Appendix 2
Laboratory investigation of ATR

The standard investigations
Provide a baseline in case of subsequent clinical deterioration and may give an early indication of whether haemolysis or platelet transfusion refractoriness has occurred

Microbiological investigations

Clinically significant transfusion of bacterially contaminated blood components is a rare but serious event, carries a high mortality and is particularly associated with platelets (Taylor et al, 2008). Clinical severity may be influenced by the type of bacteria involved (Gram-negative organisms cause more severe reactions with rapid onset), bacterial load infused (which may be dependent on component storage time) and the recipient's clinical status (Ramirez-Arcos et al, 2007). To reduce the risk, UK blood services have now introduced automated bacterial screening of platelet components.

Bacterial reactions may present as a severe febrile ATR and a high index of suspicion is important. There is usually a sustained reaction with a temperature rise of 2^{o}C or more and/or rigors and the onset is usually rapid (Blajchman & Goldman, 2001). Nausea, vomiting, severe hypotension leading to shock and pain in the chest, back, abdomen or transfusion site often occur (Hewitt, 2009). In those where a decision is made to perform bacterial testing of the unit, whether by the hospital or by a blood service laboratory, the blood service should be informed so that associated components from the donation can be withdrawn.

Visual inspection of the component for discoloration, abnormal clumps or signs of leaks or damage is important, but many contaminated units appear normal.

Blood cultures from a peripheral vein and any central lines should be performed. The component should be sealed and transported to the transfusion laboratory as soon as possible. The transfusion laboratory should have an agreed policy for culture of the component in the hospital microbiology laboratory or referral to a blood transfusion service laboratory. The microbiology laboratory should have standard operating procedures for sampling the pack with minimal risk of contamination.
Where the hospital site does not consider suitable local facilities for microbiological sampling and testing are present the implicated blood component, appropriately secured, should be sent to the relevant transfusion service bacteriology laboratory. Referral to a blood transfusion service reference laboratory should also be considered if bacterial contamination is the most likely cause of the reaction. Clinically significant local culture results should be confirmed by the blood service reference laboratory, where molecular typing of the organism to assist investigation of the donor can be performed.

Whenever culture of an implicated unit is performed for a severe or sustained moderate febrile transfusion reaction, the local haematologist must be informed and the blood service contacted ***immediately*** so that any associated components from the implicated donation can be withdrawn and other patients protected from harm. All UK blood services provide access 24/7 to expert transfusion medicine advice.

Compatibility testing
When the patient presents with moderate or severe febrile symptoms, hypotension or back/loin pain, compatibility testing should be performed. Testing should include repeat ABO/D grouping of the patient repeat antibody screen, crossmatch and a direct antiglobulin test. (Milkins, 2011)

Mast cell tryptase
Serum levels of mast cell tryptase (MCT) are transiently raised after serious allergic/anaphylactic reactions. Although the clinical value of serum MCT is controversial, the current UK guidelines on the management of anaphylactic reactions recommend its measurement (UKRC, 2008). Its utility lies in retrospective *confirmation* that an ATR was anaphylactic, rather than assisting immediate management of the patient and is particularly useful in a patient who is unable to describe their symptoms or where signs may be masked: e.g. by anaesthesia. (Payne & Kam, 2004) Ideally, blood samples are taken as soon as possible after the reaction, (without delaying resuscitation), then at 3 and 24 hours. Levels rise within 30-60 minutes of the onset of anaphylaxis, peak at 3-4 hours and fall to baseline (<13 mcg/L) by 6-8 hours. Post-mortem sampling may help in the differential diagnosis of patients who die of a suspected ATR (Yunginger et al, 1991) but persistent elevation of MCT may occur in myelodysplastic syndromes, systemic mastocytosis and patients with chronic kidney disease and pruritus (Payne and Kam, 2004).

