeding
- Surgical interventions, such as cardiovascular surgery, injury, poisoning and other consequences of external causes; orthopedics and general surgery;
- Obstetric and gynecological conditions; and
- Neonatal Conditions (PAHO Estimating Blood Needs)

These groups were further elaborated as follows:

Clinical conditions
Anemias and diseases of the blood
Leukemias and lymphomas
Non-hematologic malignant tumors (clinical needs)
Anemia associated with gastrointestinal bleeding

Surgical interventions
Cardiovascular surgery
Injury, poisoning, and other consequences of external causes
Orthopedics
General surgery

Obstetric and gynecological conditions
Obstetrics
Gynecology

Neonatal conditions

The results of the validation survey conducted in Nicaragua are summarized as follows:

TABLE A6. Percentage of transfusion recipients by clinical condition, Nicaragua, 2009

Clinical condition	Patients admitted	Number (and percentage) of transfusion recipients	Units/ patient
Neoplasms	83	23 (28)	2.39
Hemorrhages of the digestive system	256	42 (16)	1.38
Diseases of the blood	236	91 (38)	1.39
Interventions in the gastrointestinal system	40	13 (33)	1.07
Injury and other consequences of external causes	317	19 (5)	1.84
Interventions in the musculoskeletal system	87	8 (9)	1.37
Interventions in the genitourinary system	155	18 (12)	1.11
Pregnancy, childbirth, and the puerperium	2.094	147 (7)	1.25
Perinatal period and congenital malformations	381	8 (2)	1.00

In addition, the following observations were noted:

- In the general hospitals included in the validation exercise, women received a higher percentage of blood transfusions than men, although the male/female ratio of transfusions varied from hospital to hospital.
- Patients aged 15-64 received the highest percentage of transfusion, with variations from hospital to hospital
- The percentage of transfusion recipients and number of units used depended on the clinical condition (Centano Mena RA, Sanchez Lopez ML).
- The need for Red Blood Cells is related to the prevalent conditions in the community, the age structure of the population, and patterns of blood use.

The overall conclusion was that, given the number of underlying conditions for which Whole Blood and Red Blood Cells are given, the target population for receipt of these therapies will be different in each country.

In addition to these data, in section 10, the effectiveness of Red Blood Cell transfusion in the treatment of thalassemia and sickle cell anemia is described. These hereditary condtions, which can require major (lifelong) Red Blood Cell use vary in prevalence geographically (both often in parallel with the prevalence of malaria).

The "thalassemia belt" includes the Mediterranean shores, the Arabian peninsula, and especially Thailand, Cambodia, and southern China, where prevalence can range from 2.5% to 15%.

In tropical Africa, the heterozygous sickle cell trait can be found in up to 20% to 40% in some areas. Sickle cell disease is also prevalent in the Mediterranean area, the Middle East, India and Southeast Asia.

9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills).

Dosage regimens and the duration of treatment depend on the underlying reasons for Red Blood Cell transfusion. Red Blood Cells are transfused to correct anemia in patients. There are multiple Clinical Guidelines that govern the appropriate use of Red Blood Cells. See section 9 references.

No special diagnostic or treatment facilities are needed, however, special capabilities of the transfusing entity include cold storage (and effective cold chains) and ABO compatibility testing. Moreover, clinician education on the appropriate use of blood, including Whole Blood and Red Blood Cells and education and training on the proper administration of Whole Blood and Red Blood Cells is required if blood is to be transfused safely. Inclusion of Whole Blood and Red Blood Cells in the WHO Model Essential Medicines List will draw much needed attention to these needs and emphasize to national regulatory authorities and health ministries that such guidelines should be audited and enforced.

10. Summary of comparative effectiveness in a variety of clinical settings:

Hemoglobin binds oxygen in the lungs at high oxygen tension and releases oxygen in the tissues at low oxygen tension. The hemoglobin oxygen binding characteristics are determined by the hemoglobin molecule itself as well as by factors such as pH, carbon dioxide concentration, and 2-3 DPG levels. Oxygen delivery is the product of the arterial oxygen content and the cardiac output, and tissue oxygen consumption is the fraction of the arterial oxygen content which is extracted by the tissues.

