Joint UKBTS Professional Advisory Committee ([1]) Summary Sheet

1. Paper for JPAC review	April 2020 (by email)
2. Date submitted:	02 April 2020
3. Title (including version no.):	Temporary extension of shelf life of red cells to 42 days
4. Author(s):	Rebecca Cardigan, Jane Davies, Mike Wiltshire, Simon Procter, Simon Stanworth, Helen New on behalf of the UK Standing Advisory Committee on Blood Components (SACBC)
5. Brief summary:	Currently the shelf life of red cells in the UK is 35 days although several other countries routinely store red cells up to 42 days. As part of the emergency response and contingency planning for COVID-19 it is proposed that the UK 35 day red cell shelf life could be safely extended to 42 days. The paper summarises current UK data on red cell quality up to 42 days, and international literature on age of blood. The data demonstrate that red cells stored up to 42 days would be likely to meet the current Red book specification for haemolysis and have acceptable quality for other parameters. There are no significant concerns over increased risk from the bacteriology point of view. Review of data from clinical studies on age of blood does not provide evidence of adverse effects of increasing storage age for red cell transfusion. However, there are limited data in the larger trials for patients receiving the oldest red cells. Therefore, the proposal to extend the shelf life for Red Cells in Additive Solution, Leucodepleted should be for a temporary period only. The proposal does not include red cells received by neonates or other red cell components with a different shelf-life such as irradiated red cells. It should be noted that although red cell shelf life is defined by the Red Book and any change will need approval by JPAC, other detailed manufacturing aspects are not. These include the length of time whole blood may be stored between 2-6°C, or whether red cells have been remanufactured from neonatal exchange units are not. It will be up to individual UK blood services to ensure their current manufacturing processes are likely to be compliant with a 42 day shelf life specification. Data from NHSBT are reviewed in the paper on the impact of varying the length of whole blood storage prior to red cell component manufacture and remanufacture of exchange units in case this is useful for other UKBTS. ***Note**: if the 42 day specification were to be used for other contingencies in the future, a similar review to that described in this paper would need to be undertaken in advance. Guidance for such a process could be developed and included on the JPAC website in readiness.*

6. Action required by JPAC: (What do you want JPAC to do in response to this paper?) e.g. • endorse a specific recommendation • advise where there is a choice of possible actions • advise on priorities within the work plan • provide a steer on policy	Review the supporting data and approve a new, temporary, 42 day shelf life specification for 'Red Cells in Additive Solution, Leucocyte Depleted, Extended Shelf life' for use during the COVID-19 period. The recommendation is to modify the wording of the current 8th Edition Red Book specification for 'Red Cells in Additive Solution, Leucocyte Depleted' (section 7.6) to create the new temporary specification as follows: *Section 7.6.3 wording on Storage* Change from: *'The component may be stored for a maximum of 35 days at a core temperature of 4 ±2°C'* To: *'The component may be stored for a maximum of 42 days at a core temperature of 4 ±2°C'* It is proposed that the specification for the product (attached) be included in a new section on 'Blood Components for Contingency Use' on the JPAC website. This will help to make it clear that this change is a temporary measure. The component name on the label will remain the same as on the current 35 day shelf life component in order to avoid confusion within hospitals. Individual UK blood services will need to ensure that their manufacturing processes are likely to be compliant with the temporary 42 day shelf life specification. *Note: Red Cells in Additive Solution for Neonates and Infants, Leucocyte Depleted which also have a 35 day shelf life are excluded. There are currently no changes proposed to other red cell components with a different shelf life, such as Irradiated or Washed red cells.*
7. Any other relevant information:	The paper has been reviewed and approved by SACBC prior to submission.

(1) **J**oint United Kingdom Blood Transfusion and Tissue Transplantation Services **P**rofessional **A**dvisory **C**ommittee (**JPAC**)

Temporary extension of shelf life of Red Cells to 42 days

Rebecca Cardigan, Jane Davies, Mike Wiltshire, Simon Procter, Simon Stanworth, Helen New on behalf of UK Standing Advisory Committee on Blood Components (SACBC)

April 2nd, 2020

Background

Currently the shelf life of red cells in the UK is 35 days. In 2005, JPAC approved changing the shelf-life of red cells in the UK from 35 days to 42 days (JPAC 05-04) which was included in the specification for red cells in the 7th Edition of the Red Book (2005). However, this was never implemented due to theoretical concerns about the combination of ambient storage of whole blood prior to component production with extended red cell storage; the former was validated in NHSBT in 2006 with routine implementation in 2008. Additionally, emerging data from retrospective studies suggesting a negative effect of age of blood on clinical outcome contributed to the decision to keep red cell shelf-life at 35 days, reflected in the specification in the 8th Edition of the Red Book.

