Monitoring International Trends

**posted November-December 2016**

The NBA monitors international developments that may influence the management of blood and blood products in Australia. Our focus is on:

* Potential new product developments and applications;
* Global regulatory and blood practice trends;
* Events that may have an impact on global supply, demand and pricing, such as changes in company structure, capacity, organisation and ownership; and
* Other emerging risks that could potentially put financial or other pressures on the Australian sector.

A selection of recent matters of interest appears below. Highlights include:

* 1. At the 58th Annual Meeting of the American Society of Hematology (ASH), San Diego, December 2016: (section 1)
     1. updates on gene therapy programs for haemophilia were presented by Spark Therapeutics, UniQure and Sangamo Biosciences.
     2. Roche reported on Phase III trials for emicizumab for haemophilia A.
     3. Alnylam presented Phase I data for its RNA interference drug, fitusiran.
     4. NovoNordisk presented a subanalysis of the SMART-7 study, evaluating the efficacy in a real-world setting of NovoSeven, its room temperature stable recombinant activated factor VIIa.
     5. Biogen and Swedish Orphan Biovitrum presented new data on their extended half-life therapies for haemophilia A and haemophilia B.
     6. CSL Behring presented a new Phase III analysis for Idelvion, the company's long-acting recombinant albumin fusion protein for haemophilia B.
     7. Shire provided an update on its safety database describing 40 years of real-world experience with the bypassing agent FEIBA. The company also presented new *in vitro* data showing the potential for excessive thrombin generation when an investigational procoagulant bispecific antibody and bypass therapy are combined for breakthrough bleeds.
     8. Shire presented the results of its Phase-III clinical trial evaluating Vonvendi in treating bleeds in elective surgical settings for adults with severe von Willebrand disease.
     9. in relation to sickle cell disease, researchers reported that high-dose crizanlizumab treatment is associated with a significantly lower rate of sickle cell-related pain crises than is placebo; Bluebird Bio presented new data on LentiGlobin; and Global Blood Therapeutics released follow-up data to its Phase I/II study of its once-a-day pill.
     10. Researchers reported on an artificial red blood cell that in lab tests in rodents effectively picked up oxygen in the lungs and delivered it to tissues round the body.
  2. ProMetic Life Sciences declared that its Phase II/III clinical trial of plasminogen in patients with plasminogen deficiency had met its primary and secondary endpoints. (section 1)
  3. Kamada announced the clinical plan for the initiation of a Phase II/III clinical trial in the US of its plasma-derived Alpha-1 Antitrypsin for the treatment of acute Graft-Versus-Host Disease. (section 1)
  4. CSL Behring announced that [The Lancet Respiratory Medicine](http://www.thelancet.com/journals/lanres/article/PIIS2213-2600(16)30430-1/fulltext) had published results of the RAPID Open Label Extension study, conducted in patients with alpha-1 antitrypsin deficiency. The study found that the use of Alpha1-Proteinase Inhibitor therapy may slow the progressive and irreversible loss of lung tissue, thereby suggesting that early intervention may be beneficial. (section 1)
  5. Portola Pharmaceuticals submitted a New Drug Application to the US Food and Drug Administration (FDA) requesting approval to market betrixaban for extended-duration prophylaxis of venous thromboembolism in acute medically ill patients. (section 2)
  6. The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) recommended granting marketing authorisation for CSL Behring’s AFSTYLA [Recombinant Human Coagulation Factor VIII, Single Chain] for patients with haemophilia A. (section 2)
  7. Vascular Solutions of Minneapolis submitted an Investigational New Drug (IND) application to the FDA for RePlas, a freeze-dried plasma product being developed in collaboration with the US Army Medical Materiel Development Activity (USAMMDA). (section 2)
  8. Bioverativ, a spin-off of Biogen’s haemophilia business, is on track to launch in early 2017 as an independent, public company. (section 3)
  9. From early 2017 Biotest will add a recombinant factor VIII to its haemophilia portfolio which will be produced using a human cell line. (section 3)
  10. Novartis acquired Selexys Pharmaceuticals and its antibody for ameliorating the pain of vaso-occlusive crises in sickle cell disease. (section 3)
  11. **Alnylam** announced that Sanofi Genzyme had elected to opt in to co-develop and co-commercialize fitusiran in the US, Canada and Western Europe. (section 3)
  12. **CSL reported encouraging results from** a clinical trial to assess the safety of CSL112, its plasma- derived drug aimed at reducing the high incidence of early recurrent heart attacks after an initial attack. (section 3)
  13. The Australian Senate received a report from its Community Affairs References Committee on *Growing evidence of an emerging tick-borne disease that causes a Lyme-like illness for many Australian patients.* Themes identified in the report were putting patients first, testing for the infection and treating the illness. The Committee made twelve recommendations. (section 4)
  14. In Canada, female donors will now need to wait 12 weeks between blood donations, rather than eight weeks, to allow iron levels to recover. (section 4)
  15. McMaster University researchers have led a large international study showing that “fresher” blood is not necessarily better for transfusion than blood which has been stored for a longer period within regulatory limits. (section 5)
  16. A recent online survey has found significant variations in massive transfusion protocols among US hospitals. (section 5)
  17. A project in the Northern Territory, led by Professor Peter Morris of The Menzies School of Health Research, is trialling giving anaemic children rapid iron infusions before they are discharged from hospital. (section 5)
  18. Scientists from John Hopkins College of Medicine have shown that large bags of red cells, platelets and unthawed plasma can maintain temperature and cellular integrity in a cooler while being transported by drones. (section 5)
  19. BloodCenter of Wisconsin and Eastman Chemical Company announced the results of a recent clinical trial evaluating a new plasticizer for blood bags. (section 5)
  20. The [Society for Neuroscience](https://www.sfn.org/annual-meeting/neuroscience-2016) annual meeting in San Diego in November was told that aging mice injected with blood plasma from 18-year-old humans exhibited improved memory and functioning. (section 6)
  21. Researchers led from Yale University have [corrected a gene mutation](http://www.nature.com/articles/ncomms13304) in mice that causes thalassemia. (section 6)
  22. The Zika virus remains a global concern. Research suggests: (section 7)
      1. that some adult brain cells may be vulnerable to damage by Zika.
      2. that in male mice Zika infection can severely damage the testes and affect fertility.
      3. that the antibiotic azithromycin can block the Zika virus from infecting foetal brain tissue cells grown in lab dishes.
      4. that a specific Zika antibody can reduce mother-to-foetus transmission of the virus in pregnant mice.
      5. that the *Aedes aegypti* mosquito can transmit the Zika and chikungunya viruses simultaneously in a single bite.
      6. that vaccinating against the dengue virus could make it easier for Zika to spread, since it appears that dengue virus antibodies can enhance the Zika virus infection.
  23. Avian flu outbreaks have been affecting domestic and wild flocks around the world. A(H7N9) avian flu in human continues to be reported periodically, with infection originating in mainland China; and a human case of A(H5N6) has also been reported from mainland China. (section 7)
  24. MERS (Middle East Respiratory Syndrome-novel Coronavirus) also continues to be reported. Work towards production and testing of a vaccine is ongoing. (section 7)

Table of Contents

[1. Products 4](#_Toc471662270)

[58th Annual Meeting of the American Society of Hematology (ASH), San Diego, 3 December to 6 December 2016. 4](#_Toc471662271)

[Gene therapy for haemophilia 4](#_Toc471662272)

[Other developments for haemophilia 4](#_Toc471662273)

[Sickle cell disease 6](#_Toc471662274)

[Paroxysmal Nocturnal Haemoglobinuria (PNH) 7](#_Toc471662275)

[Other 7](#_Toc471662276)

[Product developments not included in the ASH reports above 8](#_Toc471662277)

[2. Regulatory 11](#_Toc471662278)

[3. Market structure and company news 12](#_Toc471662279)

[4. Country-specific events 14](#_Toc471662280)

[5. Safety and patient blood management 16](#_Toc471662281)

[Appropriate Transfusion 16](#_Toc471662282)

[Treating anaemia 18](#_Toc471662283)

[Other 18](#_Toc471662284)

[6. Research (not elsewhere included) 20](#_Toc471662285)

[7. Infectious diseases 21](#_Toc471662286)

[Zika Virus 21](#_Toc471662287)

[Other mosquito-borne diseases 21](#_Toc471662288)

[Influenza: strains, spread, prevention and treatment 22](#_Toc471662289)

[MERS-CoV (Middle East Respiratory Syndrome-Coronavirus) 22](#_Toc471662290)

[Ebola virus disease 23](#_Toc471662291)

[Other diseases: occurrence, diagnosis, prevention and treatment 23](#_Toc471662292)

# Products

*Here the NBA follows the progress in research and clinical trials that may within a reasonable timeframe make new products available, or may lead to new uses or changes in use for existing products.*

## 58th Annual Meeting of the American Society of Hematology (ASH), San Diego, 3 December to 6 December 2016.

### Gene therapy for haemophilia

* 1. Spark Therapeutics announced that two patients in its Phase 1 trial[[1]](#footnote-1) have developed an immune response to its gene therapy, SPK-9001. The responses lowered both patients’ levels of replacement Factor IX, but so far those levels have not dropped low enough to cause bleeds or require other treatments. Spark is optimistic that temporary treatment with tapering doses of steroids will halt the immune response before it causes factor IX levels to fall to a point where bleeding risk emerges[[2]](#footnote-2).
  2. UniQure’s haemophilia B patients also showed meaningful reductions in bleeds. One commentator referred to “turning severe haemophiliacs into mild haemophiliacs”.
  3. Sangamo Biosciences presented preclinical and manufacturing data on SB-525, its gene therapy program for haemophilia A. A single intravenous administration of SB-525 resulted in the expression of significant levels of human FVIII in mice and non-human primates and correction of the bleeding defect in a mouse model of haemophilia A. Sangamo's president and CEO, Sandy Macrae said: "We have developed an improved gene therapy vector and we remain on track to file an Investigational New Drug (IND) application for our clinical program by the end of 2016. We look forward to initiating a clinical trial in 2017 to evaluate SB-525."