In otherwise healthy patients, compensatory mechanisms occur to preserve tissue oxygen consumption in the face of increasingly severe anemia. Decreased blood viscosity and sympathetic stimulation lead to increased cardiac output both by increasing stroke volume and heart rate. Blood flow is redistributed so that preference is given to critical organs such as the heart and brain. In addition, oxygen extraction in the tissues is increased, allowing tissue oxygen consumption to be maintained at acceptable level in spite of decreases in oxygen delivery. However, there are limits to the ability of the body to compensate.

<u>Red Blood Cell transfusion to increase oxygen delivery to the tissues</u>

In most clinical situations where red cells are transfused, the rationale is to increase the oxygen carrying capacity of the blood, ultimately to deliver additional oxygen to the tissues. Severe anemia may occur as a result of a variety of clinical conditions including major surgery, trauma, obstetrical hemorrhage, malaria, gastrointestinal bleeding, or various hematological disorders, clinical situations which occur both in the developed and underdeveloped world. The need for transfusion is

particularly important if the patient is so anemic that the body's ability to compensate for the lack of red cells has been exceeded. Unfortunately there is no gold standard against which to mesure when this point has been reached. The patient's hemoglobin level is the simplest gauge of the severity of the anemia, but it is only a reliable indicator of tissue hypoxia when it is very low (< 5-6 g/dL). Patients who are otherwise healthy can often tolerate chronic hemoglobin levels as low as 5-6 gm/dL, whereas patients with comorbidities such as cardiovascular disease may exhibit signs and symptoms of tissue oxygen deprivation and may require transfusion at much higher hemoglobin levels. The mortality of untransfused anemic patients with underlying cardiovascular disease is substantially higher than patients without cardiovascular disease (Carson 1996). Modest inadequate tissue oxygenation may be indicated by symptoms such as weakness and exertional fatigue, symptoms which do not usually prompt transfusion. However patients with more serious indicators of inadequate oxygen delivery, such as dyspnea, tachypnea, or mental status changes should be transfused.

Blood transfusion has been used for nearly 100 years to treat patients with life-threatening anemia and severe tissue hypoxia. The usefulness of transfusion in these settings is so clearly evident that controlled trials to determine efficacy would be considered unethical and have not been performed. A few observational studies have supported the need for transfusion in severe anemia. In a study of transfusion of children with severe anemia in Kenya (English 2002), most of whom had malaria but for whom blood was not always available, transfusion resulted in a marked and statistically significant improvement in mortality. Eighty nine percent (8/9) of non-transfused children with prostration, respiratory distress, and a hemoglobin less than 4g/dL died, whereas only 23% (15/65) of those transfused died. A retrospective observational study of 1928 surgical patients who refused transfusion for religious reasons demonstrated a direct relationship between the degree of anemia and mortality with 28% of the deaths being attributed to anemia (Carson 1996).

The benefit of transfusion for patients with less severe anemia, usually defined as hemoglobin levels between 7 and 10 g/dL, has been the subject of a number of controlled studies. Hebert et al (Hebert 1999) randomized 838 intensive care unit patients to a restrictive or liberal transfusion strategy. Patients in the liberal arm were transfused for hemoglobin levels > 10g/dL and the hemoglobin level maintained at the 10-12 g/dL level. Patients in the restrictive arm were transfused when the hemoglobin was < 7 g/dL to maintain hemoglobin levels between 7 and 9 g/dL. No statistically significant differences were seen between the groups in terms of mortality or the severity of organ dysfunction. Carson et al (Carson 2011) studied 2016 patients whose hemoglobin level was <10g/dL after hip fracture surgery. All patients were over the age of 50 and had a history of either cardiovascular disease or cardiovascular risk factors. The patients were randomized to a liberal (transfuse for hemoglobin < 10g/dL) or restrictive (transfuse for hemoglobin < 8g/dL or for symptoms of anemia) strategy. No differences were seen between the groups in terms of mortality or ability to walk across the room without assistance 60 days after the surgery. The results indicated no advantage to the liberal transfusion strategy and suggested that it was reasonable to limit transfusion, in the absence of symptoms of anemia, to those patients with hemoglobin < 8 g/dL. A Cochrane Summary of the existing literature evaluated 19 controlled studies comparing restrictive vs liberal transfusion strategies involving 6264 patients. Restrictive strategies were not associated with an increase in patient adverse events such as cardiovascular incidents or mortality. (Carson 2012).

