Richtlijn “Erytrocytentransfusies bij kinderen & neonaten met kanker”

Versie 2
Mei 2022

INITIATIEF
Nederlandse Vereniging voor Kindergeneeskunde

IN SAMENWERKING MET
Nederlandse Vereniging voor Anesthesiologie
Nederlandse Vereniging voor Bloedtransfusie
Nederlandse Vereniging voor Heelkunde
Nederlandse Vereniging voor Klinische Chemie en Laboratoriumgeneeskunde
Nederlandse Vereniging voor Radiotherapie en Oncologie
Stichting Kinderoncologie Nederland
Vereniging Kinderkanker Nederland
Verpleegkundigen & Verzorgenden Nederland

MET ONDERSTEUNING VAN
Prinses Máxima Centrum voor Kinderoncologie, Utrecht

FINANCIERING
De richtlijnontwikkeling werd gefinancierd uit de Stichting Kwaliteitsgelden Medisch Specialisten (SKMS)

COLOFON

RICHTLIJN ERYTROCYTENTRANSFUSIES BIJ KINDEREN EN NEONATEN MET KANKER ©, 2022

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Inhoudsopgave

Lijst met afkortingen

AGREE II	Appraisal of Guidelines for Research & Evaluation II
ASCO	American Society of Clinical Oncology
BCSH	British Committee for Standards in Haematology
FMS	Federatie Medisch Specialisten/Dutch Association of Medical Specialists
GIN	Guidelines International Network
GRADE	Grading Recommendations Assessment, Development and Evaluation
Hb	Hemoglobine
IGHG	International Guideline Harmonization Group
iPOG	International Pediatric Oncology Group
JPAC	Joint Professional Advisory Committee
NICE	National Institute for Health and Care Excellence
NVA	Nederlandse Vereniging voor Anesthesiologie
NVB	Nederlandse Vereniging voor Bloedtransfusie
NVH	Nederlandse Vereniging voor Heelkunde
NVK	Nederlandse Vereniging voor Kindergeneeskunde
NVKC	Nederlandse Vereniging voor Klinische Chemie en Laboratoriumgeneeskunde
NVRO	Nederlandse Vereniging voor Radiotherapie en Oncologie
RBC	Red blood cell
RCT	Randomized controlled trial (NL: gerandomiseerde gecontroleerde studie)
RevMan	Review Manager
RoB	Risk of Bias
SCT	Stamceltransplantatie
SKION	Stichting Kinderoncologie Nederland
VKN	Vereniging Kinderkanker Nederland
V&VN	Verpleegkundigen & Verzorgenden Nederland

Omrekentabel hemoglobine (Hb) waarden

Hb in g/dL	Hb in mmol/L
1 g/dL	0.6 mmol/L
2 g/dL	1.2 mmol/L
3 g/dL	1.9 mmol/L
4 g/dL	2.5 mmol/L
5 g/dL	3.1 mmol/L
6 g/dL	3.7 mmol/L
7 g/dL	4.3 mmol/L
8 g/dL	5.0 mmol/L
9 g/dL	5.6 mmol/L
10 g/dL	6.2 mmol/L
11 g/dL	6.8 mmol/L
12 g/dL	7.5 mmol/L

Samenstelling werkgroep

Samenstelling kernwerkgroep

- Drs. D.M. (Demi) Kruimer, ANIOS kindergeneeskunde, MSc Healthcare Management en arts-onderzoeker kinderoncologie Prinses Máxima Centrum, Utrecht, op persoonlijke titel
- Dr. E.A.H. (Erik) Loeffen, AIOS kindergeneeskunde, epidemioloog en postdoc onderzoeker kinderoncologie Prinses Máxima Centrum, Utrecht en Beatrix Kinderziekenhuis (Universitair Medisch Centrum Groningen), NVK
- Drs. D.C. (Debbie) Stavleu, arts-onderzoeker kinderoncologie Prinses Máxima Centrum, Utrecht en Beatrix Kinderziekenhuis (Universitair Medisch Centrum Groningen), op persoonlijke titel
- Dr. R.L. (Renée) Mulder, postdoc onderzoeker, richtlijn ontwikkelaar, methodoloog, Prinses Máxima Centrum, Utrecht, op persoonlijke titel
- Prof. Dr. L.C.M. (Leontien) Kremer, kinderarts, hoogleraar late effecten in kinderoncologie, Prinses Máxima Centrum, Utrecht en hoogleraar gepaste zorg, Amsterdam UMC, Amsterdam, NVK
- Prof. Dr. W.J.E. (Wim) Tissing, kinderoncoloog, hoogleraar Supportive Care, Prinses Máxima Centrum, Utrecht en Beatrix Kinderziekenhuis (Universitair Medisch Centrum Groningen), NVK

Samenstelling werkgroep

- Dr. D. (Dorine) Bresters, kinderoncoloog, Prinses Máxima Centrum, Utrecht, NVK
- Mw. J.H.P. (Janneke) Evers, MANP, verpleegkundig specialist, Prinses Máxima Centrum, Utrecht, V&VN
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- Dr. M.M. (Melanie) Hagleitner, kinderoncoloog, Prinses Máxima Centrum, Utrecht, NVK
- Dr. K.J.M. (Katja) Heitink-Pollé, kinderhematoloog-oncoloog, Prinses Máxima Centrum, Utrecht, NVK
- Drs. E.J. (Elise) Huisman, kinderarts-hematoloog, Sophia Kinderziekenhuis (Erasmus MC), Rotterdam, NVB
- Dhr. dr. G.O.R. (Geert) Janssens, kinderradiotherapeut, UMC Utrecht, Utrecht, NVRO
- Dr. P.H.M. (Philip) Kuijper, labaratorium specialist hematologie, Máxima Medisch Centrum, Veldhoven, NvKC
- Dhr. M.O. (Maarten) Mensink, kinderanesthesioloog, Prinses Máxima Centrum, Utrecht, NVA
- Dr. J.G. (Jeroen) Noordzij, kinderarts, Reinier de Graaf Gasthuis, Delft, NVK
- Mw. I. (Ida) Ophorst, MSc, kinderoncologie verpleegkundige, expert verpleegkundig onderzoek, Prinses Máxima Centrum, Utrecht, V&VN
- Mw. W. (Willemijn) Plieger, beleidsmedewerker VKN (Vereniging Kinderkanker Nederland)
- Dr. J. (Judith) Spijkerman, kinderarts, fellow kinderoncologie, Prinses Máxima Centrum, Utrecht, NVK
- Dr. A.F.W. (Lideke) van der Steeg, kinderchirurg, Prinses Máxima Centrum, Utrecht, NVvH
- Dr. M.D. (Marianne) van de Wetering, kinderoncoloog, Prinses Máxima Centrum, Utrecht, SKION

Bijzondere dank aan:

- Mw. E. (Erika) Heerema, onafhankelijk voorzitter

Samenvatting (Nederlands)

Doelstelling. Het doel is het ontwikkelen van een evidence-based richtlijn met aanbevelingen over het geven van profylactische erytrocytentransfusies bij kinderen met kanker die een curatieve behandeling ondergaan.

Definities. Neonaten zijn in deze richtlijn gedefinieerd als personen met een leeftijd tussen de 0 en 28 dagen. Kinderen zijn gedefinieerd als personen met een leeftijd tussen de 28 dagen en 18 jaar. Onder het woord 'kanker' vallen alle kwaadaardige neoplasmata. In geval van kinderkanker gaat het specifiek om de groepen hemato-oncologie, neuro-oncologie en de solide tumoren.

Probleemomschrijving. Eén van de effecten van de behandeling van kinderkanker is beenmergonderdrukking, wat kan resulteren in onder andere een anemie, waarvoor er een erytrocytentransfusie gegeven kan worden. Deze transfusies worden over het algemeen goed getolereerd, maar ze zijn geassocieerd met nadelige korte- en langetermijneffecten. Daarbij komt dat bloedproducten dure, maar ook een beperkte hulpbron zijn in de huidige gezondheidszorg. Vanwege deze kosten en de potentiële schade moet het geven van erytrocytentransfusies beperkt worden tot het noodzakelijke. Die balans wordt in deze richtlijn gezocht, zodat er zo min mogelijk bloedproducten gegeven hoeven te worden, met zo min mogelijk bijwerkingen.

Aanbevelingen.
Onderstaande is een samenvatting van de aanbevelingen uit de richtlijn "Erytrocytentransfusies bij kinderen met kanker". In deze samenvatting ontbreken het wetenschappelijk bewijs en de overwegingen die tot de aanbevelingen geleid hebben. Lezers van deze samenvatting worden voor deze informatie verwezen naar de volledige richtlijn. Deze samenvatting van aanbevelingen staat niet op zichzelf.

<u>Kinderen met kanker algemeen</u>

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence	Overweeg een hemoglobine (Hb) grens van 4.3 mmol/L voor erytrocytentransfusie bij kinderen met kanker.
ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence	Wij adviseren *tegen* een hemoglobine (Hb) grens van 3.7 mmol/L voor erytrocytentransfusie bij kinderen met kanker.
STERKE aanbeveling, ZEER LAGE KWALITEIT evidence	Wij adviseren sterk *tegen* een hemoglobine (Hb) grens van 3.1 mmol/L of lager voor erytrocytentransfusie bij kinderen met kanker.

<u>Neonaten met kanker algemeen</u>

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence	Overweeg een hemoglobine (Hb) grens van 6.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker indien ze minder dan 1 week oud zijn.
ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence	Overweeg een hemoglobine (Hb) grens van 5.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker indien ze tussen de 1 en 3 weken oud zijn.

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence	Overweeg een hemoglobine (Hb) grens van 4.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker indien ze tussen de 3 en 4 weken oud zijn.

Kinderen met kanker en sepsis

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence	Overweeg een hemoglobine (Hb) grens van 4.3 mmol/L voor erytrocytentransfusies bij stabiele kinderen met kanker en sepsis.

ZWAKKE aanbeveling, EXPERT EVIDENCE	De werkgroep is van mening dat het aanbevolen wordt om voor hemodynamisch onstabiele kinderen met kanker en sepsis en tekenen van zuurstoftekort (bijv. gebruik van inotropen, verhoogd lactaatgehaalte) een Hb grens te overwegen die varieert tussen 4.3 mmol/L en 6.2 mmol/L.

Neonaten met kanker en sepsis

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence	Overweeg een hemoglobine (Hb) grens van 6.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker en sepsis indien ze minder dan 1 week oud zijn.

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence	Overweeg een hemoglobine (Hb) grens van 5.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker en sepsis indien ze tussen de 1 en 3 weken oud zijn.

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence	Overweeg een hemoglobine (Hb) grens van 4.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker en sepsis indien ze tussen de 3 en 4 weken oud zijn.

Kinderen met kanker die radiotherapie ondergaan

ZWAKKE aanbeveling, EXPERT EVIDENCE	De werkgroep is van mening dat een hemoglobine (Hb) grens van 4.3 mmol/L voor erytrocytentransfusie moet worden gehandhaafd bij kinderen met kanker die radiotherapie ondergaan.

Neonaten met kanker die radiotherapie ondergaan

ZWAKKE aanbeveling, EXPERT EVIDENCE	De werkgroep is van mening dat een hemoglobine (Hb) grens van 6.5 mmol/L voor erytrocytentransfusie moet worden gehandhaafd bij neonaten met kanker die radiotherapie ondergaan indien ze minder dan 1 week oud zijn.

ZWAKKE aanbeveling, EXPERT EVIDENCE	De werkgroep is van mening dat een hemoglobine (Hb) grens van 5.5 mmol/L voor erytrocytentransfusie moet worden gehandhaafd bij neonaten met kanker die radiotherapie ondergaan indien ze tussen de 1 en 3 weken oud zijn.

ZWAKKE aanbeveling, EXPERT EVIDENCE	De werkgroep is van mening dat een hemoglobine (Hb) grens van 4.5 mmol/L voor erytrocytentransfusie moet worden gehandhaafd bij neonaten met kanker die radiotherapie ondergaan indien ze tussen de 3 en 4 weken oud zijn.

Kinderen met kanker en cardiale en/of pulmonale comorbiditeiten

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence	Overweeg een hemoglobine (Hb) grens van 4.3 mmol/L voor erytrocytentransfusies bij kinderen met kanker en cardiale en pulmonale comorbiditeiten.

ZWAKKE aanbeveling, EXPERT EVIDENCE	De werkgroep is van mening dat bij een hemodynamisch instabiel kind met kanker en pulmonale en/of cardiale comorbiditeiten (bijv. gebruik van inotropica, verhoogd lactaatgehalte) een hogere Hb grens worden kan overwogen.

ZWAKKE aanbeveling, EXPERT EVIDENCE	Voor kinderen aan de ECMO: - Bij ernstig zieke kinderen aan ECMO raden we aan maatregelen te nemen om het aantal blootstellingen van donoren te minimaliseren. - Bij ernstig zieke kinderen aan ECMO raden we aan om naast de Hb concentratie ook fysiologische meetwaarden en biomarkers voor zuurstoftoevoer te gebruiken om een erytrocytentransfusie te geven. Toediening van een erytrocytentransfusie moet gebaseerd zijn op tekenen van onvoldoende cardiorespiratoire ondersteuning of verminderde systemische en/of regionale zuurstoftoediening. - Bij ernstig zieke kinderen aan ECMO is er onvoldoende bewijs om een specifieke strategie aan te bevelen over het nemen van beslissingen over erytrocytentransfusies met behulp van fysiologische metrieken en biomarkers.

Neonaten met kanker en cardiale en/of pulmonale comorbiditeiten

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence	Overweeg een hemoglobine (Hb) grens van 7.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker en cardiale en pulmonale comorbiditeiten indien ze minder dan 1 week oud zijn.

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence	Overweeg een hemoglobine (Hb) grens van 6.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker en cardiale en pulmonale comorbiditeiten indien ze tussen de 1 en 3 weken oud zijn.

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence	Overweeg een hemoglobine (Hb) grens van 5.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker en cardiale en pulmonale comorbiditeiten indien ze tussen de 3 en 4 weken oud zijn.

Kinderen en neonaten met kanker en hyperleukocytose

ZWAKKE aanbeveling, EXPERT EVIDENCE	Bij kinderen en neonaten met kanker en hyperleukocytose, zijn wij van mening dat een erytrocytentransfusie terughoudend moet worden gegeven tot het aantal leukocyten gedaald is tot 100 x 10^9/L of lager, tenzij er klinische tekenen zijn van een ernstige anemie of in geval van een Hb lager dan 3.1 mmol/L. Indien nodig, alleen transfunderen met maximaal 5 ml/kg/3-4 uur.

Bestraalde bloedproducten bij kinderen en neonaten met kanker

ZWAKKE aanbeveling, EXPERT EVIDENCE	De werkgroep is van mening dat bestraalde bloedproducten moeten worden gebruikt in het geval van een HLA-gelijkenis tussen donor (product) en ontvanger: a) Transfusie tussen 1e tot en met 3e graads verwanten van cel houdende bloedproducten; b) HLA compatibele trombocytenconcentraten.

ZWAKKE aanbeveling, EXPERT EVIDENCE	De werkgroep is van mening dat het granulocyten transfusieproduct bestraald moeten worden.

ZWAKKE aanbeveling, EXPERT EVIDENCE	De werkgroep is van mening dat bestraalde bloedproducten moeten worden gebruikt afhankelijk van de immuunstatus van de patiënt: a) Tijdens intra-uteriene transfusies, daarna tot en met 6 maanden na de à terme datum; b) Kinderen met aangeboren gecombineerde immuundeficiëntie (bijv. SCID); c) Verworven immuundeficiëntie zoals bij: - Allogene stamceltransplantatie tot 1 jaar na transplantatie; - Autologe stamceltransplantatie tot 6 maanden na transplantatie; - Na toepassing van donor lymfocyten infusie (DLI) of infusie van cytotoxische T-lymfocyten (CTL) tot 1 jaar na transfusie.