### Other developments for haemophilia

* 1. Alnylam Pharmaceuticals presented Phase I data for its RNA interference drug, fitusiran. This has exhibited the potential to reduce bleeds without significant safety problems, although some patients have experienced a rise in liver enzymes which could suggest potential problems. Alnylam has said the cases were reversible. The company expects to begin a late-stage trial next year.
  2. NovoNordisk presented a subanalysis of the SMART-7 study, evaluating the efficacy in a real-world setting of NovoSeven, its room temperature stable recombinant activated factor VIIa. It said the drug resolved 96.5 per cent of bleeds when initiated within one hour after onset of bleeding, demonstrating efficacy of early treatment in people with haemophilia A or B with inhibitors. Efficacy remained high for bleeds treated after 4 hours.
  3. Roche’s emicizumab is in Phase III trials and has shown promise reducing bleeds, but when administered in conjunction with a bypassing agent thrombosis has been a problem[[3]](#footnote-3).
  4. Biogen and Swedish Orphan Biovitrum (Sobi) presented[[4]](#footnote-4) new data, including updated longitudinal safety and efficacy findings from phase III and extension studies, on the companies’ extended half-life therapies, Eloctate [Antihaemophilic Factor (Recombinant), Fc Fusion Protein][[5]](#footnote-5) for haemophilia A and Alprolix [Coagulation Factor IX (Recombinant), Fc Fusion Protein] for haemophilia B. Efficacy data showed low target joint annual bleeding rates and effective target joint resolution[[6]](#footnote-6) in paediatric, adolescent and adult patients on long-term prophylaxis with Eloctate. An 18 per cent improvement in haemophilia-related quality of life measures was observed in adolescents and adults who experienced target joint resolution with prophylactic treatment with Eloctate, compared with baseline measurements at phase III study enrolment[[7]](#footnote-7).
  5. Biogen also presented[[8]](#footnote-8) preclinical data on recombinant FIXFc-XTEN, its fusion protein designed for once-weekly, subcutaneous treatment of haemophilia B. The rFIXFc-XTEN investigation is the sole responsibility of Biogen, using XTEN technology licensed from Amunix. Subject to various conditions, the drug may carry a future opt-in right by Sobi.
  6. CSL Behring presented new Phase III analysis for Idelvion, the company's long-acting recombinant albumin fusion protein for haemophilia B[[9]](#footnote-9). The results, from a pooled analysis of clinical studies from the global PROLONG-9FP program, examined the relationship between estimated factor IX activity levels and bleeding risk in adult haemophilia B patients given Idelvion as prophylaxis or on-demand. Analysis of factor IX activity versus efficacy showed that adult patients achieving sustained factor IX activity levels above 5 or 10 per cent have around 80 per cent lower risk of bleeding events over one year compared with patients having factor IX activity levels below these thresholds.
  7. Shire provided an update on its safety database describing 40 years of real-world experience with the bypassing agent FEIBA [Anti-Inhibitor Coagulant Complex][[10]](#footnote-10). Inhibitors affect fewer than ten per cent of patients with haemopjilia A. Their immune systems attack the molecules in factor therapy. Bypassing agents help bypass the inhibitor to help the blood clotting. FEIBA carries a boxed warning for identified thromboembolic risk.
  8. Shire also presented new *in vitro* data showing the potential for excessive thrombin generation when an investigational procoagulant bispecific antibody and bypass therapy are combined for breakthrough bleeds[[11]](#footnote-11). The company analysed *in vitro* a sequence analogue biosimilar of emicizumab, in combination with bypassing agents. They found a multi-fold increase in thrombin generation, suggesting a potential thrombotic risk for patients given emicizumab together with an approved bypass agent.

### Sickle cell disease

* 1. According to a study published[[12]](#footnote-12) to coincide with a presentation to the ASH meeting, high-dose crizanlizumab[[13]](#footnote-13) treatment is associated with a significantly lower rate of sickle cell-related pain crises than is placebo[[14]](#footnote-14).
  2. Bluebird Bio presented new data from the ongoing open-label, single-centre Phase I/II HGB-205 clinical study[[15]](#footnote-15) evaluating its LentiGlobin candidate in patients with transfusion-dependent β-thalassemia (TDT) and severe sickle cell disease (SCD). David Davidson, chief medical officer of Bluebird Bio, commented: “We believe the enduring responses seen in this study - in the patients with TDT as well as the patient with SCD - demonstrate the continued promise of LentiGlobin gene therapy in both of these patient populations. We have seen nearly three years of transfusion independence in TDT in certain patients, providing important data on the long-term safety and durability of this therapy. In addition, it is encouraging that the patient with SCD has remained free of acute SCD-related clinical events in the 21 months since treatment, when he previously required monthly blood transfusions to help control his SCD symptoms. This patient’s successful outcome not only offers hope for the potential of LentiGlobin to benefit other patients with SCD, but also provides important insights into this complex disease that we are applying to our ongoing HGB-206 study.”
  3. ArQule presented preclinical data[[16]](#footnote-16) on its proprietary AKT inhibitor, ARQ 092. ARQ 092 is being studied in sickle cell disease. The study suggests that ARQ 092 inhibits activation, and effectively blocks heterotypic aggregation, of neutrophils and platelets in SCD patients in vitro. *Ex vivo* studies suggest that ARQ 092 inhibits activation of neutrophils and platelets isolated from SCD mice after oral administration.
  4. Study results suggested that treatment with moderate doses of hydroxyurea for primary stroke prevention is feasible for Nigerian children with sickle cell anaemia who have elevated transcranial Doppler measurements[[17]](#footnote-17). A Phase III trial will follow.
  5. Global Blood Therapeutics has been developing a once-a-day pill to reduce the sickling of blood cells. At the meeting, Global released follow-up data to its Phase I/II study, continuing to show consistent and durable haemoglobin responses to GBT440 with 700 mg and 900 mg doses. The company expects to start a Phase III trial in January, with data available in 2019.
  6. Imara shared preclinical efficacy and safety data supporting the development of IMR-687, aimed at reducing the sickling of red blood cells and blood vessel occlusion. IMR-687 is being studied as a once-daily oral, potent and selective phosphodiesterase 9 (PDE9) inhibitor.

### Paroxysmal Nocturnal Haemoglobinuria (PNH)

* 1. Alnylam Pharmaceuticals presented in a poster new results from Part C of its Phase I/II clinical trial with ALN-CC5, a subcutaneously delivered investigational RNAi therapeutic targeting complement component 5 (C5) for the treatment of complement-mediated diseases. Part C evaluated the tolerability and clinical activity of ALN-CC5 in six patients with paroxysmal nocturnal hemoglobinuria (PNH), a rare haematologic disease where acquired mutations in the PIG-A gene lead to complement-mediated destruction of red blood cells. ALN-CC5 was evaluated in combination with eculizumab, an approved anti-C5 monoclonal antibody used for treatment of PNH. The new results show that ALN-CC5-mediated knockdown of serum C5 has the potential to reduce the dose level and frequency of eculizumab in patients with PNH, and to improve disease control in patients with an inadequate response to eculizumab.

### Other

* 1. Acceleron Pharma presented some Phase II data for luspatercept, its infusable protein drug which, with its partner Celgene, it hopes will eliminate or reduce the need for transfusions in myelodysplastic syndrome[[18]](#footnote-18). Patients are being enrolled in a Phase III trial.
  2. Agios Pharmaceuticals is developing two drugs for pyruvate kinase deficiency[[19]](#footnote-19), AG-348 and AG-519, only one of which it will advance to late-stage trials. Shares fell more than 12 per cent after Agios disclosed at ASH a single case of liver inflammation in a patient on AG-519.
  3. Shire presented the results of its Phase-III clinical trial evaluating Vonvendi [von Willebrand factor (Recombinant)], in treating bleeds in elective surgical settings for adults with severe von Willebrand disease. The drug was found to be effective in controlling the bleeding during surgical procedures in these patients, and the company plans to submit a sBLA (supplemental biological license application) to the FDA, to file for regulatory approval in Europe during 2017 and in other markets round the world.
  4. Researchers[[20]](#footnote-20) reported on an artificial red blood cell that in lab tests in rats and mice effectively picked up oxygen in the lungs and delivered it to tissues round the body[[21]](#footnote-21). This artificial blood can be freeze-dried, for combat medics and paramedics to have on hand for reconstitution with sterile water in emergencies. The artificial cell is about one-fiftieth the size of a normal red blood cell, and is manufactured from purified human haemoglobin proteins that have been coated with a synthetic polymer[[22]](#footnote-22). The surface chemistry of the polymer responds to the pH level of blood as it travels through the body, capturing oxygen when blood pH is high as jn the lungs, and releasing oxygen when blood pH is low, as in tissue, especially where the tissue does not have enough oxygen. The polymer coating also prevents the haemoglobin from reacting with nitric oxide in the bloodstream, which would constrict the blood vessels. The polymer coating is "immune silent," so the artificial blood can be used regardless of patient blood type. Researchers cautioned, however, that while a normal red blood cell circulates for around 120 days, these artificial cells might circulate for up to half a day, although further work might extend that just a little. They are designed solely to deliver oxygen, and don’t perform other functions of red cells, such as antioxidant protection of tissues, regulation of blood flow, assistance in immune response, and aid in forming blood clots and scabs.