Whether these same findings will apply to other groups of patients such as those with significant cardiovascular disease, acute coronary syndromes, severe trauma, or those undergoing hematopoietic stem cell transplantation has yet to be determined.

Red Blood Cell transfusion unrelated to oxygen delivery

Transfusion in Thalassemia

Severe thalassemia is characterized by massive ineffective erythropoiesis with a hyperplastic marrow, skeletal abnormalities with a typical facies, hepatosplenomegaly, stunted growth, increased iron absorption resulting in iron overload, cardiomegaly with eventual cardiac failure, and early death. As with other disorders, patients with severe anemia due to thalassemia do require transfusion to maintain minimal physical activity, and this was the primary role of transfusion in this disorder until the 1960s. At that time it was observed that hypertransfusion, transfusing patients to much higher hematocrit levels than necessary to maintain basic oxygen delivery, had a profound effect on the clinical manifestations of the disease. With this transfusion strategy, designed to suppress increased erythropoiesis and its effects, several investigators demonstrated that bony abnormalities could be avoided, cardiomegaly and cardiac failure avoided or even reversed, hepatosplenomegaly minimized, iron absorption reduced, and normal growth patterns achieved. Wolman (Woman 1964) first observed that children who had been more heavily transfused were taller and had less hepatosplenomegaly, bony abnormalities, and cardiac problems. Piomelli (Piomelli 1969) described four patients transfused to maintain hemoglobin levels of 10-12 g/dL. No patient developed either the typical bone changes or marked hepatosplenomegaly. A follow-up study (Piomelli 1974) confirmed that patients who were maintained at a hematocrit of at least 28% from the time of diagnosis did not develop the typical facies, experienced regression of any bone changes within one year and regression of cardiomegaly within six months. Kattamis (Kattamis 1970) studied 74 patients and demonstrated that growth rates depended on the level of hemoglobin concentration achieved; patients maintained at a hemoglobin level of > 8 g/dL had a normal growth rates. Subsequent studies and debates have focused on the optimal target hemoglobin levels. Transfusion to even higher levels (hemoglobin >14) has been advocated; this strategy does provide additional suppression of erythropoiesis but at the expense of additional iron overload, and most experts do not recommend it. Cazzola et al (Cazzola 1997) studied 32 patients on chelation therapy who had been maintained at an average pre-transfusion hemoglobin level of 11.3 g/dL and examined the effect of switching to an average pre-transfusion hemoglobin level of 9.4. They noted a substantial decrease in red cell requirements, decreased iron accumulation, an increase in spontaneous prepubertal development (indicating less iron toxicity), and levels of erythroid activity not exceeding 2-3 times the normal level.

The result of these developments was that the treatment of thalassemia was dramatically changed, at least in those parts of the world where transfusion and chelation therapy was available. The downside of this approach was that additional iron accumulation occurred as a result of the frequent transfusions, a problem that can be successfully handled by modern iron chelation therapy.

Red Blood Cell Transfusion in Sickle Cell Disease

Transfusion is used in patients with severe anemia for the same reason that it's used in other patients, to increase the oxygen carrying capacity of the blood. But it is also often used for an entirely different purpose, to decrease the fraction of sickle red cells. One of the devastating consequences of sickle cell disease is the high incidence of stroke and other cerebrovascular events. Approximately 6-10% of sickle cell patients experience strokes, and once a patient has had a stroke, there is a 60-70% chance that additional strokes will occur, usually within the next year or two. It was observed by in the 1970's that the incidence of stroke could be reduced by regular transfusion (Lusher 1976). Twenty one patients with previous strokes were transfused regularly for up to six years with no recurrent events. The one patient who did have a recurrent stroke was not transfused regularly. Russell et al studied 30 patients with a history of stroke (Russell 1984). Twenty three of the patients had multiple cerebral vessel abnormalities by angiography; these patients were placed on a transfusion program designed to keep the hemoglobin concentration between 12-14 g/dL and the % hemoglobin S < 30%. The result was marked decrease in the incidence of recurrent stroke when compared to historical controls (10% vs 90%). Wilimas et al showed that if such a transfusion program is discontinued after 1-2 years, the incidence of recurrent stroke rapidly returns to the previous high level (Wilimas 1980).