ZWAKKE aanbeveling, EXPERT EVIDENCE	De werkgroep is van mening dat bestraalde bloedproducten moeten worden gebruikt in geval van patiënten met een langdurige T-cel depletie na medicatie: a) Fludarabine of andere T-cel depleterende therapie zoals het farmacotherapeutisch kompas dat aangeeft (tot 6 maanden na staken therapie); b) Medicatie die in combinatie met de ziekte een langdurige T-cel depletie geven, zoals anti-CD52 behandeling bij hematologische ziekten en ATG-behandeling bij aplastische anemie vanaf de instelling van de toediening tot 6 maanden na het voltooien van de behandeling.

ZWAKKE aanbeveling, EXPERT EVIDENCE	De werkgroep is van mening dat bestraalde bloedproducten moeten worden gebruikt in patiënten die CAR-T celtherapie krijgen vanaf 4 weken voor de leukaferese tot 1 jaar na de infusie. Tenzij anders beschreven in het onderzoeksprotocol.

Erytrocytentransfusievolume bij kinderen met kanker

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence	Overweeg een transfusievolume van 10-15 ml/kg bij kinderen met kanker.

ZWAKKE aanbeveling, EXPERT EVIDENCE	Overweeg een transfusievolume van maximaal 2 donoreenheden (volume tussen 500-600 ml).

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence	Wij adviseren *tegen* een transfusievolume van 20 ml/kg of hoger bij kinderen met kanker.

Erytrocytentransfusievolume bij neonaten met kanker

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence	Overweeg een transfusievolume van 10-15 ml/kg bij neonaten met kanker.

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence	Wij adviseren *tegen* een transfusievolume van 20 ml/kg of hoger bij neonaten met kanker.

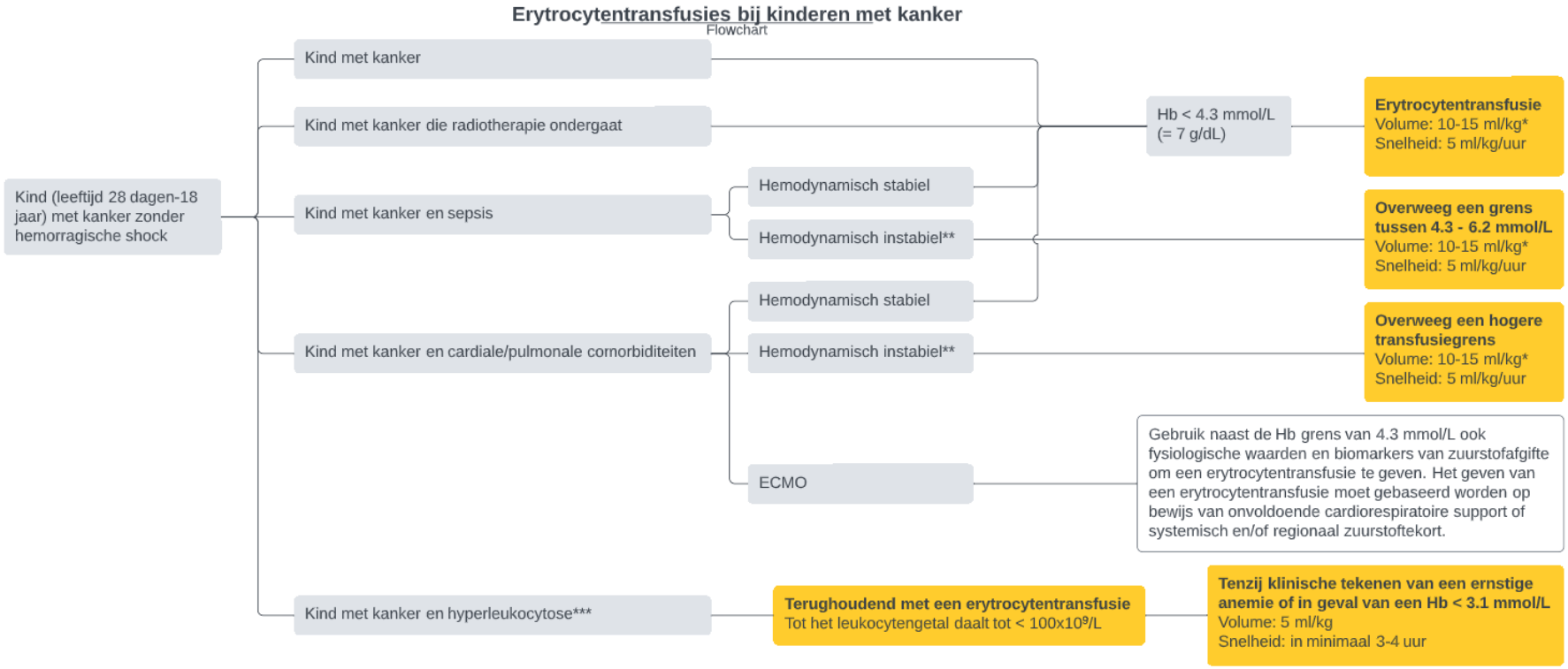
Transfusiesnelheden van erytrocytentransfusies bij kinderen met kanker

ZWAKKE aanbeveling, EXPERT EVIDENCE	De werkgroep is van mening dat de transfusiesnelheid van een erytrocytentransfusie bij kinderen met kanker 5 ml/kg/uur moet zijn.

Transfusiesnelheden van erytrocytentransfusies bij neonaten met kanker

ZWAKKE aanbeveling, EXPERT EVIDENCE	De werkgroep is van mening dat de transfusiesnelheid van een erytrocytentransfusie bij neonaten met kanker 5 ml/kg/uur moet zijn.

Flowchart van de aanbevelingen bij kinderen met kanker



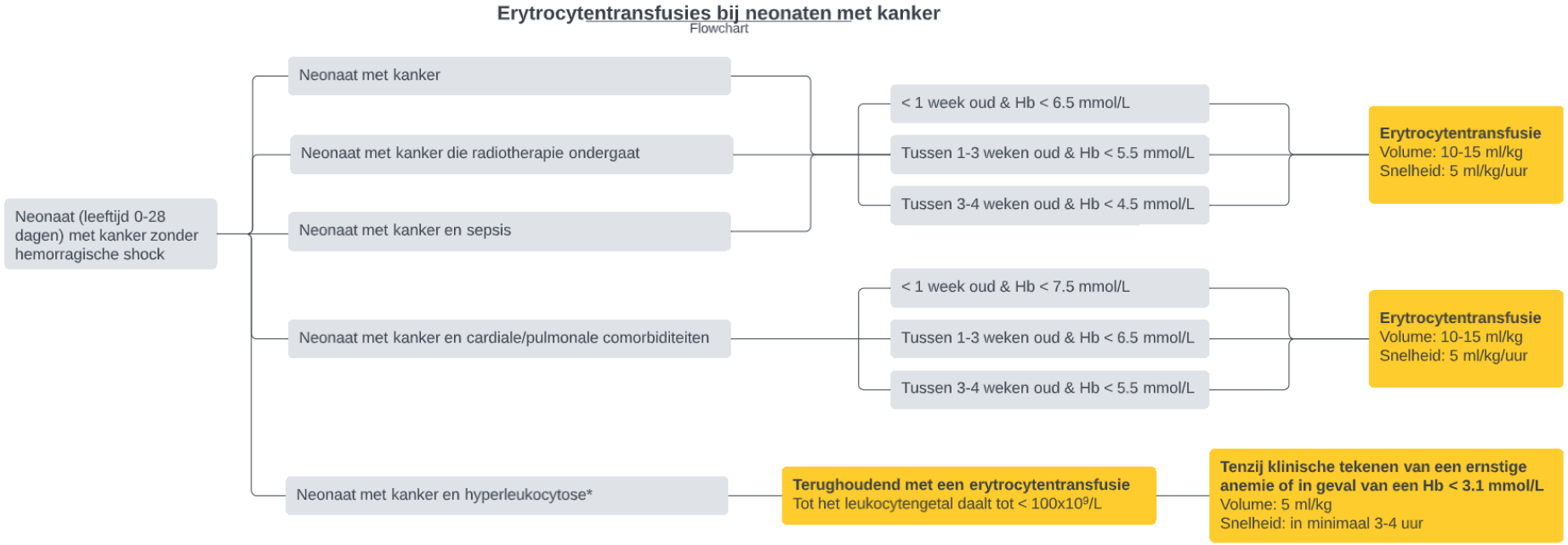
Indicaties voor bestraalde erytrocytenproducten bij kinderen met kanker

- Bij HLA gerelateerde producten en donoren:
  a) Transfusie tussen 1e tot en met 3e graads verwanten van cel houdende bloedproducten;
  b) HLA compatibele trombocytenconcentraten.
- Granulocyten transfusies.
- Afhankelijk van de immuunstatus van de patiënt:
  a) Intra-uteriene transfusies, daarna tot en met 6 maanden na à terme datum;
  b) Kinderen met aangeboren gecombineerde immuundeficiëntie (zoals SCID).
  c) Verworven immuundeficiëntie zoals bij:
     - Allogene stamceltransplantatie tot 1 jaar na transplantatie;
     - Autologe stamceltransplantatie tot 6 maanden na transplantatie;
     - Na toepassing van donor lymfocyten infusie (DLI) of infusie van cytotoxische T-lymfocyten (CTL) tot 1 jaar na transfusie.

- Patiënten met een langdurige T-cel depletie na medictatie;
  a) Fludarabine of andere T-cel depleterende therapie als het farmacotherapeutisch kompas dit aangeeft (tot 6 maanden na het staken van de therapie).
  b) Medicatie die in combinatie met de ziekte een langdurige T-cel depletie geven, zoals anti-CD52 behandeling bij hematologische ziekten en ATG behandeling bij aplastische anemie vanaf de instelling van de toediening tot 6 maanden na het voltooien van de behandeling.
- Patiënten die een CAR-T cel behandeling ondergaan vanaf 4 weken voor de leukaferese tot 1 jaar na de infusie. Tenzij anders beschreven in het onderzoeksprotocol.

* Met maximaal 2 donoreenheden (500-600 ml).
** Bijv. gebruik van inotropica, verhoogd lactaatgehalte.
*** In geval van een klinisch relevante hyperleukocytose en een leukocytaferese noodzakelijk is, kan een erytrocytentransfusie gebruikt als vervangingsvloeistof om de anemie isovolemisch en gedoseerd te corrigeren.

Flowchart van de aanbevelingen bij neonaten met kanker



Indicaties voor bestraalde erytrocytenproducten bij neonaten met kanker
- Bij HLA gerelateerde producten en donoren:
  a) Transfusie tussen 1e tot en met 3e graads verwanten van cel houdende bloedproducten;
  b) HLA compatibele trombocytenconcentraten.
- Granulocyten transfusies.
- Afhankelijk van de immuunstatus van de patiënt:
  a) Intra-uteriene transfusies, daarna tot en met 6 maanden na à terme datum;
  b) Kinderen met aangeboren gecombineerde immuundeficiëntie (zoals SCID).
  c) Verworven immuundeficiëntie zoals bij:
    - Allogene stamceltransplantatie tot 1 jaar na transplantatie;
    - Autologe stamceltransplantatie tot 6 maanden na transplantatie;
    - Na toepassing van donor lymfocyten infusie (DLI) of infusie van cytotoxische T-lymfocyten (CTL) tot 1 jaar na transfusie.

- Patiënten met een langdurige T-cel depletie na medictatie;
  a) Fludarabine of andere T-cel depleterende therapie als het farmacotherapeutisch kompas dit aangeeft (tot 6 maanden na het staken van de therapie).
  b) Medicatie die in combinatie met de ziekte een langdurige T-cel depletie geven, zoals anti-CD52 behandeling bij hematologische ziekten en ATG behandeling bij aplastische anemie vanaf de instelling van de toediening tot 6 maanden na het voltooien van de behandeling.
- Patiënten die een CAR-T cel behandeling ondergaan vanaf 4 weken voor de leukaferese tot 1 jaar na de infusie. Tenzij anders beschreven in het onderzoeksprotocol.

* In geval van een klinisch relevante hyperleukocytose en een leukocytaferese noodzakelijk is, kan een erytrocytentransfusie gebruikt als vervangingsvloeistof om de anemie isovolemisch en gedoseerd te corrigeren.

Algemene inleiding (Nederlands)

Aanleiding voor het maken van de richtlijn

Erytrocytentransfusies zijn een belangrijke schakel binnen de ondersteunende zorg (*supportive care*) bij kinderen met kanker en degenen die stamceltransplantaties (SCT) moeten ondergaan. Kinderen met kanker kunnen bijvoorbeeld een erytrocytentransfusie nodig hebben als gevolg van de onderliggende oncologische ziekte of vanwege beenmergdepressie gedurende hun behandeling als gevolg van de chemotherapie. Een stabiel kind met kanker heeft mogelijk andere hemoglobine (Hb) grenzen voor een transfusie nodig dan een instabiel kind met kanker, zoals het geval is bij bijvoorbeeld sepsis. Neonaten met kanker of kinderen met kanker en comorbiditeiten, zoals hart- of longaandoeningen, zijn mogelijke unieke populaties waarin de optimale grens voor erytrocytentransfusies kan verschillen.
Er is echter beperkt bewijs beschikbaar met betrekking tot transfusiebeleid in deze populatie. Deze richtlijn is de eerste richtlijnen die specifiek voor de kinderoncologie is opgesteld. Deze richtlijn beoogt antwoorden te geven op onder andere de belangrijke vragen bij welk Hb grens een kind of neonaat met kanker een erytrocytentransfusie moet krijgen, met welk volume en met welke snelheid deze gegeven dient te worden. Dit alles is gebaseerd op het best beschikbare wetenschappelijke onderzoek, welke zal worden besproken in deze richtlijn. Deze richtlijn is bedoeld als leidraad voor een verantwoord en wenselijk handelen voor de zorgverleners binnen de kinderoncologie in de dagelijkse klinische praktijk.
De volgende onderwerpen komen aan in deze richtlijn aan bod:

1. Erytrocytentransfusies bij kinderen en neonaten met kanker;
2. Erytrocytentransfusies bij kinderen en neonaten met kanker en sepsis;
3. Erytrocytentransfusies bij kinderen en neonaten met kanker die radiotherapie ondergaan;
4. Erytrocytentransfusies bij kinderen en neonaten met kanker en cardiale en/of pulmonale comorbiditeiten;
5. Erytrocytentransfusies bij kinderen en neonaten met kanker en hyperleukocytose;
6. Bestraalde erytrocytentransfusies bij kinderen en neonaten met kanker;
7. Erytrocytentransfusievolume bij kinderen en neonaten met kanker;
8. Transfusiesnelheden van erytrocytentransfusies bij kinderen en neonaten met kanker.

Doel van de richtlijn

Het doel van deze richtlijn is het ontwikkelen van een evidence-based richtlijn met aanbevelingen over het geven van profylactische erytrocytentransfusies bij kinderen met kanker die een curatieve behandeling ondergaan. Deze richtlijn is niet bedoeld om aanbevelingen te doen voor kinderen met kanker in een niet-curatieve setting of voor kinderen met kanker en actief bloedverlies.