## Product developments not included in the ASH reports above

* 1. [BioMarin Pharmaceuticals](http://www.biomarin.com/)’ Phase I/II clinical trial evaluating the investigational [gene therapy](https://bionews-tx.com/news/news-tags/gene-therapy/) [BMN 270](http://www.biomarin.com/products/pipeline/bmn-270/) as a treatment for severe haemophilia A has resumed patient enrolment with approval from the Medicines and Healthcare Products Regulatory Agency ([MHRA](https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency)) for the UK. BioMarin suspended patient dosing mjd-year because of increasing levels of alanine aminotransferase (a biomarker of hepatocyte injury) observed in the first nine patients given the gene therapy. The increases surpassed a pre-specified limit set in the trial’s protocol. However, after the regulatory agency examined efficacy and safety data on those nine adult patients, it permitted resumption of enrolment. In mouse models of haemophilia A, BMN 270 restored factor VIII plasma concentrations to levels declared adequate for normal clotting in humans.
  2. ProMetic Life Sciences of Laval, Canada, announced that its Phase II/III clinical trial of plasminogen[[23]](#footnote-23) in patients with plasminogen deficiency[[24]](#footnote-24) had met its primary and secondary endpoints with the intravenous plasminogen treatment. As well as being safe, well tolerated and without any drug related serious adverse events, the treatment achieved a 100 per cent success rate in its primary endpoint, a targeted increase in the blood plasma concentration level of plasminogen. All trial participants who had active visible lesions when enrolled had complete healing of their lesions within weeks of treatment, a 100 per cent response rate for the secondary endpoint. After the pre-BLA meeting held with the FDA, it was agreed that ProMetic would continue along the Accelerated Approval Regulatory Pathway and file the pharmacokinetic safety data on 10 plasminogen deficient patients along with efficacy data available for each of these patients who have completed 12 weeks of treatment. Dr John Moran, Chief Medical Officer of ProMetic, said: "We will continue to treat the patients for an additional period of 36 weeks to demonstrate the durability of the positive clinical activity observed to date. This additional clinical data will be submitted as a supplement to our BLA after our plasminogen receives the expected accelerated approval in 2017". Dr Moran also commented: "The data we have seen so far indicates that a significant number of patients will need prophylactic treatment for their entire life. Most if not all patients will in addition require more aggressive treatment ahead of critical events such as elective surgery or following unexpected events such as injuries, or intercurrent illnesses."
  3. Kamada announced the clinical plan for the initiation of a Phase II/III clinical trial in the US of its plasma-derived Alpha-1 Antitrypsin (G1-AAT IV) for the treatment of acute Graft-Versus-Host Disease (GvHD), in collaboration with Shire[[25]](#footnote-25). GvHD is a life-threatening disease. It can follow a stem cell or bone marrow transplant, where transplanted donor cells attack the recipient. G1-AAT IV previously received orphan drug designation from the FDA and the European Medicines Agency (EMA) for the treatment of GvHD, and an Investigational New Drug Application was submitted to the FDA in 2016. This trial will be a two-part, multi-centre, prospective study to evaluate the safety and efficacy of G1-AAT IV as an add-on biopharmacotherapy to standard steroid treatment in up to 168 patients with acute GvHD with lower gastrointestinal involvement (LGI-aGvHD). Dr. Eran Schenker, Vice President and Medical Director at Kamada, said: “Recent extensive clinical research indicates that AAT has an immune-modulatory, tolerance effect, in addition to the previously established anti-inflammatory, tissue-protective and anti-apoptotic effects. AAT may reduce inflammation by lowering levels of pro-inflammatory mediators, such as specific cytokines, chemokines and other factors that are associated with GvHD. The previously completed interim analysis from the Phase I/II clinical trial[[26]](#footnote-26) indicated that continuous administration of G1-AAT IV as a therapy for steroid-refractory gut GvHD is feasible in this subject population.”
  4. CSL Behring announced on 2 December 2016 that [The Lancet Respiratory Medicine](http://www.thelancet.com/journals/lanres/article/PIIS2213-2600(16)30430-1/fulltext) had published results of the RAPID Open Label Extension study, conducted in patients with alpha-1 antitrypsin deficiency (AATD)[[27]](#footnote-27). Study findings showed that the use of Alpha1-Proteinase Inhibitor (A1-PI) therapy may slow the progressive and irreversible loss of lung tissue, thereby suggesting that early intervention may be beneficial. The RAPID Open Label Extension study (Randomized, Placebo-controlled Trial of Augmentation Therapy in Alpha-1 Proteinase Inhibitor Deficiency Open Label Extension) consisted of eligible patients who continued for another two years from the original two-year RAPID trial, the largest and longest placebo-controlled AATD trial to have been conducted globally. The trial set out to measure the progression of emphysema, assessed by volume-adjusted lung density. The RAPID extension study consisted of two groups of patients. The "Early-Start" group received A1-PI therapy during both trials, providing up to four years of continuous treatment, while the "Delayed-Start" group received placebo during the first two years and then switched to CSL’s **Zemaira**[[28]](#footnote-28) in the extension trial, providing up to two years of active treatment. While a similar rate of decline was observed in both groups between months 24 and 48, an advantage was sustained over the four-year period for the "Early-Start" group, which experienced a lower overall rate of lung density decline. During the extension trial, the "Delayed-Start" group did not catch-up to their "Early-Start" counterparts.
  5. In May 2016, the results of the SIPPET study were published[[29]](#footnote-29). This showed the rate of inhibitor development in haemophilia A was 87 per cent higher in patients treated with recombinant factor VIII (rFVIII)compared with those who received plasma-derived FVIII (pdFVIII) products containing von Willebrand factor. Yet plasma- derived products are generally considered less safe, because they may contain unknown pathogens. The World Federation of Haemophilia (WFH), the European Haemophilia Consortium (EHC) and the National Haemophilia Foundation’s Medical and Scientific Advisory Council (MASAC) have all provided statements and recommendations on the SIPPET study findings, and their implications for clinical practice, and these were included in Issue 19 of *Haemophilia News*, an Australian e-newsletter edited by Dr Scott Dunkley, Director of the Haemophilia Treatment Centre at Royal Prince Alfred Hospital. An Australian perspective on the implications of the study for treating previously untreated patients was also presented by Dr Julie Curtin, Senior Staff Specialist in Haematology at Westmead Children’s Hospital. One of the EHC recommendations, relevant to trials such as that of Roche’s ACE910 is “that clinical trials of novel rFVIII products in previously untreated patients should continue as they may prove to be less immunogenic than conventional products, and as many previously untreated patients as possible should be enrolled in formal prospective trials”. In his commentary, Dr Dunkley, having drawn attention to some elements of serious concern about the original study said: “My fear, having done much work in developing adult prophylaxis, is that countries will use this to justify using pdFVIII alone which ultimately will mean they cannot escalate the IU/capita to enable adequate prophylaxis. In Australia we could not treat patients at adequate levels (supply constraints) to enable use of pdFVIII in previously treated patients”. Dr Curtin in her perspective recognised that inhibitors are a problem in haemophilia A, but emphasised the growing evidence to support anecdotal experience that not all factor products are equal. She recognised that although plasma-derived products are safer now than they were historically, and various methods of viral inactivation are employed, they are not perfect. Viruses such as non-enveloped viruses (e.g. parvovirus) can still be transmitted, and there is always TNV (the next virus). In discussing possible strategies to reduce inhibitor risk she emphasised the uncertainties that make the treating doctor’s judgment and advice still a very important factor in the outcome.

# Regulatory

*The NBA monitors overseas regulatory decisions on products, processes or procedures which are or may be of relevance to its responsibilities.*

* 1. Swedish Orphan Biovitrum (SOBI) announced that the Swiss Agency for Therapeutic Products, Swissmedic, had approved Alprolix® (eftrenonacog alfa) for the treatment of haemophilia B.
  2. Ethicon announced that the FDA had approved an expanded indication for Evarrest Fibrin Sealant Patch, which stops problematic bleeding during surgery. The expanded indication supports the use of Evarrest as an adjunctive haemostat across a broad range of challenging patient types and surgical situations, including coagulopathic and anticoagulated patients.
  3. Portola Pharmaceuticals submitted a New Drug Application (NDA) to the FDA requesting approval to market betrixaban for extended-duration prophylaxis of venous thromboembolism in acute medically ill patients. Betrixaban, an oral, once-daily Factor Xa inhibitor anticoagulant is already an FDA Fast Track-designated investigational drug.
  4. The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) recommended granting marketing authorisation for CSL Behring’s AFSTYLA [Recombinant Human Coagulation Factor VIII, Single Chain] for patients with haemophilia A.
  5. Vascular Solutions of Minneapolis submitted an Investigational New Drug (IND) application to the FDA for RePlas, a freeze-dried plasma product being developed in collaboration with the US Army Medical Materiel Development Activity (USAMMDA)[[30]](#footnote-30). Clinical studies and a Biologics License Application (BLA) were expected to follow, with the partners hoping for a commercial launch in the US in 2019-2020 and initial production devoted to meeting the battlefield needs of the US Army.
  6. [Pluristem Therapeutics, of Israel develops](https://www.globenewswire.com/Tracker?data=6PUYOGszpG0EfDk0N3R4SrcoPH7dGLV3y8cLdL7c8HsloRUD7C3PnN-x0SxYJA33zTFw3em7RweEOne-Emzug0q_E2j2Cf2hsrM0Nwcvdek=) placenta-based cell therapy products. On 6 December, 2016 it announced a milestone in its development of PLX-R18, which is being evaluated as a treatment for the haematologic components of Acute Radiation Syndrome (ARS)[[31]](#footnote-31) by the National Institute of Allergy and Infectious Diseases (NIAID), a part of the US National Institutes of Health (NIH). The FDA previously advised Pluristem to conduct a pilot study in large animals to determine the optimal dosage of PLX-R18 as a treatment for the component of ARS that affects bone marrow function. NIAID has now completed the dosing of the first cohort and is preparing to initiate dosing of the second and final cohort. Results are expected in the first half of 2017. Based on these data the optimal treatment dose will be chosen for a pivotal large animal study designed to meet the requirements for a Biologics License Application (BLA) submission under the FDA’s Animal Rule regulatory pathway[[32]](#footnote-32).

# Market structure and company news

*The NBA’s business intelligence follows company profitability, business forecasts, capital raisings or returns, mergers and takeovers, arrangements for joint research and/or development, contracts for supply of manufacturing inputs, and marketing agreements. Companies considered include suppliers, potential suppliers and developers of products which may be of interest.*