Immunoglobulin A deficiency
IgA deficiency in transfusion recipients was commonly held to be the most common identifiable cause of severe allergic or anaphylactic transfusion reactions. However, this was based on case reports published before 1985, when diagnostic criteria for IgA deficiency were not well-defined, and some of these cases might now be classified as TRALI (Sandler, 2006). Since 1996, there have only been ten reports of ATR associated with IgA deficiency to SHOT, and in one of these the reaction was febrile in type rather than allergic (Knowles & Cohen, 2010). However, IgA levels were not measured in many of the other reported cases of anaphylaxis. A recent unpublished review of cases referred to NHS Blood and Transplant in England and North Wales found very few cases of confirmed IgA deficiency among patients who had experienced transfusion reactions.

IgA deficiency is most common in Caucasians, occurring in around 1 in 700 of the UK population (Munks et al, 1998). It is defined as a selective deficiency of IgA with a serum level of less than 0.07 g/L (in patients above 4 years of age), in whom other causes of hypogammaglobulinemia have been excluded (European Society for Immunodeficiencies, 2005). Reactions to IgA in blood components are thought to occur particularly in IgA deficient patients who have anti-IgA antibodies, but a review of published data suggests the presence of antibodies is of low predictive value (Lilic and Sewell, 2001).
As there remains significant concern that IgA deficiency presents a transfusion risk, and the relationship between deficiency and transfusion reactions is unclear, we recommend that serum IgA is measured in all patients who have moderate or severe allergic transfusion reactions. Low results, especially if measured by nephelometric assay, should be confirmed by an alternative method, provided generalised hypogammaglobulinaemia has been excluded and investigation for IgA antibodies should be requested. Patients with confirmed IgA deficiency after ATR should be discussed with a clinical immunologist for expert assessment and advice about the need for IgA-deficient blood components. Follow up may be appropriate as IgA deficiency may be associated with the development of subsequent health problems including chronic infections and autoimmune disease. (Lilic and Sewell, 2001; Latiff and Kerr, 2007)

Haptoglobin deficiency
Haptoglobin deficiency, with haptoglobin antibodies, is said to be found in 1 in 60 cases of transfusion-related anaphylaxis in Thai or Japanese patients (Shimada et al, 2002) and should be considered in patients of appropriate ethnic origin.

Testing the patient for leucocyte (HLA), platelet (HPA) or neutrophil-specific (HNA) antibodies

The association of these antibodies and ATR, mainly febrile reactions, is problematic. HLA class I or II antibodies are found in 1-2% of male and 9 -17% of female blood donors (MacLennan et al 2004; Reil 2008 et al; Triulzi et al, 2009). HPA and HNA antibodies develop in 2-10% of patients receiving repeated transfusions (Kiefel et al, 2001; TRAP, 1997). Hence, they may be an incidental finding in patients or donors who are investigated in the setting of transfusion reactions. Indeed, ATR occurred at a similar frequency when HLA-matched or single donor, non-HLA-matched platelets were transfused (Chambers et al, 1990; Mangano et al, 1991) and most studies of HLA antibodies and platelet refractoriness do not show a link with ATR. In contrast leucocyte depletion is known to reduce the likelihood of transfusion reactions (TRAP 1997; Yazeret al, 2004; Paglino et al, 2004; King et al, 2004; Tobian et al, 2011) and plasma removal appears to have been a useful strategy prior to prestorage leucodepletion (Heddle et al, 1999; Vo et al, 2001). This suggests that HLA matching of leucocyte depleted components would have limited impact in reducing ATR (although there is anecdotal experience of patients with alloimmune platelet refractoriness and recurrent ATR who achieved good increments with HLA-matched platelets and ceased to have reactions).
In patients with recurrent troublesome reactions to leucocyte-depleted components, plasma reduction (washing of red cells or resuspension of platelets in platelet additive solution) to remove residual soluble leucocyte or platelet antigenic material and inflammatory mediators is the logical first step. Testing for leucocyte, platelet and neutrophil-specific antibodies should be reserved for patients with evidence of refractoriness and/or who do not respond to plasma reduction as management of reactions (Robson et al, 2008).