As part of the emergency response and contingency planning for COVID-19 a question has arisen as to whether this could be safely extended to 42 days. This paper summarises current UK data on red cell quality to 42 days, and international literature on age of blood and clinical outcomes. Data are also reviewed on the impact of varying the length of whole blood storage prior to manufacture of red cell components in view of the concerns raised in 2005-2008 in relation to extended red cell storage. A possible longer extension to 49 days has not been addressed as we do not have UK quality data at 49 days and do not have confidence from the 42 day data that 49 days would be acceptable.

Current blood stocks data (for NHSBT) show that reduction in red cell collection is being compensated by a concomitant reduction in red cell demand, and that as of April 1st, 2020 the rising age of stock is resulting in increased red cell expiries. **However, given the length of red cell shelf life it is important to consider and apply any shelf life extension measure now while red cells stocks are reasonable, in order to maximise their future availability if and when demand outstrips supply. At that point an extension to shelf life is likely to be less helpful**.

A change to red cell shelf life would be implemented on a temporary basis only, analogous to the approval to manufacture and supply liquid plasma if needed as part of contingency planning for a possible large outbreak of enterohaemorrhagic E.coli during the London Olympics in 2012 (JPAC12-54). Decisions will need to be taken by Blood Services regarding the length of temporary implementation of the 42 day red cell specification during the COVID-19 period. It should be noted that if the 42 day specification were to be used for other contingencies in the future a similar review to that described in this paper would need to be undertaken in advance. Guidance for such a process could be captured in a document in the proposed 'Blood Components for Contingency Use' section on the JPAC website.

Current guidelines and regulations

The table below summarises current guidelines and regulations with respect the shelf life of leucocyte depleted red cells in additive solution. The shelf life of red cells could be changed to 42 days by changing UK guidelines. This would remain within CoE Guide, the BSQR and EU Directive.

Red Book 8th ed	35 days
CoE 20th ed	The storage time depends on the processing system and anticoagulant/ preservative solution used and should be validated.
AABB	42 days for red cells in additive solution
BSQR	28 to 49 days according to the processes used for collection, processing and storage
EU directive	28 to 49 days according to the processes used for collection, processing and storage

Likely benefit of 42 day shelf life

(Data kindly provided by Mathew Bend, Manager, Blood Stocks Management Scheme).

The most recent data available on all red cells was reviewed. Of those issued to hospitals, 2.7% of red cells are wasted. Of this 2.7%, 70% of the wastage is due to time expiry (TIMEX). This equates to approximately 26,000 per year. For O negative red cells the wastage as a percentage of those issued is 5.4%, with time expiry accounting for around 7,000 units per year.

It is unlikely that extension of the shelf life of red cells by one week will have a positive effect on current red cell wastage. However, should demand outstrip supply in future months, placing an extension on the shelf life of red cell issued by blood services now would be predicted to maximise the use of red cells currently in stock.

The possibility of extending the shelf life of red cell units already within hospital stocks has also been considered. While this would have a more immediate impact on red cell stocks, it would be likely to be extremely difficult to implement due to regulatory aspects and the configuration of hospital blood bank LIMS systems. As red cell stocks are predicted to be adequate for at least several weeks (in NHSBT) the option of extending shelf life of red cells already issued to hospitals has therefore not been considered in any detail.

Summary of Laboratory data and NHSBT manufacturing practice

(Data kindly provided 23.03.2020 by Dr Athina Meli, CDL)

A number of physical and biochemical changes occur when red cells are stored for transfusion, termed the storage lesion. This includes a change in red cell morphology from their normal discoid shape, an increase in release of microparticles, and an increase in the number of red cells that lyse (haemolysis). There are many metabolic changes in red cells that occur with increasing duration of

storage including reduction in levels of ATP, 2,3 DPG, increased lactate generation and markers of oxidative damage.