Probleemomschrijving en afbakening

Jaarlijks krijgen ongeveer 600 kinderen in Nederland kanker (Bron: *Wat is kinderkanker?* | *Prinses Máxima Centrum,* 2021). De kans om kinderkanker te overleven is in de afgelopen 30 jaar drastisch veranderd. In de jaren ‘75 was de overleving minder dan 20 procent, ten opzichte van meer dan 70-80% gemiddeld in het nieuwe millennium in de hoge-inkomenslanden. Bij volwassenen manifesteert kanker zich in meer dan 80% van de gevallen in epitheliale organen, longen en gastro-intestinaal. Bij de kinderoncologie ligt dat anders, daar spelen vaker embryonale en immature cellen een rol, die zich voortdurend vermenigvuldigen en niet uitrijpen (Imbrach, 2014). De behandeling van kinderkanker kan bestaan uit chemotherapie, immunotherapie, radiotherapie en/of operaties. Eén van de effecten van de behandeling van kanker is beenmergonderdrukking wat kan resulteren in onder andere een anemie, waarvoor er een erytrocytentransfusie gegeven kan worden (Schrijvers, 2011). Deze transfusies worden over het algemeen goed getolereerd, maar zijn geassocieerd met nadelige korte- en lange-termijn effecten. Korte termijneffecten zijn onder andere volumeoverbelasting, transfusiereacties (waaronder de zeldzame doch ernstige complicatie anafylaxie), virale transmissie en transfusie-gerelateerd acute longschade (Bateman, 2008). Op de lange termijn komt onder andere ijzerstapeling voor (Lucarelli, 1990). Daarbij komt ook dat bloedproducten dure, maar ook een beperkte hulpbron zijn in de huidige gezondheidszorg (*De prijs van bloed*, n.d.). Als laatste vermindert een bloedtransfusie de kwaliteit van leven van de kinderen en het gezin, gezien de noodzakelijke (dag)opname. Vanwege voornoemde nadelen moet het gebruik van bloedtransfusies worden geoptimaliseerd. In de afgelopen jaren zijn steeds meer conservatieve erytrocytentransfusie strategieën geïmplementeerd, waaronder ook in de kindergeneeskunde. Echter, een te laag Hb gehalte is potentieel dodelijk (Viele & Weiskopf, 1994). Verscheidene studies hebben laten zien dat een beperkter transfusiebeleid niet per se leidt tot meer mortaliteit, dan wel morbiditeit (Lacroix, 2007; Hébert, 1999; Bell, 2005). Die balans wordt in deze richtlijn uitgezocht, zodat er zo min mogelijk bloedproducten gegeven hoeven te worden, met zo min mogelijk bijwerkingen en een optimale kwaliteit van leven.

In deze richtlijn worden alleen en specifiek indicaties voor profylactische erytrocytentransfusies beschreven. Andere (medicamenteuze) interventies of factoren die van invloed zijn op het Hb van de patiënt vallen buiten de scoop van deze richtlijn. De richtlijn is gericht op kinderen met kanker (0 tot 18 jaar) en hun ouders of verzorgers.

Beoogde gebruikers van deze richtlijn

Deze richtlijn is geschreven voor alle zorgverleners die betrokken zijn bij de zorg voor kinderen met kanker. Deze aanbevelingen zullen ook beschikbaar worden, met een meer toegankelijke uitleg, voor kinderen met kanker en hun ouders en verzorgers.

Definities

Door de werkgroep zijn neonaten in deze richtlijn gedefinieerd als een personen met een leeftijd tussen de 0 en 28 dagen. Kinderen zijn gedefinieerd als personen met een leeftijd tussen de 28 dagen en 18 jaar. Sepsis is niet van tevoren gedefinieerd door de werkgroep, maar besloten de definitie van de auteur van de betreffende studie te volgen. Hyperleukocytose is gedefinieerd als het aantal witte bloedcellen > $100x10^9$/L, veroorzaakt door proliferatie van leukemische cellen. Door de werkgroep is besloten dat onder het woord 'kanker' alle kwaadaardige neoplasmata vallen. In geval van kinderkanker gaat het specifiek om de groepen hemato-oncologie, neuro-oncologie en de solide tumoren. Actief bloedverlies is gedefinieerd als een beschadiging van de bloedvaten, waardoor er bloed buiten het vaatbed treedt.

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Verantwoording Algemeen (Nederlands)

Geldigheid van richtlijn
Voor het beoordelen van de actualiteit van deze richtlijn is de werkgroep niet in stand gehouden. Uiterlijk in 2027 bepaalt het bestuur van de Nederlandse Vereniging voor Kindergeneeskunde (NVK) of de modules van deze richtlijn nog actueel zijn. De geldigheid van de richtlijn komt eerder te vervallen indien nieuwe ontwikkelingen aanleiding zijn een herzieningstraject te starten.
De NVK is regiehouder van deze richtlijn en eerstverantwoordelijke op het gebied van de actualiteitsbeoordeling van de richtlijn. De andere aan deze richtlijn deelnemende wetenschappelijke verenigingen of gebruikers van de richtlijn delen de verantwoordelijkheid en informeren de regiehouder over relevante ontwikkelingen binnen hun vakgebied.

Initiatief
NVK.

Algemene gegevens
De richtlijnontwikkeling werd gefinancierd uit de Stichting Kwaliteitsgelden Medisch Specialisten (SKMS). De financier heeft geen enkele invloed gehad op de inhoud van de richtlijn.

Doelgroepen
Voor wie is deze richtlijn bedoeld?
Deze richtlijn is geschreven voor alle leden van de beroepsgroepen die betrokken zijn bij de zorg voor kinderen en neonaten met kanker die een curatieve behandeling ondergaan zoals, maar niet beperkt tot: medisch specialisten, verpleegkundigen of andere zorgverleners en patiënten die te maken hebben met kinderen met kanker.

Voor patiënten
Transfusies van rode bloedcellen zijn een belangrijk onderdeel van de ondersteunende zorg tijdens de behandeling van kinderkanker. Door bijvoorbeeld het geven van chemotherapie kan er beenmergonderdrukking ontstaan en kan er een tekort ontstaan aan rode bloedcellen. De behandelend arts kan een transfusie van rode bloedcellen voorschrijven wanneer deze noodzakelijk is en nadat er toestemming is gegeven door de wettelijk vertegenwoordiger (mits er geen sprake is van een acute en levensbedreigende situatie). Deze rode bloedcellen heten ook wel erytrocyten. Om het gebruik van bloedtransfusies zo optimaal mogelijk te houden, zijn in deze richtlijn adviezen voor erytrocytentransfusies bij kinderen met kanker vastgesteld, zodat ieder kind met kanker op het juiste moment een bloedproduct kan krijgen.

Samenstelling werkgroep
Voor het ontwikkelen van de richtlijn is in 2019 een werkgroep ingesteld, bestaande uit vertegenwoordigers van alle relevante specialismen die betrokken zijn bij de zorg voor kinderen met kanker (zie hiervoor de samenstelling van de werkgroep op pagina 6).

Belangenverklaringen
Alle werkgroep leden hebben schriftelijk verklaard of zij directe financiële belangen (betrekking bij een commercieel bedrijf, persoonlijke financiële belangen, onderzoeksfinanciering) of indirecte belangen (persoonlijke relaties, reputatiemanagement, kennisvalorisatie) hebben gehad. Een overzicht van de belangen van werkgroep leden en het oordeel over het omgaan met eventuele belangen vindt u in onderstaande tabel. De ondertekende belangenverklaringen zijn op te vragen bij het secretariaat van de NVK.

Kernwerkgroep

Kernwerkgroeplid	Functie	Nevenfuncties	Gemelde belangen	Ondernomen actie
Kruimer	Arts-onderzoeker kinderoncologie Prinses Máxima Centrum, Utrecht	ANIOS Kindergeneeskunde	Geen	Geen
Loeffen	Postdoc onderzoeker kinderoncologie Prinses Máxima Centrum, Utrecht en Beatrix Kinderziekenhuis (Universitair Medisch Centrum Groningen)	AIOS Kindergeneeskunde Epidemioloog B, Voorzitter Stichting Kinderboek & Wetenschap	Geen	Geen
Stavleu	Arts-onderzoeker kinderoncologie Prinses Máxima Centrum, Utrecht en Beatrix Kinderziekenhuis	Geen	Geen	Geen

	(Universitair Medisch Centrum Groningen)			
Mulder	Postdoc onderzoeker, richtlijn ontwikkelaar, methodoloog, Prinses Máxima Centrum, Utrecht	Geen	Geen	Geen
Tissing	Kinderoncoloog, hoogleraar Supportive Care, Prinses Máxima Centrum, Utrecht en Beatrix Kinderziekenhuis (Universitair Medisch Centrum Groningen)	Geen	Geen	Geen
Kremer	Kinderarts, hoogleraar late effecten in kinderoncologie, Prinses Máxima Centrum, Utrecht en hoogleraar gepaste zorg, Amsterdam UMC, Amsterdam	Adviseur kenniscentrum palliatieve zorg, beurzen via KiKa, KWF, ZonMW in het kader van werkzaamheden onderzoeksgroep Late Effecten	Geen	Geen

Werkgroep

Werkgroeplid	Functie	Nevenfuncties	Gemelde belangen	Ondernomen actie
Bresters	Kinderoncoloog, Prinses Máxima Centrum, Utrecht	Geen	Geen	Geen
Evers	Verpleegkundig specialist, Prinses Máxima Centrum, Utrecht	Geen	Geen	Geen
Gestel, van	Kinderarts-intensivist, Wilhelmina Kinderziekenhuis, Utrecht	Geen	Geen	Geen
Hagleitner	Kinderoncoloog, Prinses Máxima Centrum, Utrecht	Geen	Geen	Geen
Heitink-Pollé	Kinderhematoloog-oncoloog, Prinses Máxima Centrum, Utrecht	Voorzitter redactie werkboek kinderhematologie	Geen	Geen
Huisman	Kinderarts-hematoloog/Transfusiespecialist, Sophia Kinderziekenhuis (Erasmus MC), Rotterdam	Transfusie specialist UTG, Sanquin Bloedvoorziening	Geen	Geen
Janssens	Kinderradiotherapeut, Wilhelmina Kinderziekenhuis, Utrecht	Geen	Geen	Geen
Kuijper	Labaratorium specialist hematologie, Máxima Medisch Centrum, Veldhoven	Docent Fontys Hogeschool	Geen	Geen
Mensink	Kinderanesthesioloog, Prinses Máxima Centrum, Utrecht	Bestuurslid sectie pijn- en palliatieve geneeskunde NVA	Geen	Geen
Noordzij	Kinderarts-infectioloog/ immunoloog, Reinier de Graad Gasthuis, Delft	Geen	Geen	Geen

Ophorst	Kinderoncologie verpleegkundige, expert verpleegkundig onderzoek, Prinses Máxima Centrum, Utrecht	Geen	Geen	Geen
Plieger	Beleidsmedewerker VKN (Vereniging Kinderkanker Nederland)	Geen	Geen	Geen
Spijkerman	Kinderarts, fellow kinderoncologie, Prinses Máxima Centrum, Utrecht	Geen	Geen	Geen
Steeg, van der	Kinderchirurg, Prinses Máxima Centrum, Utrecht	Geen	Geen	Geen
Wetering, van de	SKION taakgroep Supportive Care, Kinderoncoloog, Prinses Máxima Centrum, Utrecht	Geen	Geen	Geen

Patiëntenperspectief

Er werd ruim aandacht besteed aan het patiëntenperspectief door de Vereniging Kinderkanker Nederland (VKN) af te vaardigen in de werkgroep en in nauw contact te blijven gedurende het hele proces.

Kostenimplicaties

Door de toenemende aandacht voor de kosten in de gezondheidszorg neemt het belang van richtlijnen die doelmatig handelen bevorderen toe. Met de totstandkoming van deze richtlijn zijn kostenimplicaties meegenomen in de beoordeling. Er is getracht de kosten zo laag mogelijk te houden.

Implementatie

Dit plan is opgesteld ter bevordering van de implementatie van de richtlijn “Erytrocytentransfusies bij kinderen en neonaten met kanker”. Voor het opstellen van dit plan is een inventarisatie gedaan van de mogelijke bevorderende en belemmerende factoren voor het naleven van de aanbevelingen. Daarbij heeft de werkgroep een advies uitgebracht over het tijdspad voor implementatie, de daarvoor benodigde randvoorwaarden en de acties die voor verschillende partijen ondernomen dienen te worden.

<u>Werkwijze</u>

De werkgroep heeft per aanbeveling geïnventariseerd:

- Per wanneer de aanbeveling geïmplementeerd moet kunnen zijn;
- De verwachte impact van implementatie van de aanbeveling op de zorgkosten;
- Randvoorwaarden om de aanbeveling te kunnen implementeren;
- Mogelijke barrières om de aanbeveling te kunnen implementeren;
- Mogelijke acties om de implementatie van de aanbeveling te bevorderen;
- Verantwoordelijke partij voor de te ondernemen acties.

Voor iedere aanbeveling is nagedacht over de hierboven genoemde punten. Er werd in deze richtlijn onderscheid gemaakt tussen ‘sterk geformuleerde aanbevelingen’ en ‘zwak geformuleerde aanbevelingen’. In het eerste geval doet de werkgroep een duidelijke uitspraak over iets dat zeker wel of zeker niet gedaan moet worden. In het tweede geval wordt de aanbeveling minder zeker gesteld (bijv. “overweeg om …”) en wordt dus meer ruimte gelaten voor alternatieve opties. Voor ‘sterk geformuleerde aanbevelingen’ geldt dat zij zo spoedig mogelijk geïmplementeerd dienen te worden.