Adams et al measured transcranial Doppler (TCD) ultrasonography (a measure of cerebral blood flow) in 190 children (age 3-18) with sickle cell disease and followed them for an average 29 months. Twenty three had an abnormal TCD; there were six strokes in this group of patients. One hundred sixty seven had normal TCD; only one of these had a stroke in the follow-up period. These results indicated a 44 fold increase in risk for those patients with abnormal TCD Adams 1992). These observations were followed by the SOP trial, a randomized controlled trial designed to prevent initial strokes by instituting chronic transfusion programs in patients with an abnormal TCD (Adams 1998). 130 patients were randomized to receive either standard care or chronic transfusion to keep the Hemoglobin S concentration less than 30%. With a mean follow-up of 19.6 months, there were 10 strokes in the control group and 1 in the transfused group. This study was stopped early because the efficacy of transfusion therapy had been proven. Follow-up analysis of the STOP study showed that compliance with the aggressive transfusion strategy also significantly lowered hospitalization rates for acute chest syndrome and for pain crises (Miller 2001) as well as resulting in improved growth rates (Wang 2005). A follow-up study, STOP II, was designed to determine whether the transfusion programs could be curtailed after a certain time. Children eligible for this study were those who had completed at least 30 months of transfusion therapy and whose Doppler measurements had revered to normal. Seventy nine patients were randomized to continue transfusion or to stop. The end points were stroke or conversion to a high risk Doppler pattern. Of the 41 patients randomized to no transfusion, 2 had strokes and 14 converted to high risk Doppler pattern. Neither of these end points was seen in the 389 patients randomized to continue transfusion (Adams 2008). The study was stopped short of the intended 100 patients.

In summary, these studies have indicated that transfusion plays an important and ever-increasing role in the optimal treatment of patients with sickle cell anemia. Much of the effect seems related to replacing sickle cells with normal cells, a rationale quite different than merely supplying additional oxygen carrying capacity. While some of the claimed effects of transfusion will need additional

confirmation, the role of transfusion in preventing the catastrophic neurologic complications have been clearly demonstrated.

DATA CHARTS

Severe Childhood Anemia in Africa

Comparison: Death

Study	Transfused	Not transfused	Risk ratio	p
English (2002)	15/65	8/9	0.26	0.0002

Transfusion Trigger

Study: Hebert (1999)

Comparison	Restrictive	Liberal	Risk ratio	Mean difference	p
30 day mortality	78/418	98/420	0.80	—	0.11
Hospital mortality	93/418	118/420	0.79	—	0.05
Hosp LOS	34.8	35.5	—	-0.7	0.58
ICU LOS	11.0	11.5	—	-0.5	0.53
Cardiac event	55/418	88/420	0.63	—	< 0.01
Pulmonary edema	22/418	45/420	0.49	—	< 0.01
Pneumonia	87/418	86/420	1.02	—	0.92

Study: Carson (2011)

Comparison	Restrictive	Liberal	Risk ratio★	Mean difference★
30 day mortality	43/1009	52/1007	0.83	—
Hospital mortality	14/1003	20/999	0.70	—
Hosp LOS	4.0	3.7	—	0.3
30 d inability to walk	481/1000	459/995	1.04	—
Cardiac events	76/1009	52/1007	1.46	—
Pulmonary edema	35/1009	27/1007	1.29	—
Stroke/TIA	3/1009	8/1007	0.37	—
Pneumonia	48/1009	60/1007	0.8	—
Thromboembolism	8/1009	12/1007	0.67	—
Infection	56/1009	74/1007	0.76	—

★ No differences are statistically significant

Thalassemia

Analysis 1.