Standard manufacturing practice within NHSBT (which will vary in detail from other UKBTS) is that red cells have a 35 day shelf life according to Red Book specification and that they are manufactured and placed into 2-6 degree controlled storage within 27 hours from whole blood donation (the preferred and most frequently used process). Alternatively, whole blood is leucocyte depleted (LD) and placed in 2-6 degree controlled storage within 24 hours of donation, and then manufactured to red cells by day 5 after venepuncture where the date of venepuncture is considered to be day 0 ('extended hold'). Since 2009 all red cells other than those for intrauterine transfusion, neonatal exchange transfusion and neonatal/infant large volume transfusion are manufactured from whole blood held at ambient temperature for up to 24 hours and placed at 2-6^{o}C within 27 hours from donation.

The data from NHSBT Component Development Laboratory (CDL) presented in this section incorporates variable aspects of these pre-storage manufacture conditions, stated specifically where appropriate. There is also discussion of the impact of ambient hold (below). Data presented below from CDL has been generated using whole blood that has been held at ambient temperature for 24 hours prior to production, unless this is not appropriate for the component being produced e.g. neonatal exchange units. However, it should be noted that there is no CDL validation data for a 42 day shelf life of LD whole blood held at 2-6 degrees prior to the manufacture of the red cells.

When NHSBT introduced ambient storage of whole blood for up to 24 hours prior to component production, the length of shelf life was reviewed, and a decision was made to keep a 35 day shelf life. This was based on the lack of data on survival of red cells to day 42 in combination with ambient storage of whole blood, and the 'rule of thumb' that exposing red cells to 24 hours storage at room temperature reduces red cell shelf life by one week (Reid et al, 1999). Data suggest that there is a very small reduction in the 24 hour recovery of red cells in vivo if stored for 42 days with ambient storage of whole blood for 24 hours (Moroff et al, 2011, summarised in table below).

Table showing mean percentage (+/-SD) in vivo red cell recovery 24 hours following infusion depending on storage age and length of hold time of whole blood at room temperature (RT)

	35d	42d	8 v 24h hold
8h hold RT	79 +/- 4 (n=9)	79 +/- 4 (n=9)	p>0.05
24 hold RT	73+/- 7 (n=9)	76 +/- 5 (n=9)	P<0.05

CDL routinely test red cells to day 42 in projects related to red cells. Figure 1 at Appendix 1 summarises CDL reference data on standard red cells in SAGM, processed by current manufacturing processes including overnight ambient hold, that has been obtained as part of studies in CDL over the last 15 years. As can be seen, there are relatively small differences in most parameters between day 35 and 42. The most striking difference is in the numbers of microvesicles, which increase more rapidly towards the end of storage.

A key parameter is ATP, as this is thought to relate to the recovery of red cells in vivo following transfusion. A value of 2.3 umol/gHb (shown on the graph) has been suggested as providing reassurance that there will be an acceptable recovery of red cells following transfusion (Heaton et al, 1992). However, this relationship is not absolute. At day 35 85% of units are above this value, which is reduced to 73% at day 42.

Implications for Red book specification and haemolysis quality monitoring data

The current specification for red cells in the UK requires that >75% of red cells have a haemolysis level <0.8% at end of shelf life: this is the only red cell QM parameter required to be tested that relates to storage age/red cell quality. It should be noted that UKBTS do not deliberately outdate red cells so that this can be measured in 1% of red cells produced. Red cells that are left in stock within NHSBT at the end of expiry are measured, and there is a requirement to annually re-validate the production process to ensure compliance with the specification. For these reasons, the number of units on which there are routine QM data of red cells at 35 days is small.

Further, it is well known that differences in sample preparation and methodology in measuring haemolysis can have a significant impact on the values obtained (Hess 2005; Almizraq et al, 2017), making comparisons in data across labs/jurisdictions difficult even if they are comfortable with their techniques and data internally. Sample preparation has a significant impact as the number of intact red cells, or large red cell microparticles remaining in the supernatant of the red cells may differ and affect the measurement of free haemoglobin in the sample. There is currently no internationally accepted standard method. This has implications for the interpretation of laboratory and QM data in the following sections.

It should also be noted that as red cell haemolysis is tested after expiry and this represents a slightly worse situation than at end of shelf life, this adds to the confidence in the quality and safety of the transfused components.

The table below summarises data from CDL on haemolysis, which complies with the specification at day 42.