Aanbeveling	**Tijdspad voor implementatie**	**Verwachte impact op zorgkosten**	**Randvoorwaarden voor implementatie**	**Mogelijke barrières voor implementatie**	**Te ondernemen acties voor implementatie**	**Verantwoordelijken voor acties**
<u>Kinderen met kanker</u>						
Overweeg een hemoglobine (Hb) grens van 4.3 mmol/L voor erytrocytentransfusie bij kinderen met kanker.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum

Wij adviseren *tegen* een hemoglobine (Hb) grens van 3.7 mmol/L voor erytrocytentransfusie bij kinderen met kanker.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
Wij adviseren sterk *tegen* een hemoglobine (Hb) grens van 3.1 mmol/L of lager voor erytrocytentransfusie bij kinderen met kanker.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
<u>Neonaten met kanker</u>						
Overweeg een hemoglobine (Hb) grens van 6.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker indien ze minder dan 1 week oud zijn.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
Overweeg een hemoglobine (Hb) grens van 5.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker indien ze tussen de 1 en 3 weken oud zijn.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
Overweeg een hemoglobine (Hb) grens van 4.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker indien ze tussen de 3 en 4 weken oud zijn.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
<u>Kinderen met kanker en sepsis</u>						
Overweeg een hemoglobine (Hb) grens van 4.3 mmol/L voor erytrocytentransfusies bij stabiele kinderen met kanker en sepsis.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
De werkgroep is van mening dat het aanbevolen wordt om voor hemodynamisch onstabiele kinderen met kanker en sepsis en tekenen van zuurstoftekort (bijv. gebruik van inotropen, verhoogd lactaatgehaalte) een Hb grens te overwegen die varieert tussen 4.3 mmol/L en 6.2 mmol/L.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
<u>Neonaten met kanker en sepsis</u>						
Overweeg een hemoglobine (Hb) grens van 6.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker en sepsis indien ze minder dan 1 week oud zijn.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
Overweeg een hemoglobine (Hb) grens van 5.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker en sepsis indien ze tussen de 1 en 3 weken oud zijn.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
Overweeg een hemoglobine (Hb) grens van 4.5 mmol/L voor	Direct	Geen	Verspreiding van de	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken	*Supportive Care* groep,

erytrocytentransfusie bij neonaten met kanker en sepsis indien ze tussen de 3 en 4 weken oud zijn.			richtlijn		beroepsgroepen/Verspreiding van de richtlijn	Prinses Máxima Centrum
Kinderen met kanker die radiotherapie ondergaan						
De werkgroep is van mening dat een hemoglobine (Hb) grens van 4.3 mmol/L voor erytrocytentransfusie moet worden gehandhaafd bij kinderen met kanker die radiotherapie ondergaan.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
Neonaten met kanker die radiotherapie ondergaan						
De werkgroep is van mening dat een hemoglobine (Hb) grens van 6.5 mmol/L voor erytrocytentransfusie moet worden gehandhaafd bij neonaten met kanker die radiotherapie ondergaan indien ze minder dan 1 week oud zijn.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
De werkgroep is van mening dat een hemoglobine (Hb) grens van 5.5 mmol/L voor erytrocytentransfusie moet worden gehandhaafd bij neonaten met kanker die radiotherapie ondergaan indien ze tussen de 1 en 3 weken oud zijn.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
De werkgroep is van mening dat een hemoglobine (Hb) grens van 4.5 mmol/L voor erytrocytentransfusie moet worden gehandhaafd bij neonaten met kanker die radiotherapie ondergaan indien ze tussen de 3 en 4 weken oud zijn.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
Kinderen met kanker en cardiale/pulmonale comorbiditeiten						
Overweeg een hemoglobine (Hb) grens van 4.3 mmol/L voor erytrocytentransfusies bij kinderen met kanker en cardiale en pulmonale comorbiditeiten.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
De werkgroep is van mening dat bij een hemodynamisch instabiel kind met kanker en pulmonale en/of cardiale comorbiditeiten (bijv. gebruik van inotropica, verhoogd lactaatgehalte) een hogere Hb grens worden kan overwogen.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
De werkgroep is van mening dat voor kinderen aan de ECMO de	Direct	Geen	Verspreiding van de	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken	*Supportive Care* groep,

aanbevelingen uit de richtlijn van Valentine (2018) overgenomen moeten worden[1].			richtlijn		beroepsgroepen/Verspreiding van de richtlijn	Prinses Máxima Centrum
<u>Neonaten met kanker en cardiale/pulmonale comorbiditeiten</u>						
Overweeg een hemoglobine (Hb) grens van 7.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker en cardiale en pulmonale comorbiditeiten indien ze minder dan 1 week oud zijn.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
Overweeg een hemoglobine (Hb) grens van 6.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker en cardiale en pulmonale comorbiditeiten indien ze tussen de 1 en 3 weken oud zijn.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
Overweeg een hemoglobine (Hb) grens van 5.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker en cardiale en pulmonale comorbiditeiten indien ze tussen de 3 en 4 weken oud zijn.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
<u>Kinderen en neonaten met kanker en hyperleukocytose</u>						
Bij kinderen en neonaten met kanker en hyperleukocytose, zijn wij van mening dat een erytrocytentransfusie terughoudend moet worden gegeven tot het aantal leukocyten gedaald is tot 100 x 10^9/L of lager, tenzij er klinische tekenen zijn van een ernstige anemie of in geval van een Hb lager dan 3.1 mmol/L. Indien nodig, alleen transfunderen met maximaal 5 ml/kg/3-4 uur.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
<u>Bestraalde erytrocytentransfusies bij kinderen en neonaten met kanker</u>						
De werkgroep is van mening dat bestraalde bloedproducten moeten worden gebruikt in het geval van een HLA-gelijkenis tussen donor (product) en ontvanger[1].	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
De werkgroep is van mening dat het granulocyten transfusieproduct bestraald moeten worden.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
De werkgroep is van mening dat bestraalde bloedproducten moeten worden gebruikt afhankelijk van de immuunstatus van de patiënt[1].	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum

De werkgroep is van mening dat bestraalde bloedproducten moeten worden gebruikt in geval van patiënten met een langdurige T-cel depletie na medicatie[1].	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
De werkgroep is van mening dat bestraalde bloedproducten moeten worden gebruikt in geval van patiënten die CAR-T celtherapie krijgen vanaf 4 weken voor de leukaferese tot 1 jaar na de infusie. Tenzij anders beschreven in het onderzoeksprotocol.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
<u>Hoog- of laag volume: kinderen met kanker</u>						
Overweeg een transfusievolume van 10-15 ml/kg bij kinderen met kanker.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
Overweeg een transfusievolume van maximaal 2 donoreenheden (volume tussen 500-600 ml).	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
Wij adviseren *tegen* een transfusievolume van 20 ml/kg of hoger bij kinderen met kanker.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
<u>Hoog- of laag volume: neonaten met kanker</u>						
Overweeg een transfusievolume van 10-15 ml/kg bij neonaten met kanker.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
Wij adviseren *tegen* een transfusievolume van 20 ml/kg of hoger bij neonaten met kanker.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
<u>Transfusiesnelheden: kinderen met kanker</u>						
De werkgroep is van mening dat de transfusiesnelheid van een erytrocytentransfusie bij kinderen met kanker 5 ml/kg/uur moet zijn.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum
<u>Transfusiesnelheden: neonaten met kanker</u>						
De werkgroep is van mening dat de transfusiesnelheid van een erytrocytentransfusie bij neonaten met kanker 5 ml/kg/uur moet zijn.	Direct	Geen	Verspreiding van de richtlijn	Geen kennis van de richtlijn	Uitrollen van de richtlijn naar de betrokken beroepsgroepen/Verspreiding van de richtlijn	*Supportive Care* groep, Prinses Máxima Centrum

[1] Voor de volledige aanbevelingen wordt er verwezen naar de desbetreffende hoofdstukken.

Te ondernemen acties per partij
De kinderoncologische zorg is Nederland is gecentraliseerd in het Prinses Máxima Centrum in Utrecht. De *Supportive Care* groep is betrokken bij het ontwikkelen en uitrollen van nieuwe (behandel)richtlijnen. Deze groep maakt de richtlijn bekend bij de direct betrokken wetenschappelijke verenigingen en beroepsorganisaties. Daarnaast is er uitgebreid contact met de *Shared Care* ziekenhuizen, minimaal twee keer per jaar, waardoor de uitrol van een richtlijn gemakkelijker wordt.

Hieronder wordt per partij toegelicht welke acties zij kunnen ondernemen om de implementatie van de richtlijn te bevorderen:

Initiatiefnemende ziekenhuis:
- Ziekenhuisbestuurders en waar van toepassing andere systeem stakeholders op de hoogte brengen van de aanbevelingen die (mogelijk) effect zullen gaan hebben op de organisatie van de zorg en op kosten en wat hierin van de betreffende partij verwacht zal worden;
- Bekend maken van de richtlijn onder andere betrokken wetenschappelijk- en beroepsverenigingen.

Alle direct betrokken wetenschappelijke verenigingen/beroepsorganisaties (NVK, SKION, VKN, NVA, NVIC, NVH, NVvH, NVI, V&VN, NVRO, NVB en NVKC):
- Bekend maken van de richtlijn onder de leden;
- Publiciteit voor de richtlijnen maken door over de richtlijn te publiceren in tijdschriften en te vertellen op congressen;
- Ontwikkelen van gerichte bijscholing/trainingen;
- Ontwikkelen en aanpassen van patiënten informatie/keuzehulpen;
- Controleren van de toepassing van de aanbevelingen middels audits en de kwaliteitsvisitatie;
- Gezamenlijk afspraken maken over en opstarten van continue modulair onderhoud van de richtlijn.

De lokale vakgroepen/individuele medisch professionals:
- Het bespreken van de aanbevelingen in de vakgroepsvergadering en lokale werkgroepen;
- Het afstemmen van lokale protocollen op de aanbevelingen in de richtlijn;
- Het volgen van bijscholing die bij deze richtlijn ontwikkeld gaat worden;
- Aanpassen lokale patiënten informatie op grond van de materialen die door de verenigingen beschikbaar gesteld zullen worden;
- Afstemmen en afspraken maken met andere betrokken disciplines om de toepassing van de aanbevelingen in de praktijk te borgen.

De systeem stakeholders (onder andere zorgverzekeraars, (koepelorganisaties van) ziekenhuisbestuurders, IGJ):
Ten aanzien van het financieren van de zorg voor kinderen met kanker, wordt van het bestuur van de ziekenhuizen verwacht dat zij bereid zijn om de nodige investeringen te doen om de aanbevelingen in deze richtlijn te kunnen implementeren. Daarnaast wordt van de bestuurders verwacht dat zij bij de betrokken medisch professionals nagaan op welke wijze zij kennis hebben genomen van de nieuwe richtlijn en deze toepassen in de praktijk. Van zorgverzekeraars wordt verwacht dat zij de zorg die in deze richtlijn wordt voorgeschreven zullen vergoeden.

Wetenschappers en subsidieverstrekkers:
- Onderzoek initiëren naar de kennislacunes, bij voorkeur in internationaal verband.

Indicatorontwikkeling
Gezien de moeilijkheid van het ontwikkelen van toepasselijke indicatoren is er besloten om (vooralsnog) geen indicatoren te ontwikkelen.

Juridische betekenis van richtlijnen
Richtlijnen zijn geen wettelijke voorschriften, maar op ‘evidence’ gebaseerde inzichten en aanbevelingen die zorgverleners helpen om kwalitatief goede zorg te verlenen. Aangezien deze aanbevelingen hoofdzakelijk gebaseerd zijn op de ‘gemiddelde patiënt’, kunnen zorgverleners op basis van hun professionele autonomie zo nodig afwijken van de richtlijn. Afwijken van richtlijnen is, als de situatie van de patiënt dat vereist, soms zelfs noodzakelijk. Wanneer van de richtlijn wordt afgeweken, dient dit beargumenteerd en gedocumenteerd te worden.

Verantwoording Methodologie (Nederlands)

Uitgangsvragen

De richtlijn bestaat uit de volgende acht uitgangsvragen:

1. Wat is het effect van een profylactische erytrocytentransfusie bij kinderen en neonaten met kanker?
2. Wat is het effect van een profylactische erytrocytentransfusie bij kinderen en neonaten met kanker en een sepsis?
3. Wat is het effect van een profylactische erytrocytentransfusie bij kinderen en neonaten met kanker die radiotherapie ondergaan?
4. Wat is het effect van een profylactische erytrocytentransfusie bij kinderen en neonaten met kanker en cardiale en/of pulmonale comorbiditeiten?
5. Wat is het effect van een profylactische erytrocytentransfusie bij kinderen en neonaten met kanker en hyperleukocytose?
6. Wat is het effect van bestraalde erytrocytentransfusies bij kinderen en neonaten met kanker?
7. Wat is het effect van een laag volume profylactische erytrocytentransfusie in vergelijking met hoog volume erytrocytentransfusie bij kinderen en neonaten met kanker?
8. Wat is het effect van een profylactische erytrocytentransfusie bij elke transfusiesnelheid in vergelijking met een erytrocytentransfusie bij elke andere infusiesnelheid bij kinderen en neonaten met kanker?

Werkwijze van de werkgroep

AGREE

Deze richtlijn is opgesteld conform de eisen vermeld in het rapport Medisch Specialistisch Richtlijnen 2.0 van de adviescommissie Richtlijnen van de Raad Kwaliteit, die gebaseerd is op de Appraisal of Guidelines for Research & Evaluation II (AGREE II) instrument die internationaal gebruikt wordt.

Kernwerkgroep

De kernwerkgroep bestond uit zes leden: een kinderoncoloog, een kinderarts, een kinderarts in opleiding/epidemioloog, een postdoc onderzoeker, een artsonderzoeker/promovendus, en een artsonderzoeker. De kernwerkgroep werd geleid door een van de artsonderzoekers (DK). De belangrijkste functies van de kernwerkgroep was het verwerven van de financiering, het definiëren van de uitgangsvragen, het samenstellen van de werkgroep, het coördineren van het literatuuronderzoek en de datacollectie, de kwaliteitsbeoordeling van de geïncludeerde studies, het organiseren en het begeleiden van de werkgroepbijeenkomsten, het maken van de aanbevelingen, het redigeren van de manuscripten voor indiening en als laatste het coördineren van de implementatie.

Opstelling werkgroep

Op basis van de uitgangsvragen werd een werkgroep ingesteld, bestaande uit de vertegenwoordigers van alle relevante specialismen die betrokken zijn bij de zorg van kinderen met kanker om de expertise in de werkgroep zo groot mogelijk te maken. De werkgroep bestond uit 21 leden. De volgende medische specialisten verenigingen waren vertegenwoordigd: Nederlandse Vereniging voor Kindergeneeskunde (NVK), Stichting Kinderoncologie Nederland (SKION), Vereniging Kinderkanker Nederland (VKN), Nederlandse Vereniging voor Anesthesiologie (NVA), Nederlandse Vereniging voor Heelkunde (NVH), Verpleegkundigen & Verzorgenden Nederland (V&VN), Nederlandse Vereniging Medische voor Radiotherapie en Oncologie (NVRO), Nederlandse Vereniging voor Bloedtransfusie (NVB) en Nederlandse Vereniging voor Klinische Chemie en Laboratoriumgeneeskunde (NVKC).

Knelpuntenanalyse

Tijdens de voorbereidende fase inventariseerde de kernwerkgroep een aantal belangrijke en omvangrijke knelpunten. Deze werden vervolgens door de gehele werkgroep, inclusief alle afgevaardigden van de wetenschappelijke verenigingen, uitgebreid besproken en beoordeeld. Tevens zijn er nieuwe knelpunten aangedragen door de werkgroepleden. Hier is een volledige sessie aan gewijd met alle werkgroepleden in september 2019. In deze knelpunteninventarisatie is expliciet rekening gehouden met zowel het klinische belang van deze uitkomsten en de organisatie van zorg zoals coördinatie, communicatie, (financiële) middelen, menskracht en infrastructuur.

Uitgangsvragen en uitkomstmaten

Op basis van de knelpuntenanalyse zijn door de kernwerkgroep een aantal concept-uitgangsvragen opgesteld. Deze uitgangsvragen zijn ontwikkeld volgens het PICO-format; *Population* (*P*), *Intervention* (*I*), *Comparison* (*C*) en *Outcome* (*O*). Deze uitgangsvragen zijn aan de volledige werkgroep voorgelegd waarna de definitieve uitgangsvragen zijn vastgelegd. Vervolgens is per uitgangsvraag geïnventariseerd door de werkgroep welke uitkomstmaten er relevant waren voor de patiënt. Hier ging het om zowel gewenste als ongewenste effecten. Deze uitkomsten zijn vervolgens groepsgewijs gerangschikt als cruciaal, belangrijk en onbelangrijk voor de besluitvorming rondom de aanbevelingen. Deze uitkomstmaten zijn door de werkgroep op basis van consensus geprioriteerd: mortaliteit, kwaliteit van leven, transfusie gerelateerde complicaties, behandelingsgerelateerde complicaties, morbiditeit en *event free survival* werden als cruciale uitkomsten beschouwd. Ziekenhuisopnames, late complicaties en kosten werden als belangrijke uitkomsten beschouwd, en er waren geen uitkomsten die als onbelangrijk werden beschouwd. Van deze uitkomsten werden mortaliteit, morbiditeit, transfusie gerelateerde

complicaties, behandelingsgerelateerde complicaties en late complicaties beschouwd als ongewenste effecten. Kwaliteit van leven, *event free survival*, daling van kosten en minder ziekenhuisopnames werden beschouwd als gewenste effecten. In totaal zijn er zestien uitgangsvragen geformuleerd.