Study: Kattamis (1970)

Hgb Levels maintainted (g/dL)	<6	6-8	>8
Height centile	7.0	22.2	55.9
Weight centile	9.9	22.5	61.2

Analysis 2.
Study: Cazzola (1997)

Comparison	Hgb 9.4	Hgb 11.3	p
Transfusion requirement (ml/kg/yr)	104	137	0.0001
Ferritin (ug/L)	816	2448	0.0001
Erythropoiesis (xN)	2.4	—	—

Sickle Cell Disease

Analysis 1.
Comparison: Stroke/TIA/Silent Infarct

Study	Transfused	Not transfused	Risk ratio	p
Lusher (1976)	0/21	—	—	—
Russell (1984)	2/20	9/10	0.11	0.001
Wilimas (1980)	0/10	7/10	0.00	—
Adams (1998)	1/63	11/67	0.10	0.001
Adams (2005)★	0/38	16/41	0.00	0.001
Abboud (2011)	3/37	11/40	0.29	0.03

★ Development of stroke or high risk transcranial Doppler pattern
Analysis 2.

Comparison: Acute Chest Syndrome

Study	Transfused	Not transfused	Risk ratio	p
Miller (2001)	2.2/100 pt yrs	15.7/100 pt yrs	0.14	0.0001
Styles (2006)	0/7	5/8	0.0	0.026

Analysis 3.

Comparison: Pain crises

Study	Transfused	Not transfused	Risk ratio	p
Miller (2001)	9.7/100 pt yrs	27.1/100 pt yrs	0.36	0.014

11. Summary of comparative evidence on safety:

11.1 Identification of variation in safety due to health systems and patient factors.

Because blood and blood components such as Red Blood Cells are produced in countries with differing levels of health care practitioner, laboratory, and technical education, training and skills, the safety of Whole Blood and Red Blood Cell transfusions may differ from country to country. One purpose in requesting placement of Whole Blood and Red

Blood Cells on the WHO Model List of Essential Medicines is to standardize the processes followed to make and use this medicine, so that the product itself becomes more standardized (and safer). Another purpose is to encourage the standardization of clinical guidelines, to improve patient care.

Moreover, because blood is a biological product and there is inherent variability in the source of the product, the safety of Whole Blood and Red Blood Cells will vary from country to country depending upon the transfusion transmissible disease incidence and prevalence rates in the local blood donor population, as well as upon the specific test kits (e.g., HIV and hepatitis) used to identify collected units at risk. The safety and quality of the biological product is, therefore, dependent on quality assurance processes (including GMPs) that ensure the quality and safety of the final biological product to be transfused into patients. Finally, there may be variations among countries in patient factors and the quality of healthcare that could affect the safety of transfusion.

11.2 Summary of comparative safety against comparators

There have been no controlled clinical trials of Whole Blood and Red Blood Cells against placebo. Today, such a trial would be unethical given that the historical experience in transfusing Whole Blood goes back to the 19th century and modern blood transfusion, including the identification of major blood groups and the development of anticoagulant-preservative solutions, began during World War I.

There is no known medicine that currently substitutes for Whole Blood and Red Blood Cells. Worldwide, seven clinical trials involving blood substitutes have been halted because of unacceptable toxicity to the recipients. (Natanson 2008)

The sole known replacement for Whole blood and Red Blood Cell transfusion, when appropriately administered, is erythropoietin. Erythropoeitin, and its analogues, were initially approved for treatment of the anemia of chronic renal disease, and used specifically in patients on long-term hemodialysis. The National Institute for Health and Clinical Excellence (NICE) in England has since issued guidance which states that epoetin alfa, epoetin beta and darbepoetin alfa (erythropoietin analogues) should be used only in limited circumstances. Specifically, they are not recommended for routine use in the management of cancer treatment-induced anaemia, but may be considered in combination with intravenous iron:

- for the management of cancer treatment-induced anaemia in women receiving platinum-based chemotherapy for ovarian cancer who have symptomatic anaemia and a haemoglobin level of 8 g/100 ml or lower

• for people who cannot be given blood transfusions and who have profound cancer treatment-related anaemia that is likely to have an impact on survival.

Recent data have shown that the adverse affects associated with the administration of erythropoietin are much greater than originally reported. As a consequence, erythropoietin is currently used more judiciously than when it was first licensed and is not widely used as a substitute for Red Blood Cells, particularly not in developing countries where its high cost is also a great impediment to use.