	Day 35 (n=272)	Day 42 (n=211)
Haemolysis (%) mean with SD	0.24 (0.15)	0.29 (0.17)
% of units <0.8%	99	98

NHSBT's routine quality monitoring data for haemolysis is higher than data from CDL. For 2018/19 QM data mean haemolysis at day 35 is 0.47% (n=317), with 86.8% < 0.8%. QM data is representative of production with a 40:60 split between BAT:TAT results. The difference between CDL and QM datasets may reflect: the proportion of Red Cell pack types in the respective populations, sample preparation methods (as CDL centrifugation processes are likely to remove more intact contaminating red cells than those applied in QM and are therefore more likely to reflect the true percentage haemolysis), and wider production process variables in the QM data which encompasses all routine collection to storage practice.

Extrapolating QM's data to predict values at day 42 suggests that mean haemolysis would be approximately 0.6% with compliance estimated to be in excess of 80%. However, while the modelling performed, using 2018/19 QM data suggests a high level of compliance, the real compliance will not be known until after a significant number of operational units have been assessed by QM following introduction of the new shelf-life. Large international data sets demonstrate LD red cells in SAGM meet regulatory requirements for haemolysis at day 42 including ambient storage of whole blood for 24 hours (Hess et al, 2009; Shih et al, 2019).

Implications of variations in manufacturing processes on haemolysis QM data (from NHSBT practice)

1. Extended hold of LD whole blood prior to manufacture

As a contingency for reduced staffing capacity, NHSBT employs the practice of delaying the manufacture of red cells by holding leucocyte depleted whole blood at 2-6 degrees for up to 5 days. The existing data show that extended hold of LD whole blood prior to manufacture of red cell components is associated with increased haemolysis. It is therefore important to consider the impact of these manufacturing processes on the proposed extension of red cell shelf life to 42 days as it may be necessary to combine the two measures. Reviewing QM data is of little help for this consideration as currently there are no routine QM data at day 42 following extended hold of LD whole blood and only very limited data at day 35. At day 35, median haemolysis values following 3/4 days hold are 0.49% (n=11), with data being 63% compliant to haemolysis <0.8%, and there are no QM data for 5 day hold. The degree of confidence associated with such a small and uncontrolled data set is low so although the data available suggests that units subject to extended hold may not meet 75% compliance if it is used in combination with a 42 day shelf life, this is not clear.

Due to the lack of QM evidence, CDL recently validated delaying the manufacture of red cells by 3 or 5 days. Data from this study supported the QM results that increasing the hold time results in increased haemolysis, but showed that units were compliant for haemolysis specification (100%) at day 35, following either 3 or 5 days extended hold (see below). The Component Strategy Group reviewed both the QM data and the CDL data and concluded that the controlled study performed by CDL was more likely to be representative of haemolysis following extended hold of LD whole blood, and so approved extended hold up to 5 days for red cells with 35 day shelf life (March 2020).

During the COVID-19 epidemic, under circumstances where there is inadequate staffing to manufacture all of the blood from a day's bleed the additional processing flexibility of holding LD whole blood will be needed by NHSBT. In the CDL validation study, delayed manufacture to day 5 was associated with an increase in haemolysis at day 35 of about 0.1%. CDL do not have data at day 42 on delayed manufactured units, but modelling for 5 day delayed manufacture, using 2018/19 QM data above, predicts a mean haemolysis of 0.67% at day 42 and a borderline 78% compliance at <0.8%. This modelling therefore suggest units may not meet 75% compliance if extended hold for 5 days is used in combination with a 42 day shelf life. At 3 days the compliance is predicted to be 78-83%. Canada routinely hold blood processed via the TAT method for 3 days at 4^{o}C prior to component production and store red cells to 42 days with acceptable levels of haemolysis (Jordan et al 2016; Shih et al 2019), although it is unclear how long they hold blood at ambient temperature prior to that. However, the exact compliance in NHSBT will not be known until after a significant number of operational units have been assessed by QM following introduction of the new shelf life. Therefore, caution is suggested beyond 3 days extended hold with a 42 day shelf-life as we are not aware this is standard practice in any other country.