Individuele search

Strategie voor zoeken en selecteren van literatuur

Samen met een medisch bibliothecaris is een uitgebreid literatuuronderzoek opgesteld en uitgevoerd aan de hand van de opgestelde uitgangsvragen. PubMed, Embase, Cochrane CENTRAL werden doorzocht tot december 2019 met in totaal 6950 resultaten, waaruit 4 artikelen zijn geïncludeerd voor deze richtlijn. Dit literatuuronderzoek is geüpdatet in december 2020, waarna geen extra artikelen zijn geïncludeerd. Het volledige literatuuronderzoek is opgenomen in de bijlage (Addendum 2).

Er is een systematische review uitgevoerd van de literatuur over erytrocytentransfusies bij kinderen en neonaten met kanker. Studies kwamen in aanmerking voor inclusie als de onderzoekspopulatie bestond uit kinderen of neonaten zoals hierboven gedefinieerd met een evaluatie van erytrocytentransfusies. Gerandomiseerde gecontroleerde studies (RCT) kregen een sterke voorkeur. Wanneer er niet voldoende van deze studies geïncludeerd konden worden, konden er ook gecontroleerde onderzoeken anderszins worden opgenomen. Artikelen werden uitgesloten van inclusie als 1) de studies niet gerelateerd waren aan de indicaties voor erytrocytentransfusies bij kinderen en neonaten met kanker in curatieve opzet; 2) de interventie niet gerelateerd was aan een erytrocytentransfusie; 3) de studiepopulatie bestond uit volwassenen (gedefinieerd als leeftijd boven de 18 jaar); 4) de studiepopulatie bestond uit gemengde pediatrische en volwassen populatie met het onvermogen om de gegevens voor de kinderen te scheiden; 5) de studiepopulatie bestond uit dieren; 6) er geen originele onderzoeksgegevens beschikbaar waren (bijvoorbeeld systematische reviews); 7) *Case-series* en *case-reports*. Er was geen jaar of taalrestrictie.

Kwaliteitsbeoordeling individuele studies

Alle artikelen werden onafhankelijk gescreend en geselecteerd door twee auteurs (DK, DS) op basis van de vooraf gedefinieerde inclusie- en exclusiecriteria met behulp van Rayyan (*Rayyan*, 2021). Discrepanties werden opgelost door een derde onafhankelijke beoordelaar (EL). De data extractie werd gelijktijdig uitgevoerd door dezelfde onafhankelijke auteurs (DK, DS) om de nauwkeurigheid te vergroten. De geïncludeerde individuele studies werden systematisch beoordeeld om het risico op vertekende studieresultaten (*risk of bias*) te kunnen inschatten. De RCTs zijn kritisch beoordeeld op *risk of bias* (RoB) met behulp van de Cochrane Risk of Bias Assessment Tool for Randomized Trials (*Cochrane Handbook for Systematic Reviews of Interventions*, 2011). In geval van niet-RCTs werd de methodologie voor de RoB-beoordeling aangepast. De RoB-tool voor observationele studies, zoals beschreven is in het handboek van de International Guideline Harmonization Group (IGHG, 2021) is gecombineerd met een aantal aspecten van de RCT-tool, zoals hierboven beschreven. Door deze RoB-tools te combineren is er getracht om de best mogelijke tool te creëren om dit soort onderzoeken te beoordelen, te vinden in de bijlage (Addendum 3). De RoB is onafhankelijk uitgevoerd door dezelfde auteurs (DK, DS) en staat vermeld in Addendum 4. Bij discrepanties werd er overlegd met een derde reviewer (EL).

Aanvullende search

Strategie voor zoeken en selecteren van aanvullende literatuur

Gezien de schaarste van de geïdentificeerde primaire studies (*n*=4) besloot de werkgroep op zoek te gaan naar aanvullende *evidence*, namelijk in bestaande richtlijnen voor erytrocytentransfusies bij kinderen met kanker, kinderen in algemeen en volwassenen met kanker. Er is eerst oriënterend gezocht naar richtlijnen en vervolgens is de zoekstrategie gefocust op de specifieke uitgangsvragen. Er is gezocht naar alle termen met betrekking tot erytrocytentransfusies, zoals gedefinieerd in de uitgangsvragen. Aanvullende evidence en richtlijnen zijn gezocht op PubMed, Google, Joint Professional Advisory Committee (JPAC), National Institute for Health and Care Excellence (NICE), Guidelines International Network (GIN), American Society of Clinical Oncology (ASCO), International Pediatric Oncology Group (iPOG), Cancer Guideline Database, Federatie Medisch Specialisten (FMS) en Sanquin. In totaal zijn zeven richtlijnen geïncludeerd. De werkgroep heeft besloten om de individuele studies achter de aanbevelingen uit de richtlijnen te gaan gebruiken. De artikelen waarop de desbetreffende richtlijn zijn aanbevelingen heeft gebaseerd zijn samengevat in duidelijke *evidence*-tabellen en uitgezet per uitgangsvraag.

Kwaliteitsbeoordeling aanvullende literatuur

De geïncludeerde richtlijnen zijn op kwaliteit beoordeeld door twee onafhankelijke auteurs (DK, EL) op de AGREE II-methodologie, zie addendum 5 (AGREE II, 2009). Richtlijnen zijn opgenomen wanneer de AGREE II-eindscore 4 of hoger bedroeg.

Samenvatten van de literatuur

De verzamelde gegevens bestonden uit onderzoeks- en patiëntkenmerken, patiëntuitkomsten en de belangrijkste bevindingen, gepresenteerd in duidelijke *evidence* tabellen. De belangrijkste bevindingen uit de literatuur werden beschreven onder het kopje "*Description of the literature*". Relatieve risico's en *p*-waarden werden geëxtraheerd uit de geïncludeerde studies en indien niet aanwezig werden ze berekend met behulp van Review Manager (RevMan) 5 (*Review Manager*, 2017). Bij voldoende overeenkomsten tussen de studies werden de gegevens middels RevMan 5 kwantitatief samengevat door middel van een meta-analyse. De mogelijkheid om de resultaten

samen te voegen werd beoordeeld op basis van de homogeniteit in de baseline kenmerken van de participanten van de desbetreffende studie en de covariabelen van de individuele onderzoeken.

Beoordelen van de kracht van het wetenschappelijke bewijs
De beoordeling van de kracht van deze literatuur vond plaats volgens de GRADE-methode (Schünemann, 2013). GRADE staat voor '*Grading Recommendations Assessment, Development and Evaluation*'. De GRADE-methode onderscheidt vier niveaus voor de kwaliteit van het wetenschappelijke bewijs: hoog, redelijk, laag en zeer laag. Deze niveaus zeggen iets over de mate van zekerheid van de bevindingen en hieruit getrokken conclusies (Schünemann, 2013).

Tabel 1. Kwaliteit van evidence volgens GRADE (Schünemann, 2013).

GRADE	Definitie
Hoog	We hebben er alle vertrouwen in dat het werkelijke effect dicht bij dat van de schatting van het effect ligt.
Redelijk	We hebben matig vertrouwen in de effectschatting: het werkelijke effect zal waarschijnlijk dicht bij de schatting van het effect liggen, maar er is een mogelijkheid dat het substantieel anders is.
Laag	Ons vertrouwen in de effectschatting is beperkt: het werkelijk effect kan aanzienlijk verschillen van de schatting van het effect.
Zeer laag	We hebben heel weinig vertrouwen in de effectschatting: het werkelijke effect zal waarschijnlijk substantieel verschillen van de schatting van het effect.

Formuleren van de conclusies
Voor elke relevante uitkomstmaat van de individuele search is het wetenschappelijk bewijs uit de *evidence tabellen* samengevat in een of meerdere literatuur conclusie tabellen met het bijbehorende niveau van bewijs, bepaald volgens de GRADE-methodiek. De werkgroepleden maakte de balans op in het zogeheten *evidence to decision framework* (Schünemann, 2013). Dit houdt in dat van elke interventie de gunstige en de ongunstige effecten van de erytrocytentransfusie bij een bepaalde Hb grens tegen elkaar af worden gewogen. Hierin werden de individuele studies uit zowel de initiële search naar kinderoncologie artikelen meegenomen als de individuele studies uit de richtlijnen.

Overwegingen (van bewijs naar aanbeveling)
Om te komen tot een aanbeveling, zijn naast de kwaliteit van het wetenschappelijke bewijs ook andere aspecten belangrijk en deze dienen meegewogen te worden, zoals de expertise van de werkgroepleden, de normen en waarden van de patiënt, voorkeuren van de ouders, beschikbaarheid van voorzieningen en organisatorische zaken. Indien deze aspecten niet meegenomen zijn in de literatuursamenvatting worden deze indien relevant vermeld onder het kopje 'Overwegingen'.

Formuleren van aanbevelingen
Op basis van het best beschikbare bewijs - gewogen in het *evidence to decision framework* - en de belangrijkste overwegen zijn aanbevelingen gemaakt die antwoord geven op de uitgangsvragen. De kracht van de aanbeveling wordt bepaald door zowel de kracht van het wetenschappelijke bewijs, maar ook door het gewicht dat door de werkgroep wordt gegeven aan de overwegingen. Dit betekent niet dat een lage bewijskracht automatisch tot een zwakke aanbeveling leidt en een hoge bewijskracht automatisch tot een sterke aanbeveling (Schünemann, 2013). Alle argumenten tezamen bepalen de uiteindelijke sterkte van de aanbeveling. Dit is conform de GRADE-methodiek.

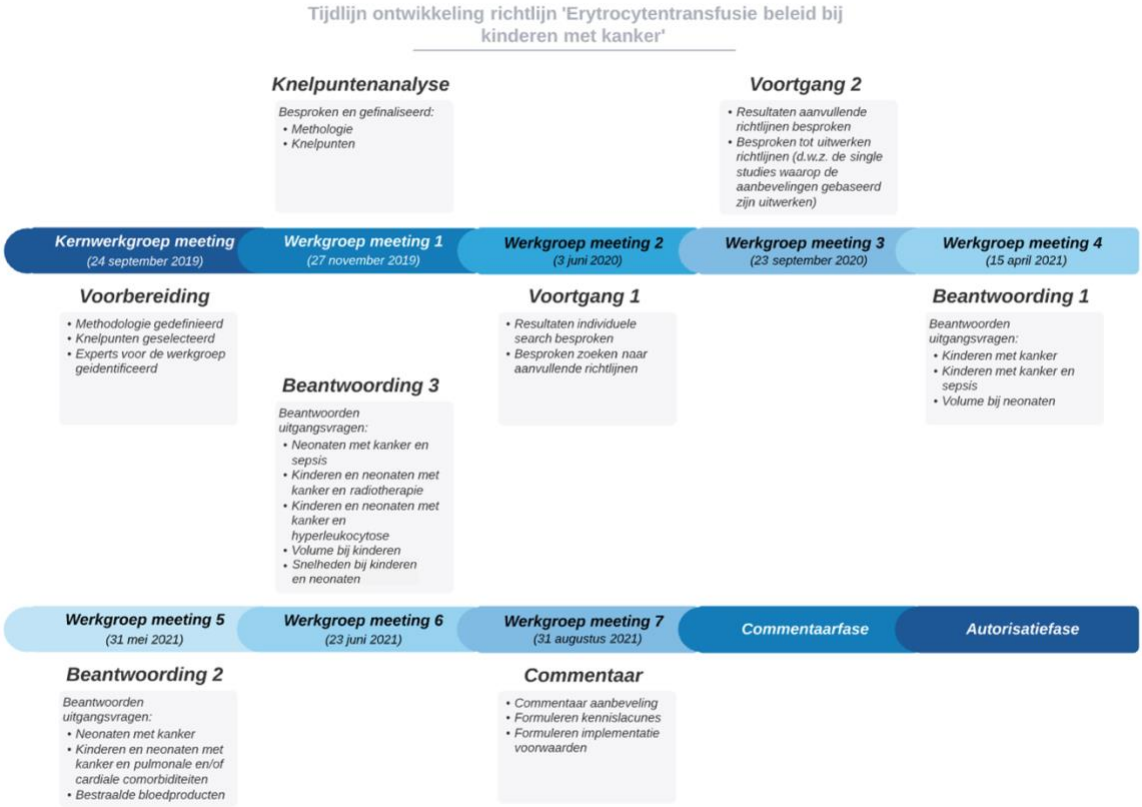
Randvoorwaarden
Bij de ontwikkeling van de richtlijn is rekening gehouden met de organisatie van de zorg. Er is gepoogd een internationale richtlijn te maken, maar voor deze Nederlandse richtlijn is specifiek rekening gehouden met de Nederlandse situatie van de gezondheidszorg. Het gaat hier om alle aspecten die randvoorwaardelijk zijn voor het verlenen van goede zorg, zoals coördinatie, communicatie, menskracht, infrastructuur en (financiële) middelen. Wanneer er relevante randvoorwaarden een onderdeel maken voor het beantwoorden van een specifieke uitgangsvraag worden deze vermeld bij het kopje 'overwegen'.

Kennislacunes
Per uitgangsvraag is door de gehele werkgroep nagegaan of er aanvullend onderzoek gedaan moet worden om de uitgangsvraag beter te kunnen beantwoorden. Een overzicht van de aanbevelingen voor aanvullend wetenschappelijk onderzoek is opgenomen in Addendum 1.

Commentaar- en autorisatiefase
De conceptrichtlijn werd aan de betrokken (kern)werkgroepleden voorgelegd. De commentaren werden verzameld en verwerkt en indien nodig besproken met de kernwerkgroep. Naar aanleiding van de commentaren werd de conceptrichtlijn aangepast naar de definitieve versie. De definitieve richtlijn werd aan de Nederlandse Vereniging voor Kindergeneeskunde voorgelegd en door hen geautoriseerd dan wel geaccordeerd.

De werkgroep werkte gedurende twee jaar, vanaf september 2019 tot september 2021, in acht vergaderingen aan de totstandkoming van de conceptrichtlijn (Zie tijdlijn). De conceptrichtlijn werd aan de betrokken (wetenschappelijke) verenigingen en (patiënt) organisaties voorgelegd ter commentaar. De commentaren werden verzameld en besproken met de werkgroep. Naar aanleiding van de commentaren werd de conceptrichtlijn aangepast en definitief vastgesteld door de werkgroep dd 26 april 2022. De definitieve richtlijn werd aan de deelnemende (wetenschappelijke) verenigingen en (patiënt) organisaties voorgelegd voor autorisatie en door hen geautoriseerd dan wel geaccordeerd dd XX-XX-XX.

Figuur 1. Tijdlijn ontwikkeling richtlijn 'Erytrocytentransfusies bij kinderen en neonaten met kanker'.



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Module 1A: Red blood cell transfusions in children with cancer - English

A. Recommendations

Research question: What is the effect of prophylactic RBC transfusion on quality of life and other outcomes in children with cancer?

A1.1: Recommendations (English)

WEAK recommendation, VERY LOW QUALITY evidence	We suggest a hemoglobin (Hb) threshold of 4.3 mmol/L for red blood cell (RBC) transfusion in children with cancer.

WEAK recommendation, VERY LOW QUALITY evidence[1]	We suggest *against* a hemoglobin (Hb) threshold of 3.7 mmol/L for red blood cell (RBC) transfusion in children with cancer.

STRONG recommendation, VERY LOW QUALITY evidence[1]	We recommend *against* a hemoglobin (Hb) threshold of 3.1 mmol/L or lower for red blood cell (RBC) transfusion in children with cancer.

[1] No primary studies in childhood cancer patients, evidence derived from studies in the pediatric and adult population.

B. Background, search and selection, relevant outcomes, and methods

B1: Background

Red blood cell (RBC) transfusions are one of the backbones in the supportive care management of children with oncologic diagnoses and those who are undergoing hematopoietic stem cell transplants (HSCT). Children with cancer may require RBC transfusions due to their underlying oncologic disease or bone marrow suppression as a result of the anti-cancer treatment. This guideline is the first guideline to be established specifically for pediatric oncology.