The safety profile of Whole Blood and Red Blood Cells is widely acknowledged to represent a favorable therapeutic index. Because transfusion has been carried out so widely and for so many years, the adverse events are well-recognized and and have been carefully quantified and studied. Recognition of adverse events has resulted in continuous improvements in safety and manufacture. Whole Blood and Red Blood Cells are arguably the most carefully studied medications and remain widely used precisely because the benefits so clearly outweigh the risks.

12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutics group:

12.1 Range of costs of the proposed medicine.

For a number of valid safety, as well as logistical reasons, Whole Blood and Red Blood Cell preparations are collected, processed, distributed and transfused within the same country. With the exceptions of rare units and emergency requests for blood, blood is not routinely shipped between countries.

In most countries that collect, test, process and distribute blood, the cost of a unit of Whole Blood and Red Blood Cells is based on a cost recovery model, i.e., the costs required to collect, test, process and distribute Whole Blood and Red Blood Cells. For that reason, costs vary from country to country. For purposes of determining and comparing the costs of blood, however, two things are important:

1. The comparative costs of Whole Blood and Red Blood Cells must be based on the collection of a unit of Whole Blood, rather than the individual component costs. Basing the comparative cost of Whole Blood and Red Blood Cells on the costs of collecting a unit of blood is important as methods of allocating costs among components can vary from country to country.

2. The cost comparisons must be based on an understanding of all costs associated with the production of a unit of blood. WHO has developed materials that both assist in

understanding the costs of providing blood, as well as a template for determining the cost in an individual country. (WHO Costing Blood Transfusion Services, Version 2001). That publication includes the following description of costs to be included in determining the cost of a unit of blood.

Chart 1

BLOOD TRANSFUSION SERVICE
Costs Allocated by Activity

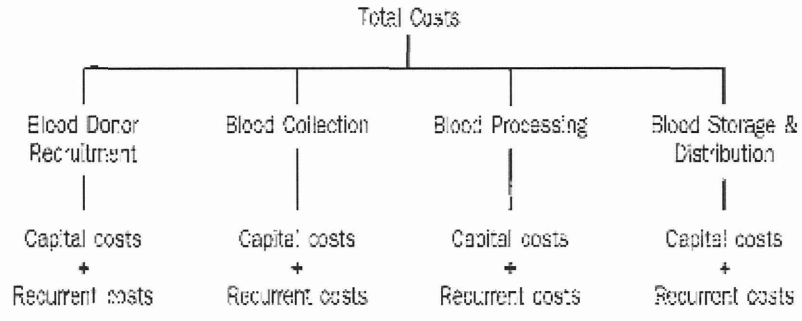
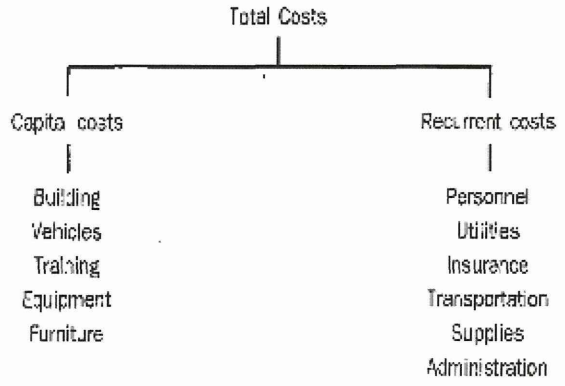


Chart 2

BLOOD TRANSFUSION SERVICE
Capital and Recurrent Costs



As a point of reference, applying this model, the average cost of producing a unit of quality assured Whole Blood in Zimbabwe is USD $128.00.

EXPENDITURE:	AMOUNT	% Expenditure
Payroll	$ 2,663,226	33.6%
Blood Procurement	$ 1,405,180	17.7%
Coordination	$ 68,759	0.9%
Finance & Administration	$ 1,205,593	15.2%
Laboratory Operations	$ 1,473,120	18.6%
Planning , Information and Reserach	$ 207,119	2.6%
Public Affairs & Communication	$ 178,347	2.3%
Safety,Health Environment & Quality	$ 111,675	1.4%
Capital	$ 612,035	7.7%
Total	$ 7,925,055	100.0%