2. Remanufacture of neonatal exchange transfusion units

As a measure to prevent the wastage of neonatal exchange transfusion units, NHSBT remanufacture the unused units up to the end of day 7 into standard red cells in SAGM. This variation in manufacturing has been validated by CDL (Meli et al, 2018). Units produced in that study had a mean haemolysis of <0.5% at 42 days, and other standard quality parameters were acceptable. These data therefore demonstrate that remanufactured units are of acceptable quality at 42 days. Currently production of Red cells in additive solution, Leucocyte depleted, from the remanufacture

of neonatal exchange units is permitted under section 7.3 of the Red Book for a 35 shelf-life and this will also be the case when extending to 42 days.

Overall implications of CDL data

Overall, CDL data suggest that the quality of red cells at day 42 would be compliant with Red Book specification. This is also likely to be the case if they undergo delayed manufacture, or are produced following remanufacture from exchange transfusion units. The increases in haemolysis percentage and supernatant potassium concentrations between day 35 and 42 shown in the CDL data are unlikely to be clinically significant in themselves but together with the decline in ATP and increase in microvesicles indicate a 'storage lesion' which has been the subject of clinical studies discussed in the next section.

Therefore, 42 day red cells could be implemented to ease stock availability provided the component is felt to be clinically acceptable on review by JPAC. This proposal has been supported by members of all Blood Establishments represented on SACBC (all UKBTS and the IBTS). An extension of red cell shelf life to day 42 will require a change to the specification and therefore JPAC approval, whereas it will be up to individual UK blood services to ensure that their manufacturing processes are likely to be compliant with a revised 42 day shelf life specification. For this reason, it is recommended that for NHSBT a 3 day extended hold limit should be the maximum allowed without additional review.

Recommendations based on the laboratory data

- 42 day shelf life with standard overnight hold is acceptable
- 42 day shelf life with up to 3 days extended hold of LD whole blood is acceptable with a likely compliance of between 78% and 83%.
- 42 day shelf life with 4 or 5 days extended hold of LD whole blood is considered borderline and therefore should only be done by review. This would be either Retrospective review following a Quality Incident (National Committee) or Prospective review by a relevant national committee in order to consider further mitigations in the event of manufacturing difficulties during the COVID-19 period (to allow 42 days plus with 4 or 5 days extended hold of LD whole blood).

Bacteriology considerations

Advice from NHSBT (Carl McDonald, Consultant Clinical Scientist, Transfusion Microbiology Bacteriology) is that the risk of bacterial growth if red cell storage is extended to 42 days compared to 35 days is likely to be minimal compared to the clinical need. The incidence of bacterial transfusion transmission in red cells is very low with a 35 day shelf life, approximately 1 in 6 million red cell transfusions in the UK (Aplin et al, 2018). His opinion is that if there were to be a psychrophilic organism in the red cell bag, there would be a problem both at 35 days or at 42 (although at 42 days the bacterial count will potentially be greater). For non-psychrophilic organisms, their numbers will be further reduced by the longer period of storage. This is evidenced by spiking studies in red cell concentrates that have been stored for up to 42 days (Chen et al, 2008).

Summary of clinical data on age of blood studies

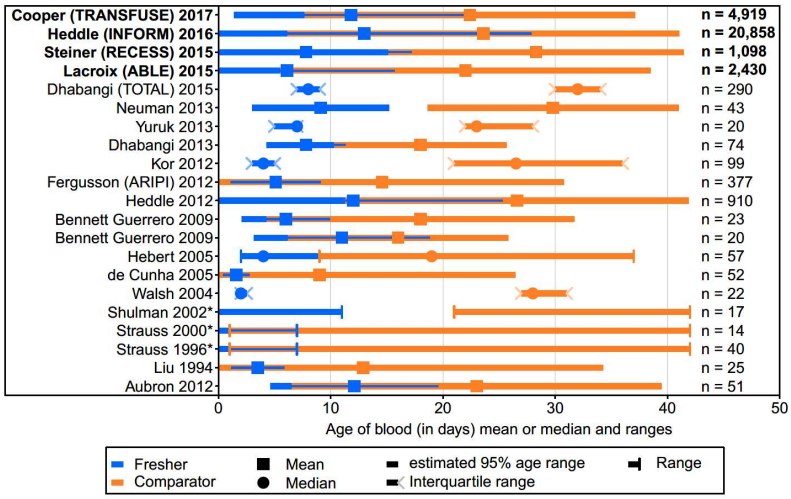
The impact of the changes in red cells during storage seen in laboratory studies has been debated for many years, with uncertainty about the clinical consequences of different storage ages of red

cells for transfusion. More recently, multiple large randomised trials, including those of high methodological quality and powered on clinical outcomes, have been conducted to better define any effect of different storage ages. These trials provide a considerable amount of data.