Investigation of "high risk" donors
Blood components from some donors may be associated with a high rate of acute transfusion reactions in different recipients, often associated with a transient severe fall in neutrophil count caused by donor HNA antibodies (Fadeyi et al, 2007; Wallis et al, 2002; Kopko et al, 2002). Passive transfer of HPA antibodies has also been linked with acute severe thrombocytopenia in rare cases (Pavenski et al, 2008). These reactions usually occur with plasma or platelet components and may be under-recognised and reported.

Appendix 3: ISBT/IHN classification of ATRs

	1 = Mild	2 = Moderate	3 = Severe
Febrile type reaction	A temperature ≥ 38 °C and a rise between 1and 2°C from pretransfusion values, but no other symptoms/signs	A rise in temperature of 2°C or more, or fever 39 °C or over and/or rigors, chills, other inflammatory symptoms/signs such as myalgia or nausea which precipitate stopping the transfusion	A rise in temperature of 2°C or more, and/or rigors, chills, or fever 39 °C or over, or other inflammatory symptoms/signs such as myalgia or nausea which precipitate stopping the transfusion, prompt medical review AND/OR directly results in, or prolongs hospital stay.
Allergic type reaction	Transient flushing, urticaria or rash	Wheeze or angioedema with or without flushing/urticaria/rash but without respiratory compromise or hypotension	Bronchospasm, stridor, angioedema or circulatory problems which require urgent medical intervention AND/OR, directly result in or prolong hospital stay, or **Anaphylaxis** (severe, life-threatening, generalised or systemic hypersensitivity reaction with rapidly developing airway and/or breathing and/or circulation problems, usually associated with skin and mucosal changes
Reaction with both allergic and febrile features	Features of mild febrile **and** mild allergic reactions	Features of both allergic and febrile reactions, at least one of which is in the moderate category.	Features of both allergic and febrile reactions, at least one of which is in the severe category.
Hypotensive reaction		Isolated fall in systolic blood pressure of 30 mm or more occurring during or within one hour of completing transfusion **and** a systolic blood pressure 80 mm. or less in the absence of allergic or anaphylactic symptoms. No/minor intervention required.	Hypotension, as previously defined, leading to shock (e.g., acidaemia, impairment of vital organ function) without allergic or inflammatory symptoms. Urgent medical intervention required.

Febrile and allergic reactions may present within 4 hours, whilst hypotensive reactions are considered as presenting within one hour

Appendix 4: Comparison of TRALI and TACO

For patients who develop respiratory distree during or shortly after transfusion, and who do not have evidence of wheeze or stridor, the following table may be of help in determining a cause. (Sources: NHSBT, 2011; Popovsky, 2008, 2010; Kopko & Holland, 1999)

	TRALI	**TACO**
Patient characteristics	More frequently reported in haematology and surgical patients	May occur at any age, but characteristically age > 70
Type of component	Usually plasma or platelets	Any
Speed of onset	During or within 6 hours of transfusion, usually within 2 hours.	Defined as occurring within 6 hours of transfusion
Oxygen saturation	Reduced	Reduced
Blood pressure	Often reduced	Often raised
JVP	Normal	Raised
Temperature	Often raised	Usually unchanged
CXR findings	Often suggestive of pulmonary oedema with normal heart size: may be a “whiteout”	Cardiomegaly, signs of pulmonary oedema
Echo findings	Normal	Abnormal
Pulmonary wedge pressure	Low	Raised
Full blood count	May be fall in neutrophils and monocytes followed by neutrophil leucocytosis	No specific changes
Response to fluid load	Improves	Worsens
Response to diuretics	Worsens	Improves

In addition to the categories of TRALI and TACO, SHOT is now collecting cases of transfusion associated dyspnoea (TAD). The International Haemovigilance Network defines TAD as “being characterized by respiratory distress within 24 hours of transfusion that does not meet the criteria of TRALI, TACO, or allergic reaction. Respiratory distress should be the most prominent clinical feature and should not be explained by the patient’s underlying condition or any other known cause.” (IHN, 2011) There are currently no other known distinguishing features to aid diagnosis of TAD.

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