* 1. Bioverativ Inc., a spin-off of Biogen’s haemophilia business, is on track to launch in early 2017 as an independent, public company focussed on the discovery, research, development and commercialization of treatments for haemophilia and other rare blood disorders. Bioverativ will continue to collaborate with Sobi on their joint development programs. Biogen’s interest in the marketed products Eloctate and Alprolix, and in the investigational drug rFIXFc-XTEN, will go to Bioverativ.
  2. From early 2017 Biotest will add a recombinant factor VIII to its haemophilia portfolio which will be produced by using a human cell line[[33]](#footnote-33). The new product is indicated for the treatment and prevention of bleeding episodes in children and adults with haemophilia A. The fourth-generation recombinant clotting factor has been shown to be safe, effective and well tolerated. Biotest will market the new drug in Germany, Austria and Switzerland in cooperation with Octapharma.
  3. In November, Novartis acquired Oklahoma-based Selexys Pharmaceuticals, and its SELG1 antibody for ameliorating the pain of vaso-occlusive crises in sickle cell disease.
  4. At the beginning of November, Cerus Corporation reported on its third quarter 2016 earnings, and outlined positive developments during the quarter: the FDA had revised its recommendations for protecting blood components from the Zika virus, calling for the use of pathogen reduction technology in all US blood centers; 17 customers in the US were initiating Intercept production, up sharply from the three blood centres which Cerus had at the beginning of the year; another 22 contracted customers were expected to begin production soon; and the company continued to make progress on its red cell system, which should be submitted for European CE Mark approval soon, with a Phase III trial to begin in the US.
  5. Ionis Pharmaceuticals [announced](http://seekingalpha.com/pr/16651973-ionis-pharmaceuticals-reports-positive-phase-2-data-ionis-fxi-rx-patients-end-stage-renal) successful results from a Phase II clinical trial of its antithrombotic candidate IONIS-FXIrx in patients with end stage renal disease on haemodialysis. Results showed statistically significant dose-dependent reductions in Factor XI activity with no clinically meaningful reductions in platelet levels and no treatment-related significant bleeding events. Ionis is set to receive a $US 55 million milestone payment from licensee Bayer triggered by the review of the Phase II data and advancement to Phase III.
  6. On 14 November, 2016 **Alnylam Pharmaceuticals** announced that, in accord with the global alliance signed in January 2014, Sanofi Genzyme had elected to opt in to co-develop and co-commercialize fitusiran, in the US, Canada and Western Europe. This expanded right is in addition to their previously exercised opt-in decision to develop and commercialize fitusiran in their rest of world territories. The opt in decision was based on recent promising interim clinical results from a Phase 1 study of fitusiran presented at the World Federation of Hemophilia conference(WFH) in July and the additional data that was later presented at the American Society of Hematology (ASH) meeting in December. Alnylam expects to initiate the fitusiran Phase III program early in 2017. Alnylam announced in early December that Sanofi Genzyme had decided not to exercise its opt-in right for the development of paroxysmal nocturnal hemoglobinuria drug ALN-CC5 in territories outside the US, Canada and Western Europe, giving Alnylam full global control of the program for further development and potential commercialization.
  7. On 24 October 2016 Dilaforettte announced its intention to undertake an initial public offering (IPO) and change its name to Modus Therapeutics Holding AB. It planned a rights issue in connection with the IPO in order to finance progress of its co-development with Ergomed of sevuparin, currently in a phase II clinical trial, for the treatment of sickle cell disease.
  8. **On 15 November 2016 CSL presented results from** a clinical trial (to assess the safety of CSL112) at the American Heart Association Scientific Sessions in New Orleans. CSL 112 is a plasma- derived drug aimed at reducing the high incidence of early recurrent heart attacks after an initial attack[[34]](#footnote-34). AEGIS-I is a multicentre, randomized, double-blind, placebo-controlled, dose-ranging, Phase IIb safety and proof of mechanism trial that enrolled 1,258 acute myocardial infarction patients. Patients were stratified by renal function and randomized to receive four weekly infusions of either CSL112 2g/dose, CSL112 6g/dose or placebo. CSL says the trial has generated positive results. CSL112 met its safety objectives, showing that it does not cause significant changes in liver or kidney function and is well tolerated when administered after a heart attack. The trial also confirmed that CSL112 enhanced cholesterol efflux capacity (that is, it could significantly remove cholesterol from the plaque in arteries). The next trial of CSL112 will determine whether increasing cholesterol efflux capacity translates into improved cardiovascular outcomes, reducing the high rate of recurrent events following a heart attack. AEGIS-I results were also published online in *Circulation[[35]](#footnote-35).*
  9. A University of Queensland biomedical scientist, Professor Mark Kendall, won the CSL Young Florey Medal for his pioneering work on needle-free vaccines. The nanopatch took 20 years to develop and is set to revolutionise immunisation around the world, delivering vaccines by targeting immune-rich cells in the upper layers of the skin. He said: "The nanopatch is a tiny piece of silicon with 20 thousand microscopic needles on one side, coated with a dry vaccine. When you apply the patch to the skin, that tough outer layer of the skin is breached and the vaccine is placed next to thousands of cells in the skin. It gets wet in the cellular environment and within just a minute the vaccine has been delivered”. Professor Kendall said the nanopatch is pain free. If it can be produced cheaply enough it could replace the 160-year-old needle and syringe. The nanopatch has been tested for every class of vaccine including influenza, malaria and cervical cancer. In 2017, Professor Kendall’s team will partner with the World Health Organisation (WHO) to run a polio vaccine trial. The nanopatch does not need refrigeration, and in the event of a pandemic, it can be mailed out for people to self-administer.
  10. Marcum LLP and Philadelphia *SmartCEO* magazine have recognized CSL Behring with the 2016 Innovator Breakthrough Award for developing novel products that save lives and improve quality of life for people with chronic and serious medical conditions[[36]](#footnote-36). In 2016 these included bringing to market two innovative recombinant factor therapies for treating haemophilia A and haemophilia B respectively. These better protect patients from bleeds while reducing the treatment burden for patients and caregivers.

# Country-specific events

*The NBA is interested in relevant safety issues which arise in particular countries, and also instances of good practice. We monitor health issues in countries from which Australia’*s *visitors and immigrants come.*

* 1. A Rand corporation study**[[37]](#footnote-37)** found the US blood system faces financial and biological threats. It found medical advances have reduced the national demand for blood, creating financial pressure on the nation's blood collection centers and threatening their survival. It suggested more government supervision may be needed to prevent blood shortages from posing a risk to public health, noting that external threats- such as the emergence of the Zika virus-were pressuring the system. Andrew Mulcahy, lead author of the study was reported as saying “We need a better, more-efficient and more-sustainable system."
  2. The **International Society for Infectious Diseases will hold its next International Congress on Infectious Diseases (ICID) in Buenos Aires, Argentina from the 1st to the 4th of March 2018.** The 18th ICID will pay particular attention to the major challenges of the region including Zika, dengue and other related viral infections, AIDS, tuberculosis, pneumonia, and enteric and parasitic infections.
  3. On 30 November 2016, the Australian Senate received a report from its Community Affairs References Committee on *Growing evidence of an emerging tick-borne disease that causes a Lyme-like illness for many Australian patients.* Themes identified in the report were putting patients first, testing for the infection and treating the illness. The Committee made twelve recommendations[[38]](#footnote-38).
  4. AABB will host the US Haemovigilance Symposium in Atlanta on 13/14 February 2017 to discuss national progress, including barriers to participation and recommendations for future improvement and harmonization.
  5. Canadian Blood Services’ stricter iron guidelines for female donors came into effect on 10 December, 2016. The agency said the change was needed to "further promote health and wellness among blood donors," as well as to ensure that recipients receive quality red blood cells. Female donors will now need to wait 12 weeks between blood donations, rather than eight weeks, to allow iron levels to recover. The current waiting period is eight weeks. Men may donate as often as before (every 56 days) but from next March there will be higher requirements for their blood haemoglobin levels. The minimum allowable haemoglobin level for male donors will increase from 125 grams per litre, to 130 grams per litre. The new iron guidelines mean more donors are needed. In Ontario alone, 6,000 new blood donors are being sought.
  6. A court in China has ruled that a nine-year-old boy from central China who was infected with HIV from a hospital blood transfusion is to be awarded 400,000 yuan (HK$ 458,000) in compensation by five medical institutions, including three hospitals. The boy’s parents, however, have filed an appeal as they had hoped to get 1.1 million yuan in compensation.
  7. Swedish Orphan Biovitrum (Sobi) announced the results from a study it funded to assess the efficacy of haemophilia care in seven countries in Europe[[39]](#footnote-39). Treatment practice varied widely between countries, and the authors not surprisingly recommended more product use. Stefan Lethagen, Vice President Medical & Clinical Sciences, Haemophilia at Sobi, said: “The overall results indicate that there is a significant need to advance standard of care within haemophilia. Even when prophylaxis is the norm, it appears that prophylactic treatment is driven to the minimal acceptable level or even lower, which increases the risk of joint injury and limits the ability to live a full and active life.” The retrospective study encompassed 1346 haemophilia A patients and 312 haemophilia B patients. Prophylaxis was the most common treatment among children with severe haemophilia A but decreased with increasing age. On-demand treatment was the most common treatment in moderate haemophilia A, with no trend across age groups. For haemophilia B patients, prophylaxis was most common in four out of seven countries. The median annualized bleeding rate (ABR) for severe haemophilia A patients on prophylaxis was as high as four in some countries and some patients experienced more than 12 bleeds per year, with possible reasons being insufficient product administered and doses too widely spaced. In moderate haemophilia A patients on prophylaxis, bleeds could be as frequent or more frequent than for those with severe disease on prophylaxis.

# Safety and patient blood management

*We follow current issues in patient safety and achieving favourable patient outcomes.*