B2: Search and selection

In order to be able to answer the clinical question, a systematic literature analysis was carried out into the following search question:

What is the effect of prophylactic RBC transfusion on quality of life and other outcomes in children with cancer?

P = Children (aged 28 days-18 years) with cancer receiving anti-cancer treatment with curative intent*
I = Prophylactic RBC transfusion (at any threshold)
C = (No prophylactic RBC transfusion or transfusion at any other threshold)
O = Quality of life, transfusion-related complications, treatment-related complications, morbidity, mortality, admission to hospital, costs, late complications, event-free survival

* Excluding the subgroups defined by the authors (e.g. sepsis and cardiac and/or pulmonary comorbidities).

B3: Relevant outcomes

The importance of outcomes and their hierarchy are discussed in the method section “Research questions and outcomes measures”.

B4: Methods

Evidence was searched in three electronic databases, in which (randomized) controlled trials including children and adolescents with cancer were eligible for inclusion. The complete inclusion process is shown in Figure 1 (Supplemental Materials). A total of 4 studies were included for the purpose of this guideline. Detailed information about the studies is shown in Table 1 and 2 (Supplemental Materials). The quality of evidence ranged from very low to low, reported in Table 3 and 4 (Supplemental Materials). Considering the scarcity of the primary evidence, the guideline panel decided that additional evidence ought to be sought in guidelines for general pediatric patients and for adults with cancer, reported in table 5 (Supplemental Materials). The full evidence to decision frameworks and overall conclusions are stated in Supplemental Materials 7 to 9.

C. Discussion of the literature

C1: Discussion of the evidence

C1.1: Evidence in pediatric oncology

Four pediatric oncology studies were included from the initial search (Robitaille, 2013; Smith, 1976; Toogood, 1978; Lightdale, 2012).

C1.2: Recommendations and evidence derived from guidelines

Two out of seven guidelines included recommendations for children with cancer. Valentine (2018) advised an Hb threshold between 4.3 and 5.0 mmol/L based on 1 general pediatric study (Lacroix, 2007) and one general adult study (Hébert, 1999). JPAC (2013) recommended an Hb threshold of 4.3 mmol/L based on the same pediatric study (Lacroix, 2007).

Three out of seven guidelines had recommendations for children. These recommendations were based on both adult and pediatric studies. Valentine (2018) advised an Hb threshold of 3.1 mmol/L in critically ill children or those at risk for critical illness. An Hb threshold higher than 4.3 mmol/L is not advised in critically ill children or those at risk for critical illness, who are hemodynamically stable. They did not make recommendations regarding Hb thresholds between 3.1 and 4.3 mmol/L due to lack of evidence. This was based on studies by English (2002), Lackritz (1992), Lackritz (1997), Akech (2008), Olupot-Olupot (2014) and Lacroix (2007). New (2016) advised an Hb threshold of 4.3 mmol/L in stable non-cyanotic patients and an Hb threshold higher than 4.3 mmol/L may be considered in unstable patients or symptomatic anemia (Lacroix, 2007; Lacroix, 2012; Carson, 2012; BCSH, 2013; Hébert & Carson, 2014; NICE, 2015). NICE (2015) has recommended an Hb threshold of 4.3 mmol/L as well (Lacroix, 2007; Cholette, 2011).

Two out of seven guidelines had recommendations for adults with cancer, however these recommendations were based merely on consensus and not on evidence. The JPAC (2013) advised an Hb threshold between 5.0 and 5.6 mmol/L based on what most hospitals in the UK followed, but it is not based on evidence. CBO (2011) stated that an Hb of 3.0 mmol/L is an absolute indication for a RBC transfusion (based on Viele & Weiskopf, 1994). Based on consensus, it is advised to give a prophylactic RBC transfusion based on the patient's cardiopulmonary compensation abilities and when there are no clear limited cardiopulmonary compensation options or risk factors, an Hb threshold between 3.5-4.5 may be used for children and adolescents under 25 years. In case of solid tumors, an Hb threshold of 6.0 mmol/L can be considered. For lymphocytic and myeloid leukemias, no recommendation could be made. In case of aplasia-inducing treatments it has been shown that a restrictive transfusion policy (4.4-5.5 mmol/L) compared to a more liberal policy (6 mmol/L) did not lead to more adverse patient outcomes (Jansen, 2004).

C2: Description of the included studies

C2.1: Pediatric oncology

Four pediatric oncology studies were included (Robitaille, 2013; Smith, 1976; Toogood, 1978; Lightdale, 2012).

The characteristics of the included studies are stated in the evidence table below. The studies differ from each other in patient population and in methodology. The full tables of characteristics are stated in supplemental materials 2 and 3.

Table 1. Characteristics of the included studies regarding children with cancer.

Included studies				
Study	**Population**	**Liberal threshold**	**Restrictive threshold**	**Outcomes**
Robitaille (2013) RCT	6 children who received an allogeneic bone marrow transplantation after receiving myeloablative condition	- 7.5 mmol/L	- 4.3 mmol/L	- Transfusion-related complications*
Lightdale (2012) Pre-post study	141 children with different types of cancer	- 5.6 mmol/L	- 4.3 mmol/L	- Mortality - Admission to hospital - Costs
Toogood (1978) RCT	26 children with acute lymphocytic leukemia	- Between 9.9 and 11.2 mmol/L	- Between 6.2 and 7.5 mmol/L	- Anti-cancer treatment-related complications - Morbidity
Smith (1976) RCT	27 children with different types of cancer	- Between 8.7 and 9.9 mmol/L	- Between 6.2 and 7.5 mmol/L	- Anti-cancer treatment-related complications - Morbidity

* This study was stopped for safety concerns when all patients in the experimental arm were diagnosed with veno-occlusive disease. The incidence of veno-occlusive disease was not statistically higher in the experimental arm, *p*=.05.

C2.2: Children in general

Five additional pediatric studies were included (English, 2002; Akech, 2008; Lackritz, 1992; Lackritz, 1997; Lacroix, 2007).

The characteristics of the included studies are stated in the evidence table below. The studies differ from each other in patient population and in methodology.

Table 2. Characteristics of the included studies regarding children.

Included studies				
Study	**Population**	**Liberal threshold**	**Restrictive threshold**	**Outcomes**
English (2002) Retrospective and prospective cohort study	1516 severely anemic children divided into 1185 children who had malaria and 331 children with other diagnoses in Kenya	- 3.1 mmol/L	- 2.5 mmol/L - 3.1 mmol/L with respiratory distress	- Mortality - Morbidity - Admission to hospital
Akech (2008) Prospective observational study	213 children who survived malaria	- 3.1 mmol/L	- 2.5 mmol/L - 3.1 mmol/L with respiratory distress	- Mortality
Lackritz (1992) Observational study	683 children with severe anemia (Hb of 3.1 mmol/L)	- Transfusion (when they had an Hb of 2.4 mmol/L)	- No transfusion (when they had an Hb of 2.4 mmol/L	- Mortality
Lackritz (1997) Prospective cohort study	303 children with severe anemia	- Transfusion (when they had an Hb of 3.1 mmol/L)	- No transfusion (when they had an Hb of 3.1 mmol/L	- Mortality
Lacroix (2007) RCT	637 stable critically ill children	- 5.0 mmol/L	- 4.3 mmol/L	- Mortality - Morbidity - Admission to hospital

C2.3: Adults

Six additional adult studies were included (Carson, 2002; Shander, 2014; Viele & Weiskopf, 1994; Carson, 2012; Hébert, 1999; Rohde, 2014).

The characteristics of the included studies are stated in the evidence table below. The studies differ from each other in patient population and in methodology.

Table 2. Characteristics of the included studies regarding adults.

Included studies				
Study	**Population**	**Liberal threshold**	**Restrictive threshold**	**Outcomes**
Carson (2002) Retrospective study	300 adults with a postoperative Hb of 5.0 mmol/L	- Different Hb concentrations		- Mortality
Shander (2014) Retrospective study	293 adults with postoperative Hb of 5.0 mmol/L	- Different Hb concentrations		- Mortality
Viele & Weskopf (1994) MEDLINE search of case reports	61 reports of non-transfused Jehovah's Witnesses with Hb concentrations of 5.0 mmol/L or hematocrits of 0.24 L/L	- Different Hb concentrations		- Mortality

Carson (2012) Review of 31 studies	12587 adult patients	- 5.6 mmol/L	- 4.3 mmol/L	- Mortality - Morbidity - Admission to hospital - Quality of life
Hébert (1999) RCT	838 critically ill patients with euvolemia	- 6.2 mmol/l	- 4.3 mmol/L	- Mortality - Morbidity - Admission to hospital
Rohde (2014) Review of 17 studies	7456 adult patients	- Between 5.6 and 8.4 mmol/L	- Between 4.0 and 6.8 mmol/L	- Morbidity

C2.4: Excluded studies

Excluded studies	
Study	**Reasons for exclusion**
Lacroix (2012)	This was a subanalysis and consisted of the same studydata as Lacroix (2007). However, the subanalyses are included in the section “Children with sepsis” and “Children with cancer and cardiac and/or pulmonary comorbidities”.
Olupot-Olupot (2014)	Not the right comparison (RBC volume instead of RBC thresholds). However, included in the section “Low or high-volume transfusions in children with cancer”.
Cholette (2011)	This study included children with cardiac comorbidities and thus was included in the section “Children with cancer and cardiac and/or pulmonary comorbidities”.
Hébert & Carson (2014)	This was an editorial.
Hajjar (2010)	This study included adults with cardiac comorbidities and thus was included in the section “Children with cancer and cardiac and/or pulmonary comorbidities”.

D. Results

D1.1: Hb of 1.2 mmol/L versus Hb greater than 1.2 mmol/L

Conclusion of evidence	**Effect**	**Level of evidence / studies**
Children with cancer – Systematic literature search		
No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
No studies	-	-
Adults – Evidence cited in existing guidelines		
Mortality		
Significantly higher mortality in the group with an Hb of 1.2 mmol/L vs. greater than 1.2 mmol/L.	**RR 6.64 (95% CI 4.76 - 9.27)**	*Very low*** / Carson 2002

** The level of evidence is taken directly from the concerned guidelines *minus* 1 level for indirectness in this guideline.

D1.2: Hb of 1.9 mmol/L versus Hb greater than 1.9 mmol/L

Conclusion of evidence	**Effect**	**Level of evidence / studies**

Children with cancer – Systematic literature search		
No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
No studies	-	-
Adults – Evidence cited in existing guidelines		
Mortality		
Significantly higher mortality in the group with an Hb of 1.9 mmol/L vs. greater than 1.9 mmol/L.	**RR 5.20 (95% CI 3.13 - 8.65)** **RR 6.83 (95% CI 2.78 - 16.81)** *Pooled effect:* **RR 5.46 (95% CI 3.49 - 8.54)**	*Very low*** / Carson 2002 *Very low*** / Shander 2014

** The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

D1.3: Hb of 2.5 mmol/L versus Hb greater than 2.5 mmol/L

Conclusion of evidence	Effect	Level of evidence / studies
Children with cancer – Systematic literature search		
No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
Mortality		
Significantly higher mortality in the group with an Hb of 2.5 mmol/L vs. greater than 2.5 mmol/L in 2 studies, however 1 study reported no significant difference.	**RR 2.08 (95% CI 1.25 - 3.46)** RR 1.12 (95% CI 0.32 - 3.94) **RR 2.51 (95% CI 1.66 - 3.79)***	*Very low*** / English 2002 *Very low*** / Akech 2008 *Very low*** / Lackritz 1992
Adults – Evidence cited in existing guidelines		
Mortality		
Significantly higher mortality in the group with an Hb of 2.5 mmol/L vs. greater than 2.5 mmol/L in 1 study, however 1 study reported no significant difference. The pooled effect showed a significantly higher mortality in the group with an Hb of 2.5 mmol/L vs. greater than 2.5 mmol/L.	**RR 2.87 (95% CI 1.34 - 6.14)** RR 2.82 (95% CI 0.93 - 8.59) *Pooled effect:* **RR 2.85 (95% CI 1.52 - 5.35)**	*Very low*** / Carson 2002 *Very low*** / Shander 2014

* Results could not be pooled due to different study populations or outcome measures.
** The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

D1.4: Hb of 3.1 mmol/L versus Hb greater than 3.1 mmol/L

Conclusion of evidence	Effect	Level of evidence / studies
Children with cancer – Systematic literature search		
No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
Mortality		
Significantly higher mortality in the group with an Hb of 3.1 mmol/L vs. greater than 3.1 mmol/L.	**RR 1.93 (95% CI 1.36 - 2.74)**	*Very low*** / Lackritz 1997

Adults – Evidence cited in existing guidelines		
Mortality		
Significantly higher mortality in the group with an Hb of 3.1 mmol/L vs. greater than 3.1 mmol/L.	**RR 3.87 (95% CI 1.56 - 9.58)** **RR 7.18 (95% CI 3.32 – 15.54)** *Pooled effect:* **RR 5.50 (95% CI 3.08 – 9.83)** **23 of 50 deaths primarily due to anemia with Hb <3.1 mmol/L**	*Very low* ** / Shander 2014 *Very low*** / Carson 2002 *Very low* ** / Viele 1994

** The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

D1.5: Hb of 3.7 mmol/L versus Hb greater than 3.7 mmol/L

Conclusion of evidence	Effect	Level of evidence / studies
Children with cancer – Systematic literature search		
No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
No studies	-	-
Adults – Evidence cited in existing guidelines		
Mortality		
Higher mortality in the group with an Hb of 3.7 mmol/L vs. an Hb greater than 3.7 mmol/L in one study. No significant effect in another study. However, the pooled effect was significant.	**RR 5.46 (95% CI 1.81 - 16.46)** RR 2.87 (95% CI 0.86 - 9.53) *Pooled effect:* **RR 4.01 (95% CI 1.80 - 8.95)**	*Very low*** / Shander 2014 *Very low*** / Carson 2002

** The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

D1.6: Hb of 4.3 mmol/L versus Hb greater than 4.3

Conclusion of evidence	Effect	Level of evidence / studies
Children with cancer – Systematic literature search		
Mortality		
No significant difference in the group with an Hb of 4.3 mmol/L vs. greater than 4.3 mmol/L.	RR 0.67 (95% CI 0.35 - 1.28)	*Very low* / Lightdale 2012
Transfusion-related complications		
No significant difference in the group with an Hb of 4.3 mmol/L vs. greater than 4.3 mmol/L.	RR 7.00 (95% CI 0.51 - 96.06)	*Low* / Robitaille 2013
Hospital admission		
No significant difference in the group with an Hb of 4.3 mmol/L vs. greater than 4.3 mmol/L.	Not significant (no effect measure reported)	*Very low* / Lightdale 2012
Costs		
Significantly lower costs in the group with an Hb of 4.3 mmol/L vs. greater than 4.3 mmol/L.	**P=0.004 (no effect measure reported)**	*Very low* / Lightdale 2012