The trials have been analysed in a recent Cochrane systematic review (Shah et al, 2018; see figure below illustrating the ranges of age of blood in the trials), which included 22 trials enrolling 42,835 participants, for a primary outcome of in-hospital and short-term mortality. The analysis was undertaken for studies comparing shorter or longer storage durations, and against standard practice, but no evidence of an effect on mortality related to length of storage of transfused RBCs was reported. The authors concluded that the common blood bank practice of issuing the oldest available RBCs did not need to be amended.

However, there are a number of limitations for this analysis. One observation was less data in neonates and children, although a subsequent RCT in critically ill children (completed after the review, Spinella et al, 2019) also found no effect of storage age on clinical outcomes. It was also not clear how the findings from the larger trials related to patients who require multiple units of transfusion components, for example with significant traumatic bleeding. A further consideration when discussing an extension to the shelf life for red cell storage age is how the storage lesion changes could impact in patients with acute infection and inflammation. Release of iron from older stored red cells could mediate toxicity during acute infection, and there is some support for this hypothesis from the results of animal experiments in a canine model of pneumonia. (Wang et al, 2014). Additionally, a range of methodological issues have been highlighted that may affect the confidence of our interpretation of these trials in systematic reviews, including dichotomising continuous variables for storage age and uncertainty about the underlying nature of any relationship between storage age and adverse outcomes which may not be linear (Trivella et al, 2019). An international initiative to undertake an individual patient data meta analysis of all randomised trials is underway (personal communication, Simon Stanworth).

In summary, the existing trial results do not provide evidence of adverse effects with storage age for red cell transfusion. However, a degree of caution is required at more extreme storage ages, not least given the limited amounts of data in the larger pragmatic trials for enrolled patients receiving the oldest (or indeed freshest) transfusions of red cells. The data are not strong enough to support identifying groups of patients who have a greater risk of harm when transfusing oldest storages of red cells and any proposals to preferentially withhold or offer oldest storage aged red cells in different patient settings is considered challenging to implement. Therefore, a temporary extension to shelf life of standard red cells at the time of predicted national shortage is considered reasonable, without restriction to particular patient groups, but currently not recommended as standard in the longer term.



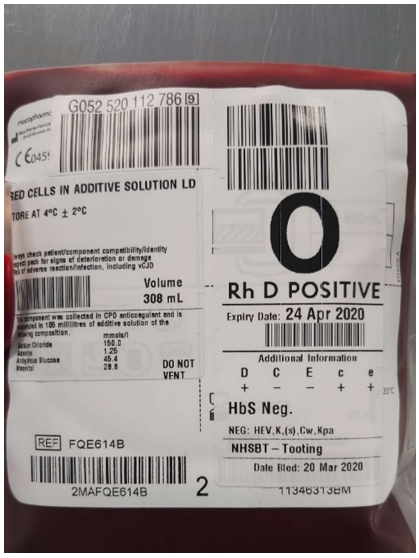
The figure illustrates the ranges of age of stored blood in the 'age of blood' studies referenced above (reproduced from Trivella et al, 2019).

International perspective

Current regulations and guidance permit a shelf life longer than 35 days. Australia, Canada, France, Sweden and some centres in Germany all currently routinely store red cells in SAGM to 42 days (Shih et al, 2019). Of note, Australia, Canada and France have similar process to NHSBT for how whole blood is handled prior to component production (24 hours at room temperature).

Operational considerations

Currently the actual expiry date of red cells (dd/mm/year) is printed on the label at the point of manufacture based on this being 35 days from the day of donation (see example below).



Changing this from 35 to 42 days is not difficult to do from a manufacturing/IT perspective (for NHSBT, and we assume similar processes would be required for the other UKBTS). There is currently nothing in the manufacturer's instructions for use or CE mark that would preclude storing red cells

to 42 days and Australia use the same storage bags from Macopharma as NHSBT. Moreover, Macopharma responded to the Euroblood pack tender to indicate that the collection system was approved for the storage of red cells up to 42 days from venepuncture, and they have now (31.3.20) provided a declaration to NHSBT that all their whole blood kits containing CPD anticoagulant allow for the storage of red blood cells in SAGM additive solution for up to 42 days after collection when maintained at a temperature of 2 - 6 ^{o}C.