## Appropriate Transfusion

* 1. McMaster University researchers have led a large international study showing that “fresher” blood is not necessarily better for transfusion than blood which has been stored for a longer period within regulatory limits.
     1. The Informing Fresh versus Old Red Cell Management (INFORM) trial involved 31,497 adult patients at six hospitals in Australia, Canada, Israel and the US[[40]](#footnote-40). It showed that having a transfusion with the freshest blood did not reduce the proportion of patients who died in hospital. The mortality rate was 9.1 per cent with people receiving the freshest blood, and 8.7 per cent among those receiving the oldest blood. There was no significant difference when looking at the patients' blood type, diagnosis[[41]](#footnote-41), institution or country.
     2. Nancy Heddle, lead author and a professor emeritus of medicine for McMaster's Michael G. DeGroote School of Medicine, is also the research director of the McMaster Centre for Transfusion Research. She said: "It's been a contentious issue, but our study finally puts an end to the question about whether stored blood could be harmful and fresher blood would be better. Our study provides strong evidence that transfusion of fresh blood does not improve patient outcomes, and this should reassure clinicians”. She added that the results are also good news for blood suppliers worldwide as having a supply of stored blood helps to ensure that blood is available when a patient needs it.
     3. John Eikelboom, a co-principal investigator of the study and professor of medicine of the Michael G. DeGroote School of Medicine, said more than 40 studies published earlier have failed to adequately answer the question about whether the freshest blood was best. He said: "Blood transfusions are a common medical intervention. Advances in blood storage now allow blood to be stored up to 42 days before transfusion and the usual practice is to use up the blood that has been in storage the longest. But, because there are biochemical, structural and functional changes in the blood during storage, there had been concerns about the use of 'older' blood. This study reassures us that aging is not bad[[42]](#footnote-42).”
     4. The study was funded by the Canadian Institutes of Health Research, Canadian Blood Services and Health Canada. Results were published in the *New England Journal of Medicine[[43]](#footnote-43)*, and presented to the annual AABB meeting.
  2. In the US, the AABB (formerly the American Association of Blood Banks) issued updated guidelines for red blood cell transfusion threshholds and optimal storage time[[44]](#footnote-44). The AABB, after consideration of a systematic review and meta-analysis incorporating 31 randomized controlled trials, recommends a restrictive haemoglobin transfusion threshold of 7g/dL for haemodynamically stable adult patients and 8 g/dl for patients undergoing orthopaedic surgery, cardiac surgery or those with pre-existing cardiovascular disease. Exceptions to this recommendation relate to acute coronary syndrome patients and those with severe thrombocytopenia or chronic transfusion-dependent anaemia. Based on evidence from 13 randomized controlled trials, AABB recommends that standard issue red blood cells should continue to be transfused since fresher red blood cells (those stored for fewer than ten days) do not improve clinical outcomes.
  3. A recent online survey[[45]](#footnote-45) (with 191 surgeons from 125 hospitals as respondents) has found significant variations in massive transfusion protocols (MTPs) among US hospitals. All but two of the responding institutions have MTPs, with 54 per cent having implemented their protocols within the past 5 years. Around half of the hospitals include 5-10 units of red blood cells in the first MTP cooler, with the rest including fewer than 5 units. Plasma is included in 87 per cent of the coolers, while 58 per cent contain platelets. Around two-thirds of the institutions use tranexamic acid, with about 25 per cent still using recombinant activated factor VII. Only 7 per cent of the responding hospitals use a validated scoring system, such as the Assessment of Blood Consumption, to determine when to activate MTPs. The report suggested future studies are needed to optimize and standardize MTPs.
  4. Meanwhile, in the UK, University of Warwick scientists are collaborating with researchers at the NIHR Surgical Reconstruction and Microbiology Research Centre (SRMRC) to investigate the effectiveness of giving patients blood products immediately after a major injury or trauma, before they reach hospital.
     1. Gavin Perkins, Professor of Critical Care Medicine at the University of Warwick's Medical School and consultant at Heart of England NHS Foundation Trust is one of the chief investigators. He said: "Major trauma is a major cause of death in the UK. Treatment with blood and clotting factors can be lifesaving, but blood is a scarce resource and we currently don't know when and where the best place to administer it is. The RePHILL study[[46]](#footnote-46) will explore whether giving blood and clotting factors outside of a hospital is safe and more effective than giving it in the resuscitation room in hospital”.
     2. Nicholas Crombie, consultant trauma anaesthetist at University Hospitals Birmingham NHS Foundation Trust and a doctor with the Midlands Air Ambulance Charity is also a chief investigator. He said: "In the trial, air ambulances and ambulances will be randomly stocked with or without blood products. Therefore, for eligible patients, the receipt of blood products prior to hospital admission will be determined by what the ambulance that attends to them is carrying. The research team will then look at a number of outcomes, including mortality as well as physical and biochemical evidence of the effectiveness of resuscitation, in order to determine whether there are any differences between those who receive blood products and those who receive clear fluids."
     3. Karim Brohi, Professor of Trauma Sciences at Barts and the London School of Medicine and consultant in trauma and vascular surgery at the Royal London Hospital, said: "The national major trauma system, with its integrated pre-hospital care, together with support from the NIHR, makes England the best place in the world to conduct such studies." The NIHR, the research arm of the NHS, has backed the project with £1.8 million funding over four years from its Efficacy and Mechanism Evaluation programme.
  5. At the 2016 American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) Conference in San Diego a team from [Vanderbilt University Medical Center](http://www.mc.vanderbilt.edu/) in Nashville presented evidence-based blood utilization practice guidelines that saved $US 2 million and reduced blood use by 30 per cent. The blood management program adopted restrictive transfusion practices and improved the processes of ordering, transporting, and storing blood[[47]](#footnote-47).
  6. The San Diego Blood Bank (SDBB), announced it is partnering with Sinopia Biosciences, a San Diego-based computational biology company, by collecting and testing the aging of whole blood units from volunteer donors to develop a solution that will improve transfusion efficacy and extend the shelf life of red blood cells. David Wellis, chief executive officer of SDBB, said: “Deep molecular characterization of the aging of whole blood may provide molecular and biochemical targets to pursue for modulation of shelf life.” Sinopia recently received notice of funding from the National Heart, Lung, and Blood Institute of the US National Institutes of Health to develop novel additive solutions to improve the quality and viability of red blood cells in storage. Eventually, Sinopia and SDBB plan to extend the studies to include platelets.
  7. A retrospective analysis[[48]](#footnote-48) of 127 patients who underwent primary, unilateral total knee arthroplasty (TKA) for knee osteoarthritis found that peri-articular injection of tranexamic acid (TXA) was as effective as an intra-articular injection in reducing postoperative blood loss.

## Treating anaemia

* 1. A project in the Northern Territory, led by Professor Peter Morris of The Menzies School of Health Research, is trialling giving anaemic children rapid iron infusions before they are discharged from hospital. In remote Indigenous communities up to one- third of children aged 0-4 years are anaemic. The use of Ferinject will remove the need for children to have follow-up injections after discharge from hospital. This requirement of the current treatment plan has been difficult to achieve.

## Other

* 1. Scientists from John Hopkins College of Medicine in the US have shown[[49]](#footnote-49) that large bags of red cells, platelets and unthawed plasma can maintain temperature and cellular integrity in a cooler while being transported by drones[[50]](#footnote-50). They had earlier examined the impact of drone transportation on the chemical, haematological and microbial composition of the blood samples and had found that they were not negatively affected[[51]](#footnote-51).
  2. BloodCenter of Wisconsin and Eastman Chemical Company announced the results of a recent clinical trial evaluating a new plasticizer for blood bags[[52]](#footnote-52). Although  
     di-2-ethylhexyl phthalate (DEHP) has provided the health sector with a stable ortho-phthalate plasticizer for a long time, regulatory trends and consumers are demanding non-phthalate alternatives. The clinical trial results showed Eastman 168™ SG non-phthalate plasticizer to be a viable alternative for medical applications. Its sponsors say it offers a clean toxicological profile.
  3. Babesia is a significant and growing cause of transfusion-associated infections in the US, but as yet no Babesia test is approved by the FDA for blood screening. Oxford Immunotec’s Imugen division has developed both a serology test and a NAT for Babesia for use in screening. Erin D. Moritz, from the American Red Cross in Gaithersburg, Maryland, and colleagues performed arrayed fluorescence immunoassays (AFIAs) for *B. microti* antibodies and real-time polymerase-chain-reaction (PCR) assays for *B. microti* DNA on blood-donation samples from Connecticut, Massachusetts, Minnesota, and Wisconsin. This clinical trial, completed under an FDA investigational new drug application, screened around 90,000 donor samples to evaluate the effectiveness of Imugen's serology and NAT testing regime in detecting Babesia-infected donors. No reported cases of transfusion-transmitted babesiosis were associated with the screened donations from high risk states as compared with 14 cases per 253,031 unscreened donations. This suggested that Imugen's testing regime is effective in detecting *Babesia microti* antibodies and DNA in blood-donation samples. The study, funded by the American Red Cross and Imugen, was published in the *New England Journal of Medicine[[53]](#footnote-53)*.
  4. Patients with thalassemia major, who require regular blood transfusions, are at risk of iron accumulation in myocardial cells, which can lead to heart failure or fatal arrhythmia; treating doctors may routinely counter the risk by ordering iron chelation therapy, using an appropriate agent to remove excess iron from the body. Now Brazilian researchers have reported[[54]](#footnote-54) that a daily dose of amlodipine combined with chelation resulted in more effective reduction of cardiac iron in a clinical trial involving 62 patients. Amlodipine is an inexpensive drug with few side effects and is already in use for treating hypertension.
  5. A global survey[[55]](#footnote-55) has explored efforts made by hospitals to prevent central line-associated bloodstream infections (CLABSI). It found that while 80 per cent of hospitals surveyed in middle income countries have written guidelines to prevent CLABSI only 23 per cent comply with them. In high-income countries, where 81 per cent of respondents had written guidelines, compliance was only 60 per cent.

# Research (not elsewhere included)

*A wide range of scientific research has some potential to affect the use of blood and blood products. However, research projects have time horizons which vary from “useful tomorrow” to “at least ten years away”. Likelihood of success of particular projects varies, and even research which achieves its desired scientific outcomes may not lead to scaled-up production, clinical trials, regulatory approval and market development.*

* 1. The [Society for Neuroscience](https://www.sfn.org/annual-meeting/neuroscience-2016) annual meeting in San Diego in November was told that aging mice injected with blood plasma from 18-year-old humans exhibited improved memory and functioning. "Young human plasma treatment can increase neurogenesis," said Sakura Minami, a scientist at Alkahest, the biotech company backing the research. Alkahest, has already begun a trial of young blood in people with Alzheimer’s disease.
  2. Researchers in Brazil have developed a test that analyses clinical samples from patients to diagnose infection by 416 viruses found in the world's tropical regions[[56]](#footnote-56). In addition to Zika and chikungunya, the platform detects other pathogens that could become epidemics. This includes Mayaro, an alphavirus related to chikungunya that is transmitted by wild mosquitoes such as *Haemagogus janthinomys*, and Oropouche, which so far has caused epidemics confined to riverine communities in the Amazon region and is transmitted mainly by midges of the species *Culicoides paraensis*. Although the platform is designed to detect pathogens transmitted by arthropods such as mosquitoes and ticks, it can also identify infectious agents transmitted by small mammals, like hantavirus.
  3. Researchers from Yale University and Carnegie Mellon University have [corrected a gene mutation](http://www.nature.com/articles/ncomms13304) in mice that causes thalassemia. They achieved this *in vivo*, not just *in vitro*. They identified a protein in bone marrow that can activate stem cells, combined the protein with synthetic molecules that act like DNA and encased the combination in nanoparticles[[57]](#footnote-57) that were intravenously injected into the mice. The synthetic DNA, known as PNAs, bound to the target gene and prompted the cell to repair the mutation[[58]](#footnote-58). Dr. Peter Glazer, a professor of therapeutic radiology and genetics at Yale, said: "The fundamental result here is that with nanoparticles containing PNAs, along with template DNA, and simple IV infusion of molecules, we achieved enough gene editing to effectively cure the anemia in mice that had thalassemia”. Because the Yale-led team’s approach uses synthetic DNA, it avoids unplanned side effects that can come with other genome-editing methods, such as CRISPR. "We demonstrated we have extremely low off-target effects," Glazer said.
  4. **US researchers have developed a new test for sepsis that requires a drop of blood. It tests for the activation of white blood cells and gives results in 4 hours.**
  5. Ivan Azarov and colleagues at the University of Pittsburgh School of Medicine examined a modified haemoglobin-like protein found in the brain called neuroglobin (Ngb), whose function is to regulate oxygen. During purification of the protein they isolated one of its naturally-occurring mutants called Ngb H64Q, and found that carbon monoxide binds five hundred times more strongly to it than it does to haemoglobin, displacing carbon monoxide from red blood cells twelve hundred times faster than air. Theoretically, an injection of this compound should remove carbon monoxide from red blood cells so oxygen can take its place. Testing in mice showed that within minutes, measures of carbon monoxide poisoning (survival, heart rate, blood pressure) became normal. The carbon monoxide was, as expected, located in the urine, bound to the neuroglobin[[59]](#footnote-59).