Children non-cancer – Evidence cited in existing guidelines		
Mortality		
No significant differences in the group with an Hb of 4.3 mmol/L vs. greater than 4.3 mmol/L.	RR 0.99 (95% CI 0.48 - 2.04)	*Low*** / Lacroix 2007
Morbidity		
No significant differences in the group with an Hb of 4.3 mmol/L vs. greater than 4.3 mmol/L.	RR 0.97 (95% CI 0.63 - 1.47)	*Low*** / Lacroix 2007
Hospital admission		
No significant differences in the group with an Hb of 4.3 mmol/L vs. greater than 4.3 mmol/L.	MD -0.46 (95% CI -0.70 - 1.70)	*Low*** / Lacroix 2007
Adults – Evidence cited in existing guidelines		
Mortality		
One study reported significantly less mortality in the group with an Hb of 4.3 mmol/L. 1 study reported significantly more mortality in the group with an Hb of 4.3 mmol/L. Others reported no significant differences in group with an Hb of 4.3 mmol/L vs. greater than 4.3 mmol/L.	**RR 0.75 (95% CI 0.59 - 0.96)** RR 0.79 (95% CI 0.63 - 1.00) **RR 19.30 (95% CI 1.09 - 342.66)** RR 3.44 (95% CI 0.59 - 20.04)*	*Low*** / Carson 2012 *Very low*** / Hébert 1999 *Very low*** / Carson 2002 *Very low*** / Shander 2014
Quality of life		
No significant differences in the group with an Hb of 4.3 mmol/L vs. greater than 4.3 mmol/L.	Not significant (no effect measure reported)	*Low*** / Carson 2012
Morbidity		
Significantly less infections in the group with an Hb of 4.3 mmol/L vs. greater than 4.3 mmol/L. No significant differences regarding other morbidities in the group with an Hb of 4.3 mmol/L vs. greater than 4.3 mmol/L.	**RR 0.81 (95% CI 0.67 - 0.98)** **RR 0.83 (95% CI 0.72 - 0.96)*** RR 1.23 (95% CI 0.67 - 2.26)	*Low*** / Carson 2012 *Low*** / Rohde 2014 *Very low*** / Hébert 1999
Hospital admission		
No significant differences in the group with an Hb of 4.3 mmol/L vs. greater than 4.3 mmol/L.	MD -0.70 (95% CI -3.37 - 1.97) MD 0.11 (95% CI -0.16 - 0.13)	*Very low*** / Hébert 1999 *Low*** / Carson 2012

* Results could not be pooled due to different study populations or outcome measures.
** The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

E. Conclusions

VERY LOW QUALITY OF EVIDENCE (GRADE)	Significantly more mortality in the group with *a hemoglobin (Hb) of 3.1 mmol/L versus a hemoglobin (Hb) greater than 3.1 mmol/L* in 4 studies. Sources (*Lackritz, 1997; Shander, 2014; Carson, 2002; Viele & Weiskopf, 1994*)

VERY LOW QUALITY OF EVIDENCE (GRADE)	Significantly more mortality in the group with *a hemoglobin (Hb) of 3.7 mmol/L versus a hemoglobin (Hb) greater than 3.7 mmol/L* in 2 studies. Sources (*Shander, 2014; Carson, 2002*)

VERY LOW QUALITY OF EVIDENCE (GRADE)	There is no increased risk for mortality, morbidity, and transfusion-related complications with *a hemoglobin (Hb) of 4.3 mmol/L versus a hemoglobin (Hb) greater than 4.3 mmol/L* in 4 out of 6 studies. However, 1 study reported significantly less mortality and 1 study reported significantly more mortality. Moreover, there were two studies who reported significantly less infections with *a hemoglobin (Hb) of 4.3 mmol/L versus a hemoglobin (Hb) greater than 4.3 mmol/L.* In addition, there are no studies reporting any other significant potential benefit from a hemoglobin (Hb) greater than 4.3 mmol/L versus a hemoglobin (Hb) of 4.3 mmol/L (5 studies). Sources (*Lightdale, 2012; Robitaille, 2013; Lacroix, 2012; Carson, 2002; Carson, 2012; Hébert, 1999; Rohde, 2014; Shander, 2014*)

F. Considerations

Regarding the comparison of an Hb threshold of 3.1 mmol/L to an Hb threshold greater than 3.1 mmol/L, three adult non-cancer studies and one pediatric non-cancer study were identified. These studies have all reported significantly more mortality in hospitalized adults and children with an Hb of 3.1 mmol/L (Carson, 2002; Lackritz, 1997; Viele & Weiskopf, 1994; Shander, 2014). Although the level of evidence is very low and mainly from adult studies, we recommend against offering this option considering the severe adverse event, death. There are no studies reporting any potential benefit from an Hb of 3.1 mmol/L and thus the guideline panel decided that the risk of mortality, the most critical outcome, overrules the uncertain desirable effects. In addition, this option is considered not acceptable for all stakeholders. Thus, the guideline panel decided against recommending an Hb threshold of 3.1 mmol/L (or lower) in children with cancer.

Regarding the comparison of an Hb threshold of 3.7 mmol/L to an Hb threshold greater than 3.7 mmol/L, two adult non-cancer studies were identified. The pooled results report a significantly increased mortality risk with an Hb of 3.7 mmol/L in comparison to an Hb greater than 3.7 mmol/L in adult patients (Shander, 2014; Carson, 2002). Moreover, there are no studies reporting any potential benefit from an Hb of 3.7 mmol/L, and thus the guideline panel decided that the risk of mortality, the most critical outcome, overrules the uncertain desirable effects. In addition, this option is considered probably not acceptable for all stakeholders. Therefore, the guideline panel decided against recommending an Hb threshold of 3.7 mmol/L in children with cancer.

Regarding the comparison of an Hb threshold of 4.3 mmol/L to an Hb threshold greater than 4.3 mmol/L, two pediatric oncology studies, one pediatric non-cancer study, and five adult non-cancer studies were identified. Based on the evidence, there is no significant increased risk for mortality, morbidity, and transfusion-related complications with an Hb of 4.3 mmol/L in comparison to an Hb greater than 4.3 mmol/L in children with cancer, children in general and adults in seven out of nine studies. However, one study did show significantly more mortality (Carson, 2002) and one study reported less mortality (Carson, 2012). The panel therefore concluded that likely there is no significant difference (Lightdale, 2012; Robitaille, 2013; Lacroix, 2007; Shander, 2014; Carson, 2002; Carson, 2012; Hébert, 1999; Rohde, 2014). And two studies reported less infections with an Hb of 4.3 mmol/L in comparison to an Hb greater than 4.3 mmol/L (Carson, 2012; Rohde, 2014). Moreover, there are no other studies reporting any significant potential benefit from a higher Hb threshold (Rohde, 2014; Lightdale, 2012; Lacroix, 2007; Lacroix, 2012; Carson, 2012). In addition, all of these studies are considered of low quality. Based on this, the guideline panel decided that the benefits of attaining an Hb threshold of 4.3 mmol/L are probably large relative to an Hb threshold greater than 4.3 mmol/L. In addition, this option is considered probably acceptable for all stakeholders. Studies that included higher restrictive Hb thresholds than an Hb threshold of 4.3 mmol/L did not report significant outcomes regarding mortality, morbidity, quality of life, admission to hospital, and anti-cancer treatment-related complications (Jansen, 2004; Carson, 2011). Therefore, the guideline panel decided to suggest an Hb threshold of 4.3 mmol/L (= 7 g/dL) in children with cancer. However, it is reasonable to consider different transfusion thresholds based on clinical judgment in these children.

Module 1A: Erytrocytentransfusies bij kinderen met kanker - Nederlands

G. Aanbevelingen (Nederlands)

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence	Overweeg een hemoglobine (Hb) grens van 4.3 mmol/L voor erytrocytentransfusie bij kinderen met kanker.

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence[1]	Wij adviseren *tegen* een hemoglobine (Hb) grens van 3.7 mmol/L voor erytrocytentransfusie bij kinderen met kanker.

STERKE aanbeveling, ZEER LAGE KWALITEIT evidence[1]	Wij adviseren sterk *tegen* een hemoglobine (Hb) grens van 3.1 mmol/L of lager voor erytrocytentransfusie bij kinderen met kanker.

[1] Geen primaire studies bij kinderen met kankerpatiënten, bewijs is afgeleid van onderzoek bij pediatrische en volwassen populaties.

H. Overwegingen (Nederlands)

Voor de vergelijking van een Hb grens van 3.1 mmol/L met een Hb grens hoger dan 3.1 mmol/L werden drie onderzoeken bij volwassenen zonder kanker één onderzoek bij kinderen zonder kanker geïncludeerd. Al deze onderzoeken rapporteerden significant meer sterfte bij gehospitaliseerde volwassenen en kinderen met Hb-waarde lager dan 3.1 mmol/L (Carson, 2002; Lackritz, 1997; Viele & Weiskopf, 1994; Shander, 2014). Hoewel het niveau van de evidence erg laag is en voornamelijk komt uit studies bij volwassenen, raden we deze optie af, gezien de ernstige bijwerking, het overlijden. Er zijn geen studies die een potentieel voordeel van een Hb lager dan 3.1 mmol/L rapporteren en daarom besloot de werkgroep dat het risico op mortaliteit, de meest kritische uitkomst, de onzekere gewenste effecten overstemt. Bovendien wordt deze optie voor alle belanghebbenden niet aanvaardbaar geacht. De werkgroep heeft daarom besloten om een Hb grens van 3.1 mmol/L (of lager) niet aan te bevelen bij kinderen met kanker.

Voor de vergelijking van een Hb grens van 3.7 mmol/L met een Hb grens hoger dan 3.7 mmol/L werden twee onderzoeken bij volwassenen zonder kanker geïdentificeerd. De gepoolde resultaten laten een significant verhoogd sterfterisico zien bij een Hb lager dan 3.7 mmol/L bij volwassenen (Shander, 2014; Carson, 2002). Bovendien zijn er geen studies die een potentieel voordeel van een Hb lager dan 3.7 mmol/L rapporteren, waarop de werkgroep heeft besloten dat het risico op mortaliteit, de meest kritische uitkomst, de onzeker gewenste effecten overstemt. Bovendien wordt deze optie waarschijnlijk niet voor alle belanghebbenden aanvaardbaar geacht. Daarom heeft de werkgroep besloten om een Hb grens van 3.7 mmol/L niet aan te bevelen bij kinderen met kanker.

Voor de vergelijking van een Hb grens van 4.3 mmol/L met een Hb grens hoger dan 4.3 mmol/L werden twee onderzoeken bij kinderen met kanker, één onderzoeken bij kinderen zonder kanker en vijf onderzoeken bij volwassenen zonder kanker geïdentificeerd. Op basis van deze literatuur is er geen significant verhoogd risico op mortaliteit, morbiditeit en transfusie gerelateerde complicaties bij een Hb lager dan 4.3 mmol/L in vergelijking met een Hb hoger dan 4.3 mmol/L bij kinderen met kanker, kinderen in algemeen en volwassenen in zeven van de negen onderzoeken. Eén studie liet significant meer mortaliteit zien (Carson, 2002), echter liet een andere studie juist significant minder mortaliteit zien (Carson, 2012). Het panel concludeerde daarom dat er naar alle waarschijnlijkheid geen significant verschil is (Lightdale, 2012; Robitaille, 2013; Lacroix, 2007; Shander, 2014; Carson, 2002; Carson, 2012; Hébert, 1999; Rohde, 2014). Bovendien, zijn er twee studies die significant minder infecties laten zien bij een Hb van 4.3 mmol/L ten opzichte van een Hb hoger dan 4.3 mmol/L (Carson, 2012; Rohde, 2014). Echter, zijn er geen studies die een significant potentieel voordeel rapporteren van een Hb hoger dan 4.3 mmol/L (Rohde, 2014; Lacroix, 2007; Carson, 2012; Lightdale, 2012). Al deze onderzoeken worden van lage kwaliteit beschouwd. Daarom is door de werkgroep besloten dat de voordelen van een Hb grens van 4.3 mmol/L waarschijnlijk groot zijn ten opzichte van een Hb grens hoger dan 4.3 mmol/L. Bovendien wordt deze optie waarschijnlijk aanvaardbaar geacht voor alle belanghebbenden. Studies met een hogere restrictieve Hb grens dan een Hb grens van 4.3 mmol/L rapporteren ook geen significante resultaten met betrekking tot mortaliteit, morbiditeit, kwaliteit van leven, ziekenhuisopname en anti-kanker behandeling gerelateerde complicaties (Jansen, 2004;

Carson, 2011). Daarom heeft de werkgroep besloten om een Hb grens van 4.3 mmol/L (= 7 g/dL) voor te stellen bij kinderen met kanker. Het is echter redelijk om verschillende transfusie drempels te overwegen op basis van het klinisch oordeel bij deze kinderen.

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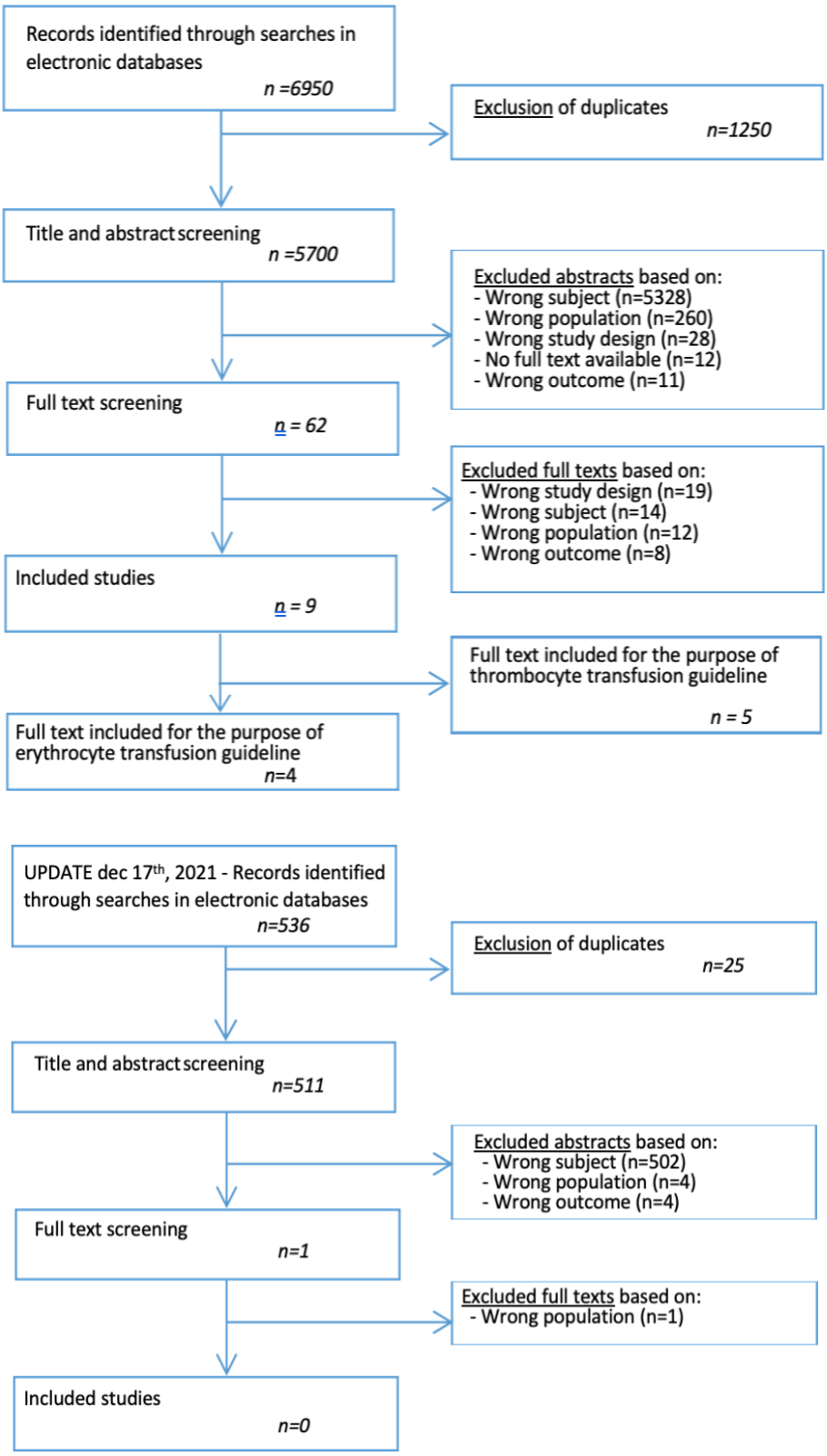
Module 1A: Supplemental materials

Supplemental materials 1: Figure 1: Inclusion flowchart



Supplemental materials 2: Table 1: Characteristics of the RCTs included (n=3)

Five studies were included. Every study was assessed by two individual researchers. The evidence was extracted, and risk of bias assessments were made. Table 1 shows the characteristics of all included RCTs and table 5 the studies that were not RCTs. The risk of bias assessment of the three RCTs is according to the Cochrane handbook (Higgings, 2011).