Once the decision is actioned any red cells validated after that point in time would have a 42-day expiry date printed on the validation label. If approved by JPAC this would likely take 7-10 days to implement if considered the highest priority, up to 3 weeks with competing high priorities for staff.

The activity needed to be completed is as follows:

The change will be undertaken within the quality assurance system with appropriate change control and risk assessment and stakeholder consideration which will include an impact assessment on any other internal IT systems.

- Change control including risk and impact assessment and a change plan.
- Notification of the change to all stake holders including but not limited to;
    - Hospital staff (including allowing time to update hospital LIMS systems – information received to date is that any change even if required is likely to be minor)
    - Clinicians
    - Internal NHSBT colleagues
    - SHOT
- An assessment of any other NHSBT IT systems that could be impacted by the change (Non-clinical Issue / Standby Issue System / Haematos / OBOS / Central Planning / BoB's reports etc.)
- On an agreed date hospital services would need to stop validation for approximately 1 hour for the change to be made. On resumption of validation after the change all red cells validated from that time would have a 42-day shelf life
- Agree a review period with advance planning to revert back to 35-day shelf life ensuring this is communicated to all relevant stakeholders and that there is no impact on hospital stocks.

For red cells that are currently in hospitals, the expiry can't be changed systematically on the label as hospitals are unable to re-label the units: this would require them to have the right equipment to do so and hold a Blood Establishment licence as this is a manufacturing step. There would also be considerable issues around the hospital LIMS systems. As discussed earlier, the possibility of extending the shelf life of units within hospital stocks is not currently being pursued due to difficulty in implementation and perceived lack of benefit.

Summary of opinion from SACBC

Laboratory data from NHSBT show that red cells in SAGM at 42 days of storage meet current specification for red cell haemolysis and are of acceptable quality for other parameters. There are no significant concerns over increased risk from the bacteriology point of view. A number of countries use a 42 day shelf life including a period of ambient hold prior to processing similar to that in the UK (Australia, France, Canada). Data from multiple prospective trials do not provide evidence of adverse effects with storage age for red cell transfusion. However, since there remains some uncertainty

with respect to extremes of red cell storage age, an extension of red cell shelf life to 42 days routinely cannot be recommended yet, nor can extension of red cell shelf life for neonatal transfusion. In times of national emergency, extending the 35 day shelf life of Red Cells in Additive Solution, LD, to 42 days is acceptable, subject to constraints around manufacturing processes for individual blood services, and without extending the shelf life of neonatal red cells or of other red cell components with a different shelf-life (such as irradiated red cells).

Recommendation for JPAC

It is recommended that JPAC approve a temporary 42 day shelf life specification for 'Red cells in Additive Solution, Leucocyte Depleted, Extended Shelf life.

The recommendation is to modify the wording of the current 8th Edition Red Book specification for 'Red Cells in Additive Solution, Leucocyte Depleted' (Section 7.6) to create the new temporary specification for use during the COVID-19 period as follows:

Section 7.6.3 wording on Storage

Change from: *'The component may be stored for a maximum of 35 days at a core temperature of 4 ±2°C'*

To:

'The component may be stored for a maximum of 42 days at a core temperature of 4 ±2°C'

It is proposed that the specification for the product (attached) be included in a new section on 'Blood Components for Contingency Use' on the JPAC website. This will help to make it clear that this change is a temporary measure. The component name on the label will remain the same as on the current 35 day shelf life component in order to avoid confusion within hospitals. Individual UK blood services will need to ensure that their manufacturing processes are likely to be compliant with the temporary 42 day shelf life specification.

Note: Red Cells in Additive Solution for Neonates and Infants, Leucocyte Depleted which also have a 35 day shelf life are excluded. There are currently no changes proposed to other red cell components with a different shelf life, such as Irradiated or Washed red cells.

Proposed component specification, within a new Red Book section: Blood Components for Contingency Use'

A5.1 Red Cells in Additive Solution, Leucocyte Depleted, Extended Shelf Life

A red cell component containing less than 1×10^6 leucocytes and suspended in an approved additive solution.