# Infectious diseases

*The NBA takes an interest in infectious diseases because: the presence of disease in individual donors (e.g. influenza), or potential disease resulting from travel (e.g. malaria) means a donor must be deferred; temporary disease burden within a community (e.g. dengue in North Queensland) may limit blood collection in the community for a time; and some people may not be permitted to donate at all (e.g. people who lived in the UK for a period critical in the history of vCJD). Blood donations are tested for a number of diseases (e.g. HIV and Hepatitis B), but there are also emerging infectious diseases for which it may become necessary to test in the future (e.g. Chagas disease, Zika virus and the tick-borne babesiosis and Lyme disease).*

## Zika Virus

* 1. Researchers found the antibiotic azithromycin can block the Zika virus from infecting foetal brain tissue cells grown in lab dishes[[60]](#footnote-60).
  2. Research with mice (by scientists at The Rockefeller University in New York City and the La Jolla Institute for Allergy and Immunology in California) suggests that certain brain cells in adults may be vulnerable to damage from Zika infection[[61]](#footnote-61).
  3. US scientists[[62]](#footnote-62) funded by the National Institute for Allergy and Infectious Diseases (NIAID) have discovered a Zika antibody that reduces mother-to-foetus transmission of the virus in pregnant mice. They isolated antibody-secreting white blood cells of three people who had previously had Zika infection, generated antibodies from these cells and found that one of them, which they called ZIKV-117, neutralized every Zika virus strain they tested.
  4. A study in mice suggests that Zika infection can severely damage the animals’ testes and affect male fertility.[[63]](#footnote-63)

## Other mosquito-borne diseases

* 1. A study[[64]](#footnote-64) of over 4,000 West Nile virus patients in Texas between 2002 and 2012 found the infection had a 13 per cent fatality rate. Some patients died in the first three months, while others died of long- term complications such as kidney disease.
  2. Scientists from Colorado State University found that the *Aedes aegypti* mosquito can transmit the Zika and chikungunya viruses simultaneously in a single bite[[65]](#footnote-65).
  3. Professor Jianhong Wu, of York University in Canada, says that vaccinating against the dengue virus could not only affect the control of Zika, it could in fact make it easier for Zika to spread. Both are part of the *Flaviviridae* family transmitted through a common mosquito host. "Recent evidence suggests that dengue virus antibodies can enhance the Zika virus infection. For that reason, we developed a new math model to investigate the effect of dengue vaccination on Zika outbreaks," said Wu. The team's model shows that vaccinations for dengue increase the number of people contracting Zika. It also shows that the more people in a given population who are vaccinated against dengue, the earlier and larger the Zika outbreak[[66]](#footnote-66).

## Influenza: strains, spread, prevention and treatment

* 1. The Health and Family Planning Commission of Guangdong Province, China, reported an additional human case of avian influenza A(H7N9) in early December. Up to that time, 778 human cases of avian influenza A(H7N9) had been reported in Mainland China since 2013. In addition to the 778 cases reported on the Mainland, 23 cases imported from China have been reported in Canada (2), Hong Kong (16), Malaysia (1) and Taiwan (4).
  2. The Hong Kong Centre for Health Protection announced that a farmer from China's southern Guangxi province had been diagnosed as having A(H5N6). Her case raised China's human cases of A(H5N6) since 2014 to 17. The farmer had contact with dead poultry before the onset of symptoms.
  3. By early December, highly pathogenic A(H5N8) avian flu outbreaks had hit over a dozen countries in Europe, and Russia reported H5 infections. Taiwan officials said tests had confirmed A(H5N8) in two outbreaks in backyard birds that it first reported in early November, and later detected A(H5N8) in a poultry slaughterhouse. A(H5N8) had also appeared in India and the Middle East, sometimes in waterfowl and birds of prey that introduce the virus to local populations. Response to outbreaks of avian flu was usually culling of flocks, for example by the end of November, 190,000 ducks had been culled in the Netherlands and South Korea in November and December culled more than 8 million chicken and ducks.
  4. Although the new A(H5N8) outbreak strain was thought to pose a low threat to humans, scientists warned the lack of human immunity and expanding range in birds warranted careful monitoring. Because of concerns about H5N8 infecting cats and dogs, experts urged precautions to protect them from exposure.

## MERS-CoV (Middle East Respiratory Syndrome-Coronavirus)

* 1. By 1pm on 10 December, Saudi Arabia had recorded 1506 laboratory-confirmed cases of MERS-CoV infection, including 624 deaths.
  2. Spanish and Dutch investigators inoculated 14 pigs, 8 llamas, 14 sheep, and 8 horses with MERS-CoV intranasally. They found[[67]](#footnote-67) pigs and llamas excreted virus in the nose. Infectious MERS-CoV was found in pigs 4 days after inoculation and in llamas 7 days after inoculation, and viral titers were lower in the pigs[[68]](#footnote-68). A 2015 study found no MERS-CoV shedding in goats, sheep, and horses[[69]](#footnote-69).
  3. The International Vaccine Institute (IVI) and GeneOne Life Science have agreed to collaborate in developing a vaccine against the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). They held a signing ceremony at IVI headquarters at Seoul National University Research Park on December 6, 2016. They will jointly conduct a clinical trial of GeneOne’s DNA-based MERS-CoV vaccine candidate, GLS-5300. Inovio Pharmaceuticals is co-developing this vaccine with GeneOne Life Science. IVI will add technical, laboratory and financial support for GLS-5300 clinical trials in Korea[[70]](#footnote-70). Dr. J. Joseph Kim, Inovio’s President & CEO and a member of the Board of Trustees of IVI, said: “This collaborative funding is part of a US$ 34 million grant publicly pledged in 2015 from the Samsung Foundation to IVI to support the development of a MERS vaccine for emergency use in Korea and internationally. The goal of this funding is to expand clinical testing of GLS-5300 toward emergency use authorization by the Korean government as well as authorities of other countries. Inovio’s GLS-5300 remains the only vaccine for MERS in clinical testing”.
  4. Researchers led b**y** Matthew B Frieman, associate professor at the University of Maryland School of Medicine, have modified a rabies virus, so that it has a protein from the MERS virus. They then treated the modified virus chemically, inactivating it so that it cannot replicate. This inactivated virus is now the vaccine, which triggers an immune response but poses no danger to the recipient. The study found that the vaccine protected mice from infection with MERS[[71]](#footnote-71).

## Ebola virus disease

* 1. At the annual Grand Challenges Meeting of the Bill and Melinda Gates Foundation in London on 26 October, 2016, Carl Davis (of the Emory Vaccine Center) and Guy Cavet, (senior vice president and chief technology officer at the biotechnology company Atreca) presented their collaborative research on Ebola virus disease. They found that antibodies generated from the blood of survivors neutralized the Ebola virus in the laboratory and protected mice from a lethal viral challenge[[72]](#footnote-72).

## Other diseases: occurrence, diagnosis, prevention and treatment

* 1. Taiwan's Centers for Disease Control announced the discovery of a virus that could be a new type of lyssavirus, following a forensic examination conducted on the carcass of a bat.
  2. A report from the US Centers for Disease Control and Prevention (CDC), World Health Organization (WHO), UNICEF and other global health organizations says nearly 400 children worldwide are dying from measles each day, 75 per cent of them in Indonesia, India, Pakistan, Ethiopia, Nigeria and the Democratic Republic of Congo.
  3. Jennifer Manne-Goehler, of Beth Israel Deaconess Medical Center in Boston, and colleagues told IDWeek 2016 in New Orleans[[73]](#footnote-73) that Chagas Disease, an infection caused by the parasite T. cruzi, now affects 300,000 people in the US. Their estimates were based on data of foreign-born Hispanics, the prevalence estimates of Chagas in those immigrants’ home countries, the number of infections identified in donated blood supply in the US, data provided by AABB[[74]](#footnote-74), and cases treated based on drug release data from the CDC. The US states in which the disease is most prevalent are California and Texas, and New York and New Jersey are among the top five.
  4. Scientists have found no evidence that bat flies have a primary role in spreading Australia’s dangerous Hendra virus[[75]](#footnote-75). (Australian native fruit bats have been identified as reservoir hosts).

http://pixel.tcog.cp1.news.com.au/track/component/article/32737d606c52314e17fc4524b983fad3?esi=true&t_template=s3/chronicle-tg_tlc_storyheader/index&t_product=HeraldSun&td_device=desktop

1. Spark included nine haemophilia B patients in the ongoing phase I/II study, yielding an average factor IX level of 28 per cent of normal, measured 12 weeks after the one-off infusion. The first treated patient has been followed for one year and has a factor IX level of 33 per cent of normal. Another three patients, followed for more than seven months have factor IX activity ranging from 36 per cent to 46 per cent. On entry to the study the patients had factor IX levels of approximately 1 per cent of normal. Shire says a minimum factor IX level of 12 per cent of normal is considered necessary to prevent chronic bleeding in the joints. *SPK-9001: Adeno-Associated Virus Mediated Gene Transfer for Hemophilia B Achieves Sustained Mean Factor IX Activity Levels of >30% without Immunosuppression* Abstract # 91358 [↑](#footnote-ref-1)
2. One of the patients with a negative immune response to SPK-9001 has a factor IX level that fell from 32 per cent to 12 per cent of normal but has now stabilized with steroids. The second patient's factor IX level fell from 71 per cent to 68 per cent. [↑](#footnote-ref-2)
3. Genentech, a member of the Roche group, presented *Bleeding Events and Safety Outcomes in Patients with Hemophilia A with Inhibitors: A Prospective, Multicenter, Non-Interventional Study.* Poster #3800. There have been three pivotal studies underway to explore the safety and efficacy of emicizumab in the treatment of haemophilia A: a Phase III study in people 12 years of age or older with haemophilia A with factor VIII inhibitors investigating weekly dosing; a Phase III study in people younger than 12 years of age with factor VIII inhibitors investigating weekly dosing; and a Phase III study in people 12 years of age or older without factor VIII inhibitors investigating weekly and every other week dosing. [↑](#footnote-ref-3)
4. *Longitudinal Analysis of Long-term Safety and Efficacy of Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) in Adults/Adolescents with Severe Hemophilia A*: Poster #1413; *Longitudinal Analysis of Long-term Safety and Efficacy of Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) in Previously Treated Children with Severe Hemophilia A:* Poster I #1414; *Clinical Outcomes in Adults/Adolescents with Hemophilia B Treated Long Term with Recombinant Factor IX Fc Fusion Protein (rFIXFc) Prophylaxis: Interim Results of the B-YOND Extension Study*: Poster #1416; and *Long-term Efficacy and Quality of Life With Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) Prophylaxis in Pediatric, Adolescent, and Adult Subjects with Target Joints and Severe Hemophilia A*: Poster #3791 T [↑](#footnote-ref-4)
5. marketed as Elocta in Europe and the Middle East [↑](#footnote-ref-5)
6. ≤2 spontaneous bleeding episodes over one year. A target joint has frequent bleeds, which may lead to chronic joint disease [↑](#footnote-ref-6)
7. Most impact (≥ 20 per cent) occurred in areas such as physical health, sports and leisure, and work and school. [↑](#footnote-ref-7)
8. *Evaluation of rFIXFc-XTEN bleeding efficacy in Hemophilia-B mouse models*: Poster #3757 [↑](#footnote-ref-8)
9. Idelvion is approved in the US, European Union, Canada, Australia, Japan and Switzerland. [↑](#footnote-ref-9)
10. Crea R. et al. *Four Decade Cumulative Review of Thrombo-Embolic Events Reported with the Use of Activated Prothrombin Complex Concentrate in Congenital Haemophilia*. American Society of Hematology. San Diego, California. December 3-6, 2016. Available at: [http://www.bloodjournal.org/content/128/22/503](http://www.bloodjournal.org/content/128/22/5031) [↑](#footnote-ref-10)
11. Knappe S, et al. *Synergistic Effects of a Procoagulant Bispecific Antibody and Rescue Therapies on Thrombin Generation- a Potential Safety Risk*. American Society of Hematology. San Diego, California. December 3-6, 2016. Available at: <http://www.bloodjournal.org/content/128/22/4952> [↑](#footnote-ref-11)
12. **online 3 December in *The New England Journal of Medicine*** [↑](#footnote-ref-12)
13. Crizanlizumab is manufactured by Novartis [↑](#footnote-ref-13)
14. Kenneth I. Ataga, from the University of North Carolina at Chapel Hill, and colleagues conducted a phase II trial over 60 sites in which 198 patients with sickle cell disease were randomized to receive low-dose crizanlizumab, high-dose crizanlizumab, or placebo administered intravenously over a period of 52 weeks. They found that the median rate of crises per year was 1.63 and 2.98 for high-dose crizanlizumab versus placebo, respectively. The median rate of uncomplicated crises per year was 1.08 and 2.91 for high-dose crizanlizumab versus placebo, respectively. The median time to the first crisis and to the second crisis was much longer with high-dose crizanlizumab therapy than with placebo (4.07 versus 1.38 months and 10.32 versus 5.09 months). See also Ataga KI et al, Abstract #1 presented at ASH. [↑](#footnote-ref-14)
15. Marina Cavazzana**,** poster presentation Abstract #2311: *Update from the HGB-205 Phase 1/2 Clinical Study of LentiGlobin Gene Therapy: Sustained Clinical Benefit in Severe Hemoglobinopathies* [↑](#footnote-ref-15)
16. *Specific inhibition of AKT with ARQ 092, an orally-available selective allosteric AKT inhibitor, attenuates acute vaso-occlusive events in sickle cell disease,* was an oral presentation by the University of Illinois College of Medicine. It can be viewed at [https://www.arqule.com/wp-content/uploads/ASH-2016-ARQ-092-in-Sickle-Cell-Disease-.pdf](http://cts.businesswire.com/ct/CT?id=smartlink&url=https%3A%2F%2Fwww.arqule.com%2Fwp-content%2Fuploads%2FASH-2016-ARQ-092-in-Sickle-Cell-Disease-.pdf&esheet=51471199&newsitemid=20161203005009&lan=en-US&anchor=https%3A%2F%2Fwww.arqule.com%2Fwp-content%2Fuploads%2FASH-2016-ARQ-092-in-Sickle-Cell-Disease-.pdf&index=1&md5=0a50a53335b4a8a5780cdfa141263c3f) [↑](#footnote-ref-16)
17. Galadanci NA, et al. Abstract 122. ASH Annual Meeting and Exposition; 3-6 December, 2016; San Diego. [↑](#footnote-ref-17)
18. In this group of disorders the bone marrow doesn’t produce enough healthy blood cells. MDS can cause anaemia and other issues, such as low numbers of white blood cells or platelets. Blood transfusions or anti-anaemia drugs like Amgen’s epoetin alfa (Epogen) come with safety risks. [↑](#footnote-ref-18)
19. a genetic problem responsible for a rare type of anaemia with no approved treatments [↑](#footnote-ref-19)
20. Senior researcher Dr. Allan Doctor, critical care specialist at Washington University School of Medicine in St. Louis. [↑](#footnote-ref-20)
21. Researchers replaced 70 per cent of mice blood volume with the blood substitute and said those mice were indistinguishable from those who received a transfusion from another mouse. [↑](#footnote-ref-21)
22. The coating was developed by the study's lead researcher, Dipanjan Pan, an assistant professor of bioengineering with the University of Illinois at Urbana-Champaign. [↑](#footnote-ref-22)
23. Plasminogen is a protein synthesized by the liver and circulated in the blood. It is essential in wound healing, cell migration, tissue remodelling, angiogenesis and embryogenesis. [↑](#footnote-ref-23)
24. A condition commonly associated with plasminogen deficiency is ligneous conjunctivitis, characterized by thick, woody growths on the conjunctiva. Untreated it can cause blindness. The growths can recur after surgical excision, and consecutive surgeries may be needed. Hypoplasminogenemia is a multiorgan disease that can affect the ears, sinuses, tracheobronchial tree, genitourinary tract, and gingiva. Tracheobronchial lesions including hyperviscous secretions can cause respiratory failure. Hydrocephalus can occur in children with severe hypoplasminogenemia, apparently related to the deposition of fibrin in the cerebral ventricular system. [↑](#footnote-ref-24)
25. Kamada and Shire (then Baxter) made an exclusive arrangement for the distribution and license of Kamada’s AAT IV in 2010. Shire is the exclusive distributor of the product in the US, Canada, Australia and New Zealand. [↑](#footnote-ref-25)
26. A Phase I/II trial with G1-AAT IV for the treatment of steroid refractory GvHD is currently ongoing at the Fred Hutchinson Cancer Research Center in Seattle, also in collaboration with Shire. An interim analysis from this study was published in 2016 in, Marcones et al, “Response of Steroid-Refractory Acute GVHD to a1-Antitrypsin*”,* *Biology of Blood and Marrow Transplantation* (2016). [↑](#footnote-ref-26)
27. AATD is a hereditary condition severely affecting lung function. Sufferers have a low level or complete absence of alpha-1-proteinase inhibitor (A1-PI), a natural protein that inhibits neutrophil elastase, thereby preventing destruction of lung tissue. Severe deficiency of A1-PI is associated with a strong tendency for the development of emphysema, a form of chronic obstructive pulmonary disease (COPD). It adversely affects quality of life and significantly reduces life expectancy. [↑](#footnote-ref-27)
28. **Zemaira** is a purified form of Alpha1 Proteinase Inhibitor (human) currently approved in the US, Canada, Brazil, and New Zealand, where it is indicated for chronic augmentation and maintenance therapy in adults with Alpha1 deficiency and clinical evidence of emphysema. CSL Behring markets **Zemaira** as Respreeza in Europe. [↑](#footnote-ref-28)
29. Flora Peyvandi et al, “A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A”, *N Engl J Med* 2016; 374:2054-2064 [May 26, 2016](http://www.nejm.org/toc/nejm/374/21/) DOI: 10.1056/NEJMoa1516437 [↑](#footnote-ref-29)
30. In April 2014, Vascular Solutions committed to a Cooperative Research And Development Program with the USAMMDA to develop RePlas. The USAMMDA funds the regulatory and clinical work and Vascular Solutions retains all ownership rights to the product and intellectual property. [↑](#footnote-ref-30)
31. ARS is caused by exposure to very high levels of radiation as in a nuclear disaster, and can lead to severe illness or death. ARS involves severe, potentially lethal damage to the bone marrow’s ability to produce blood cells and platelets, as well as to other systems and organs. Catastrophic damage to bone marrow quickly makes victims vulnerable to life-threatening haemorrhage, infection and anaemia. [↑](#footnote-ref-31)
32. The Animal Rule regulatory pathway allows for approval of treatments for diseases such as ARS in which human trials are not ethical or feasible. With this pathway, the FDA uses animal efficacy studies and human safety data as the basis for product approval. The NIAID has supported and completed two previous studies of PLX-R18, in which small animal models were used to evaluate the efficacy and mode of action of PLX-R18 as a potential treatment for the hematologic disorders associated with ARS. The more recent of the studies showed that intramuscular administration of PLX-R18 resulted in a statistically significant improvement in the recovery of white blood cell, red blood cell, and platelet levels in animals exposed to high levels of radiation, and described the treatment’s mechanism of action. NIAID’s initial studies of PLX-R18 showed a substantial, statistically significant improvement in 30-day survival and overall survival of irradiated rodents given PLX-R18 versus a control group. [↑](#footnote-ref-32)
33. The factor VIII preparation thereby recreates a wild-type preparation. Unlike conventional recombinant factor VIII preparations, which are produced using hamster cells, the wild-type factor VIII shows natural human structures. Dr Thomas Becker, Senior Director Haematology of Biotest, says: “… a recombinant factor VIII preparation from a human cell line…has many of the advantages of a natural plasma clotting factor…” [↑](#footnote-ref-33)
34. About one in five people who experience a heart attack have another one within a year, often within the first month. [↑](#footnote-ref-34)
35. # C.Michael Gibson et al, “Safety and Tolerability of CSL112, a Reconstituted, Infusible, Plasma-Derived Apolipoprotein A-I, After Acute Myocardial Infarction: The AEGIS-I Trial (ApoA-I Event Reducing in Ischemic Syndromes I)”, https://doi.org/10.1161/CIRCULATIONAHA.116.025687

    Originally published November 15, 2016 [↑](#footnote-ref-35)
36. The Marcum awards have a local constraint, in that they recognize companies and individuals who add to the vitality and stability of the Philadelphia area. Dennis Jackman, CSL Behring's senior vice president of Global Healthcare Policy and External Affairs, expressed the company's ongoing commitment to the region, and said he was honoured to accept the award on behalf of CSL Behring and its more than 14,000 employees worldwide, including more than 500 in King of Prussia. [↑](#footnote-ref-36)
37. The study, "Toward a Sustainable Blood Supply in the United States: An Analysis of the Current System and Alternatives for the Future," is available at [http://www.rand.org](http://www.rand.org/). [↑](#footnote-ref-37)
38. Recommendations:

    1. that the Australian Government Department of Health engage with stakeholders following the publication of the National Serology Reference Laboratory review to discuss the findings of the review and any bearing those may have on testing for Lyme disease in Australia.
    2. that the Australian Government increase funding for research into tick-borne pathogens as a matter of urgency. This funding should include funding for research on pathogens which may cause infection; funding for research on whether newly-identified pathogens can cause illness in humans; and funding for the development of diagnostic tests which can detect infection by any newly-identified pathogens endemic to Australia.
    3. that government medical authorities, in consultation with stakeholders including the Australian Chronic Infectious and Inflammatory Diseases Society (ACIIDS) and the Karl McManus Foundation, establish a clinical trial of treatment guidelines developed by ACIIDS with the aim of determining a safe treatment protocol for patients with tick-borne illness.
    4. that the Australian Government allocate funding for research into medically-appropriate treatment of tick-borne disease, and that medical authorities measure the value of treatment in terms of patient recovery and return to health. The best treatment options must then be developed into clinical treatment guidelines.
    5. that the Australian Government Department of Health facilitate, as a matter of urgency, a summit to develop a cooperative framework which can accommodate patient and medical needs with the objective of establishing a multidisciplinary approach to addressing tick-borne illness across all jurisdictions.
    6. that federal, state and territory health agencies, through the Council of Australian Governments Health Council, develop a consistent, national approach to addressing tick-borne illness.
    7. that the Australian Government Department of Health urgently undertake an epidemiological assessment of the prevalence of suspected tick-borne illness in Australia, the process and findings of which are to be made publicly available.
    8. that the Australian Government Department of Health establish the prevalence and geographical distribution of overseas-acquired Lyme disease in Australia.
    9. that Australian medical authorities and practitioners addressing suspected tick-borne illness consistently adopt a patient-centric approach that focusses on individual patient symptoms, rather than a disease label; and that they remove 'chronic Lyme disease', 'Lyme-like illness' and similar 'Lyme' phrases from diagnostic discussions.
    10. that, to help the referral of patients for guided and comprehensive pathology testing, medical practitioners work with pathologists, especially microbiologists, immunologists, chemical pathologists and hæmatologists to optimise diagnostic testing for each patient.
    11. that the Australian Government Department of Health work closely with the Australian Medical Association and Royal Australian College of General Practitioners to ensure that general practitioners have a better understanding of how to treat patients who present with complex symptoms.
    12. that treatment guidelines developed by Australian medical authorities emphasise the importance of a multidisciplinary, case conference approach to patient care, involving consultation between general practitioners and specialists with expertise in neurology, psychiatry, rheumatology, immunology, infectious diseases and microbiology

    [↑](#footnote-ref-38)
39. # E. Berntop et al, “European retrospective study of real-life haemophilia treatment”, *Haemophilia,* DOI: 10.1111/hae.13111

    [↑](#footnote-ref-39)
40. Patients were randomized in a 1:2 ratio to receive either fresh red blood cells (11 days; interquartile range 8-16) or standard issue red blood cells (23 days; interquartile range, 16-31) for transfusion.  [↑](#footnote-ref-40)
41. including cardiovascular surgery, intensive care, and cancer patients [↑](#footnote-ref-41)
42. Although further research is needed to evaluate whether red blood cells stored during the last week of storage (35-42 days) are associated with increased mortality. [↑](#footnote-ref-42)
43. [Heddle NM, Cook RJ, Arnold DM, et al. “Effect of short-term vs. long-term blood storage on mortality after transfusion”. *N Engl J Med.* [e-published 24 October 2016] DOI: 10.1056/NEJMoa1609014](https://www.ncbi.nlm.nih.gov/pubmed/27775503) [↑](#footnote-ref-43)
44. [Carson JL, Guyatt G, Heddle NM, Grossman BJ, Cohn CS, Fung MK, Gernsheimer T, Holcomb JB, Kaplan LJ, Katz LM, Peterson N, Ramsey G, Rao SV, Roback JD, Shander A, Tobian AAR. “Clinical practice guidelines from the AABB:  red blood cell transfusion thresholds and storage”,*JAMA*. [e-published 12 Oct 2016].](https://www.ncbi.nlm.nih.gov/pubmed/?term=.++Clinical+practice+guidelines+from+the+AABB%3A++red+blood+cell+transfusion+thresholds+and+storage.) [↑](#footnote-ref-44)
45. [Etchill E, Sperry J, Zuckerbraun B, Alarcon L, Brown J, Schuster K, Kaplan L, Piper G, Peitzman A, Neal MD. “The confusion continues: results from an American Association for the Surgery of Trauma survey on massive transfusion practices among United States trauma centers”. *Transfusion* 2016;**56**: 2478-86.](http://onlinelibrary.wiley.com/doi/10.1111/trf.13755/full) [↑](#footnote-ref-45)
46. RePHILL (REsuscitation with Pre-HospItaL bLood products) multi-centre randomised controlled trial [↑](#footnote-ref-46)
47. *Blood Management Guidelines Can Reduce Blood Wastage and Save Millions of Dollars.* American College of Surgeons. <https://www.facs.org/media/press-releases/2016/nsqip-blood-071716> [↑](#footnote-ref-47)
48. # Zhenyang Mao et al, “A comparative, retrospective study of peri-articular and intra-articular injection of tranexamic acid for the management of postoperative blood loss after total knee arthroplasty”, *BMC Musculoskeletal Disorders,* D**OI**:**** 10.1186/s12891-016-1293-3BM

    [↑](#footnote-ref-48)
49. Timothy Amukele et al., “Drone transportation of blood products”, *Transfusion.*11 November 2016, DOI: 10.1111/trf.13900 [↑](#footnote-ref-49)
50. The drone was flown by remote control for around 13 kms to 20 kms while 100 metres above ground for about 26.5 minutes. [↑](#footnote-ref-50)
51. See the Journal of Clinical Microbiology, August 2016 [↑](#footnote-ref-51)
52. The clinical trial was reported at the 2016 AABB Annual Meeting in Orlando, Florida, on 24 October by Sharon Graminske, manager of applied research at BloodCenter of Wisconsin: *In Vitro Evaluation of DEHT Plasticized PVC Blood Bags for Red Blood Cell Storage in AS-1 and PAGGSM Preservative Solutions.*  [↑](#footnote-ref-52)
53. 8 December 2016 [↑](#footnote-ref-53)
54. # Juliano L. Fernandes et al, “A randomized trial of amlodipine in addition to standard chelation therapy in patients with thalassemia major”.

    *Blood* 2016 128:1555-1561; doi: https://doi.org/10.1182/blood-2016-06-721183 [↑](#footnote-ref-54)
55. # Cristina Valencia et al, “Poor adherence to guidelines for preventing central line-associated bloodstream infections (CLABSI): results of a worldwide survey”, Antimicrobial Resistance & Infection Control2016**5**:49, **DOI:** 10.1186/s13756-016-0139-y **Published:** 22 November 2016

    [↑](#footnote-ref-55)
56. Reported in the journal *PLoS Neglected Tropical Diseases* [↑](#footnote-ref-56)
57. These nanoparticles are nontoxic and nonimmunogenic, already approved by FDA for treatment of neurodegenerative diseases. [↑](#footnote-ref-57)
58. Peter Glazer, Mark Saltzman et al, “In vivo correction of anaemia in β-thalassemic mice by γPNA-mediated gene editing with nanoparticle delivery.” *Nature Communications* 7, doi:10.1038/ncomms13304 [↑](#footnote-ref-58)
59. Ivan Azarov et al. "Five-coordinate H64Q neuroglobin as a ligand-trap antidote for carbon monoxide poisoning." *Science Translational Medicine* 8 (368): 368ra173. Published: 7-Dec-2016. DOI: 10.1126/scitranslmed.aah6571 [↑](#footnote-ref-59)
60. Hanna Retallacka,et al, “Zika virus cell tropism in the developing human brain and inhibition by azithromycin”, *Proceedings of the National Academy of Sciences*, 2016. [↑](#footnote-ref-60)
61. La Jolla Institute for Allergy and Immunology, news release, Oct. 24, 2016 [↑](#footnote-ref-61)
62. from Vanderbilt University, Washington University in St. Louis and Philadelphia-based Integral Molecular [↑](#footnote-ref-62)
63. The study was published in *Nature* [↑](#footnote-ref-63)
64. presented at the 2016 Meeting of the American Society of Tropical Medicine and Hygiene [↑](#footnote-ref-64)
65. The study results were presented at a meeting of the American Society of Tropical Medicine and Hygiene. [↑](#footnote-ref-65)
66. The study was published in the journal *Scientific Report*. [↑](#footnote-ref-66)
67. Vergara-Alert J, van den Brand JMA, Widagdo W, Muñoz M, Raj VS, Schipper D, et al. “Livestock susceptibility to infection with Middle East respiratory syndrome coronavirus”. *Emerging Infectious Diseases*. February 2017 <http://dx.doi.org/10.3201/eid2302.161239> [↑](#footnote-ref-67)
68. The authors wrote: "The finding that pigs can be infected with MERS-CoV suggests that other members of the family Suidae could be susceptible to the virus, such as common warthogs (Phacochoerus africanus), bushpigs (Potamochoerus larvatus), and wild boars (Sus scrofa scrofa). Indeed, these animals are commonly found in the Greater Horn of Africa or the Middle East, sharing territories and water sources with dromedaries." [↑](#footnote-ref-68)
69. [Danielle R. Adney](http://www.mdpi.com/search?authors=Danielle%20R.%20Adney&orcid=) et al., “Inoculation of Goats, Sheep, and Horses with MERS-CoV Does Not Result in Productive Viral Shedding”, *Viruses,* 19 August 2015. Viruses 2016, 8(8), 230; doi:[10.3390/v8080230](http://dx.doi.org/10.3390/v8080230) [↑](#footnote-ref-69)
70. Inovio, GeneOne and its academic collaborators have evaluated GLS-5300 in mice, rhesus macaques and camels. As reported in Science Translational Medicine, the vaccine induced robust immune responses in all three species. GLS-5300 has been specifically able to induce 100 per cent protection from a live virus challenge in a rhesus macaque non-human primate study. The results of the non-human primate study supported the conduct of the first phase I clinical trial of 75 healthy volunteers in the US in collaboration with the Walter Reed Army Institute of Research. Interim data is expected early in 2017. [↑](#footnote-ref-70)
71. Christoph Wirblich et al, “Vaccines and Antiviral Agents: One-Health: a Safe, Efficient, Dual-Use Vaccine for Humans and Animals against Middle East Respiratory Syndrome Coronavirus and Rabies Virus”, J. Virol. *January 2017 91:2 15 e02040-16; Accepted manuscript posted online 2 November 2016,* doi: 10.1128/JVI.02040-16 [↑](#footnote-ref-71)
72. The Gates Foundation funded the Atreca antibody research and the US Defense Advanced Research Projects Agency (DARPA) funded the studies led by Emory. The antibodies were evaluated by a DARPA-funded consortium that included teams at the Aaron Diamond Aids Research Center, the US Centers for Disease Control and Prevention (CDC), the Scripps Research Institute, Stanford University, the University of Wisconsin School of Veterinary Medicine, and the US Army Medical Research Institute of Infectious Diseases (USAMRIID). [↑](#footnote-ref-72)
73. <http://www.mdmag.com/conference-coverage/idweek-2016/chagas-disease-affects-more-than-300000-in-us#sthash.rXdZnO9k.dpuf> [↑](#footnote-ref-73)
74. Formerly the American Association of Blood Banks [↑](#footnote-ref-74)
75. Vidgen, M. E., et al, (2016), “No Evidence of Hendra Virus Infection in the Australian Flying-fox Ectoparasite Genus Cyclopodia”, *Zoonoses and Public Health*. doi:10.1111/zph.12303 [↑](#footnote-ref-75)