A5.1.1: Technical information

- A red cell component prepared by removing a proportion of the plasma from leucocyte-depleted whole blood and suspending in an approved additive solution. Leucodepletion may be carried out on either the whole blood starting material or on the final component.
- Red Cells in Additive Solution, Leucocyte Depleted, Extended Shelf Life should be transfused through a 170–200 µm filter.
- May be produced by remanufacture of Red Cells for Exchange Transfusion, Leucocyte Depleted (section 7.24) up to 6 days after donation.

A5.1.2: Labelling

For general guidelines, see section 6.6.

The following shall be included on the label:

(* = in eye-readable and UKBTS approved barcode format)

- Red Cells in Additive Solution, Leucocyte Depleted* and volume
- the blood component producer's name*
- the donation number*
- the ABO group*
- the RhD group stated as positive or negative*
- the name, composition and volume of the additive solution
- the date of collection
- the expiry date*
- the temperature of storage
- the blood pack lot number.*

In addition, the following statements should be made:

INSTRUCTION

Always check patient/component compatibility/identity

Inspect pack and contents for signs of deterioration or damage

Risk of adverse reaction/infection, including vCJD

A5.1.3: Storage

For general guidelines, see section 6.7.

- The component may be stored for a maximum of 42 days at a core temperature of 4 ±2°C.
- Variation from the core temperature of 4 ±2°C of the finished component must be kept to a minimum during storage at all stages of the blood supply chain and restricted to any short period necessary for examining, labelling or issuing the component.
- Exceptionally, i.e. due to equipment failure at a Blood Centre or hospital, for temperature excursions where the core temperature has not exceeded 10°C or fallen below 1°C, components may be released for transfusion provided that:
    - the component has been exposed to such a temperature change on one occasion only
    - the duration of the temperature excursion has not exceeded 5 hours
    - a documented system is available in each Blood Centre or hospital to cover such eventualities
    - adequate records of the incident are compiled and retained.

A5.1.4: Testing

In addition to the mandatory and other tests required for blood donations described in Chapter 9, and leucocyte counting (see sections 6.3 and 7.1), a minimum of 75% of those components tested for the parameters shown in Table A5.1 shall meet the specified values.

Table A5.1 Red Cells in Additive Solution, Leucocyte Depleted, Extended Shelf Life – additional tests

Parameter	Frequency of test	Specification
Volume	1% or as determined by statistical process control (if ≤10 components produced per month then test every available component)	280 ±60 mL**
Haemoglobin content		≥40 g/unit***
Haemolysis	As per section 7.2	<0.8% of red cell mass
Leucocyte count*	As per sections 6.3 and 7.1	<1 × 10^6/unit

* Methods validated for counting low numbers of leucocytes must be used
**Units measured and found to be >375 mL should not be issued for transfusion
***Units tested and found to have <30 g/unit should not be issued for transfusion

A5.1.5: Transportation

For general guidelines, see section 6.11.

For red cell components, transit containers, packing materials and procedures should have been validated to ensure the component surface temperature can be maintained between 2°C and 10°C during transportation. Additionally:

- the validation exercise should be repeated periodically
- if melting ice is used, it should not come into direct contact with the components
- dead air space in packaging containers should be minimised
- as far as is practicable, transit containers should be equilibrated to their storage temperature prior to filling with components
- for transportation between blood supplier and hospital an upper limit of 10°C surface temperature is acceptable but should be limited to one occasion, not exceeding 12 hours

In some instances it is necessary to issue red cell components from the blood supplier to hospitals that have not been cooled to their storage temperature prior to placing in the transit container. The transport temperature specified above is not applicable for such consignments.

Removal from and return to 2-6°C controlled storage within hospitals

For occasions when red cells are removed from 2-6°C controlled storage (e.g. when issued to a clinical area immediately prior to transfusion) and returned then:

- If possible, time out of a controlled temperature environment should be restricted to under 30 minutes
- if 30 minutes is exceeded the unit should not be returned to the issue location in the refrigerator, but returned to the transfusion laboratory or quarantined remotely using electronic blood tracking
- up to 60 minutes out of controlled temperature is acceptable, provided the unit is then quarantined by placing in a secure refrigerator for at least 6 hours prior to reissue, to allow the unit to return to 2-6°C
- Hospitals will need to identify such units so that they are not subject to being out of controlled temperature storage for between 30 and 60 minutes on more than three occasions.

Transfusion should be completed within 4 hours of issue out of a controlled temperature environment.

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Appendix 1. Figure 1 CDL Historic red cell storage data (2004 – 2019)