Table 1. Characteristics of the RCT included studies.

Study **Author, year** **Study type**	Population **a. No. of patients** **b. Age (years)** **c. Gender (% males)** **d. Diagnosis**	Intervention group **a. Intervention (including dosage)** **b. No. of patients** **c. Transfusion duration/dosage**	Control Group **a. Intervention (including dosage)** **b. No. of patients** **c. Transfusion time/dosage**	Included outcomes	Risk of bias assessment **a. Selection bias (random sequence generation)** **b. Selection bias (allocation concealment)** **c. Performance bias** **d. Detection bias** **e. Attrition bias** **f. Reporting bias** **g. Other bias[1]**
Robitaille, 2013 RCT	a. 6 b. Mean 11.65 years c. 33.3% male d. Allogeneic HSCT	a. Hb threshold <7.5 mmol/L b. 3 patients c. 10-15 mL/kg	a. Hb threshold <4.3 mmol/L b. 3 patients c. 10-15 mL/kg	- Transfusion-related complications	a. Low b. Unclear c. Unclear d. Unclear e. Low f. High g. High
Smith, 1976 RCT	a. 30 b. 3-14 years c. 56.7% male d. ALL, AML, Histiocytosis X, rhabdomyosarcoma	a. Hb threshold 8.69-9.93 mmol/L b. 11 patients c. Not stated	a. Hb threshold 6.2-7.5 mmol/L b. 16 patients c. Not stated	- Anti-cancer treatment-related complications - Morbidity	a. Unclear b. Unclear c. Unclear d. Unclear e. Low f. Unclear g. High
Toogood, 1978 RCT	a. 26 b. Median 4 years (range 18 months-14 years 2 months c. 69% male d. ALL	a. Hb threshold 6.2-7.5 mmol/L b. 13 patients c. Not stated	a. Hb threshold 9.93-11.17 mmol/L b. 13 patients c. Not stated	- Anti-cancer treatment-related complications - Morbidity	a. Unclear b. Unclear c. Unclear d. Unclear e. High f. Unclear g. High

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Supplemental materials 3: Table 2: Characteristics of the non-RCTs included (n=1)

Risk of Bias non-RCTs
As only three of the studies were RCTs, the methodology for Risk of Bias assessment had to be adjusted for the non-RCTs. The Risk of Bias tool for observational studies, as described in the IGHG Handbook (2), is combined with a couple of aspects of the RCT tool as described earlier. By combining these tools, we aimed to have the best possible tool to assess the Risk of Bias in these types of studies. See also Addendum 3.

Table 2. Characteristics of the non-RCT included studies.

Study **Author, year** **Study type**	Population **a. No. of patients** **b. Age (years)** **c. Gender (% males)** **d. Diagnosis**	Intervention group **a. Intervention (including dosage)** **b. No. of patients** **c. Transfusion duration/dosage**	Control Group **a. Intervention (including dosage)** **b. No. of patients** **c. Transfusion time/dosage**	Included outcomes	Risk of bias assessment **a. Selection bias** **b. Attrition bias** **c. Detection bias** **d. Reporting bias** **e. Confounding bias** **f. Other bias**
Lightdale, 2012 Pre-post trial	a. 141 b. Pre 6 (IQR 2-12.3), post 6 (3-13) c. Pre 43.9%, post 73.3% male d. HSCT: hematological malignancies, lymphoma, solid tumor, non-malignant hematology, neuroblastoma	a. Hb threshold <4.3 mmol/L b. 75 patients c. Not stated	a. Hb threshold <5.6 mmol/L b. 66 patients c. Not stated	- Mortality - Admission to hospital - Costs	a. Low b. High c. Low[1] d. High e. Low f. High

[1] Low considering that the included outcomes are not likely to be biased.

Referenties

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Supplemental materials 4: Table 3. Evidence table of research question 1A

Outcome reported in study	Author, study design	No. of participants, total (cases vs controls) & Group definition	Results (outcome: infections, number of patients infected, infection rates etc.)	Statistical methods	Effect size	Quality of evidence
Mortality						
100-day mortality	1. Lightdale, Pre-post trial	1. 141 (66 vs 75), Children with cancer. Pre: routine RBC transfusion <5.6 mmol/L. Post: routine RBC transfusion <4.3 mmol/L	1. Pre: Total 17 (25.8%), relapse related: 9 (13.6%), transplantation related 8 (12.1%). Post: Total 13 (17.3%), relapse related: 6 (8.0%), transplantation related 7 (9.3%).	1. Wilcoxon rank-sum test	1. *p*=.22	⨁◯◯◯[A] VERY LOW
				Total Risk Ratio (95% CI)	**RR 0.67 (0.35 - 1.28)**	
Quality of life	-	-	-	-	-	-
Transfusion- related complications						
Incidence of VOD	1. Robitaille, RCT	1. 6 (3 vs 3), Children with cancer. Control >4.3 mmol/L, experimental >7.5 mmol/L.	1. control: 0, experimental: 3.	1. Unilateral Fisher exact test	1. *p*=.05	⨁⨁◯◯[B] LOW
				Total Risk Ratio (95% CI)	**RR 7.00 (0.51 - 96.06)**	
Anti-cancer treatment related complications						
Deferred chemotherapy	1. Smith, RCT	1. 27 (16 vs 11), Children with cancer. Control: 6.2-7.5 mmol/L, experimental: 8.69-9.93 mmol/L.	1. control 7/16, experimental 0/11	1. Chi squared	1. .02<*p*<.05	⨁⨁◯◯[C1] LOW
				Total Risk Ratio (95% CI)	**RR 0.09 (0.01 - 1.49**	
	2. Toogood, RCT	2. 26 (13 vs 13), Children with cancer. Control: 6.2-7.5 mmol/L, experimental: 9.93-11.17 mmol/L	2. control 5, experimental 0	2. non-parametric Wilcoxon rank-sum test and the X2 test with Yates' correction	2. .02<*p*<.05	⨁⨁◯◯[C2] LOW

				Total Risk Ratio (95% CI)	**RR = 0.09 (0.01 - 1.49)**	
Morbidity						
Incidence of infections	1. Toogood, RCT	1. 26 (13 vs 13), Children with cancer. Control: 6.2-7.5 mmol/L, experimental: 9.93-11.17 mmol/L	1. Control: Total 7, at presentation 3, acquired 4. Experimental: Total 5, at presentation 4, acquired 1	1. Wilcoxon rank-sum test & x2 test with Yates's correction	1. 0.3<*p*<0.5	⊕⊕◯◯[D1] LOW
				Total Risk Ratio (95% CI)	**RR 0.71 (0.30 - 1.67)**	
	2. Smith, RCT	2. 27 (16 vs 11), Children with cancer. Control: 6.2-7.5 mmol/L, experimental: 8.69-9.93 mmol/L.	2. Control 11, experimental 1	2. Chi squared	2. .02<*p*<.05	⊕⊕◯◯[D2] LOW
				Total Risk Ratio (95% CI)	**RR 0.13 (0.02 - 0.88)**	
Event-free survival	-	-	-	-	-	-
Admission to hospital						
Length of stay	1. Lightdale, Pre-post trial	1. 141 (66 vs 75), Children with cancer. Pre: routine RBC transfusion <5.6 mmol/L. Post: routine RBC transfusion <4.3 mmol/L	1. Pre: Median (IQR): 37 (30, 46), Post: Median 37 (29, 51)	1. Wilcoxon rank-sum test*	1. *p*=.69*	⊕◯◯◯[E] VERY LOW
Late complications	-	-	-	-	-	-
Costs	1. Lightdale, Pre-post trial	1. 141 (66 vs 75), Children with cancer. Pre: routine RBC transfusion <5.6 mmol/L. Post: routine RBC transfusion <4.3 mmol/L	1. Pre: Median (IQR): $3624 (2265, $6040). Post: $2185 (1812, 3997).	1. Wilcoxon rank-sum test*	1. *p*=.004*	⊕◯◯◯[F] VERY LOW

* Reported from study

GRADE assessment
A. Design is pre-post trial, inconsistency not serious, indirectness not serious, imprecision serious (downgraded one level because of few cases), publication bias unlikely, downgraded 1 level because of serious risk of bias (selection bias low, attrition bias high, detection bias low, reporting bias high, confounding bias low, other bias high).

B. Design is randomized control trial, inconsistency not serious, indirectness not serious, imprecision serious (downgraded one level because of few cases), publication bias unlikely, downgraded 1 level because of serious risk of bias (random sequence generation bias low, allocation concealment unclear, performance bias unclear, detection bias unclear, attrition bias low, reporting bias low, other bias high).

C1. Design is randomized control trial, inconsistency not serious, indirectness not serious, imprecision serious (downgraded one level because of few cases), publication bias unlikely, downgraded 1 level because of serious risk of bias (random sequence generation bias unclear, allocation concealment unclear, performance bias unclear, detection bias unclear, attrition bias low, reporting bias unclear, other bias high).

C2. Design is randomized control trial, inconsistency not serious, indirectness not serious, imprecision serious (downgraded one level because of few cases), publication bias unlikely, downgraded 1 level because of serious risk of bias (random sequence generation bias unclear, allocation concealment unclear, performance bias unclear, detection bias unclear, attrition bias high, reporting bias low, other bias high).

D1. Design is randomized control trial, inconsistency not serious, indirectness not serious, imprecision serious (downgraded one level because of few cases), publication bias unlikely, downgraded 1 level because of serious risk of bias (random sequence generation bias unclear, allocation concealment unclear, performance bias unclear, detection bias unclear, attrition bias high, reporting bias unclear, other bias high).

D2. Design is randomized control trial, inconsistency not serious, indirectness not serious, imprecision serious (downgraded one level because of few cases), publication bias unlikely, downgraded 1 level because of serious risk of bias (random sequence generation bias unclear, allocation concealment unclear, performance bias unclear, detection bias unclear, attrition bias low, reporting bias unclear, other bias high).

E. Design is pre-post study, inconsistency not serious, indirectness not serious, imprecision serious (downgraded one level because of few cases), publication bias unlikely, downgraded 1 level because of serious risk of bias (selection bias low, attrition bias high, detection bias low, reporting bias high, confounding bias low, other bias high).

F. Design is pre-post study, inconsistency not serious, indirectness not serious, imprecision serious (downgraded one level because of few cases), publication bias unlikely, downgraded 1 level because of serious risk of bias (selection bias low, attrition bias high, detection bias low, reporting bias high, confounding bias low, other bias high).

Supplemental materials 5: Table 4: Conclusions of evidence

What is the effect of prophylactic RBC transfusion on quality of life and other outcomes in children with cancer?	
Mortality	**Quality of evidence**
100-days mortality: There is no significant difference in mortality between children with cancer who received RBC transfusion of a traditional threshold (Hb of 5.6 mmol/L) or a conservative threshold (Hb of 4.3 mmol/L).	⊕◯◯◯ (1 study) VERY LOW
Quality of life	**Quality of evidence**
No included studies	
Transfusion-related complications	**Quality of evidence**
Incidence of VOD: There is no significant difference in incidence of VOD between children after SCT who received a RBC transfusion at a higher threshold (Hb of 7.5 mmol/L) in comparison to a lower threshold (Hb of 4.3 mmol/L).	⊕⊕◯◯ (1 study) LOW
Anti-cancer treatment-related complications	**Quality of evidence**
Deferred chemotherapy: Less delay of chemotherapy occurred in children with cancer who received a RBC transfusion at a higher threshold (Hb of 8.69-11.17 mmol/L) in comparison to patients with lower threshold (Hb of 6.2-7.5 mmol/L).	⊕⊕◯◯ (2 studies) LOW
Morbidity	**Quality of evidence**
Incidence of infections: Inconclusive results, in one study less infections occurred in the higher RBC transfusion level (Hb of 8.69- 9.93 mmol/L versus 6.2-7.5 mmol/L) and in the other study there was no difference (Hb of 9.93-11.17 mmol/L versus 6.2-7.5 mmol/L).	⊕⊕◯◯ (1 study) LOW ⊕⊕◯◯ (1 study) LOW
Event-free survival	**Quality of evidence**
No included studies	
Admission to hospital	**Quality of evidence**
Length of stay: There was no significant difference in length of stay between children with cancer who received RBC transfusion at a higher threshold (Hb of 5.6 mmol/L) and a lower threshold (Hb of 4.3 mmol/L).	⊕◯◯◯ (1 study) VERY LOW
Late complications	**Quality of evidence**
No included studies	
Costs	**Quality of evidence**
Higher costs are associated with a RBC transfusion in children with cancer at a higher threshold (Hb of 5.6 mmol/L) in comparison to a lower threshold (Hb of 4.3 mmol/L).	⊕◯◯◯ (1 study) VERY LOW

Supplemental materials 6: Table 5: Additional guidelines

The full description of the additional guidelines and the AGREE II-scores are presented in Addendum 5.

Research question 1A - The effect of prophylactic RBC transfusion in children with cancer	
Recommendations for pediatric oncology:	**Valentine (2018): Consensus Recommendations for RBC Transfusion Practice in Critically Ill Children From the Pediatric Critical Care Transfusion and Anemia Expertise Initiative. Pediatric Critical Care Medicine (Steiner, 2018).** *AGREE II assessment: Domain 1 = 89%, Domain 2 = 44%, Domain 3 = 79%, Domain 4 = 78%, Domain 5 = 63%, Domain 6 = 92%, Overall Guideline Assessment: Score 5.* Recommendations for critically ill children with hematologic and oncologic diagnosis according to Valentine (2018): - In children with oncologic diagnosis who are critically ill or at risk for critical illness, **an Hb concentration between 4.3 and 5.0 mmol/dL is advised**. Weak recommendation, Low quality pediatric evidence (2C) 88% Agreement, (n=35), Median 8, IQR 7-8. - Supportive arguments: The recommendation is based on consensus, due to lack of evidence, which is mostly based on adult data (Lacroix, 2007; Hébert, 1999). - In children undergoing a HSCT who are critically ill or at risk for critical illness and are hemodynamically stable, **an Hb concentration between 4.3 and 5.0 mmol/dL is advised**. Weak recommendation, Low quality pediatric evidence (2C) 88% Agreement, (n=35), Median 8, IQR 7-8. - Supportive arguments: The recommendation is based on consensus, due to lack of evidence, which is mostly based on adult data (Lacroix, 2007; Hébert, 1999).
	JPAC (2013): Transfusion Handbook *AGREE II assessment: Domain 1 = 94%, Domain 2 = 56%, Domain 3 = 35%, Domain 4 = 56%, Domain 5 = 58%, Domain 6 = 25%, Overall Guideline Assessment: Score 4.* Recommendation according to the Transfusion Handbook from the JPAC (2013): - **An Hb threshold <4.3 mmol/L** in case of pediatric hemato-oncology patients. - Supporting arguments: The TRIPICU study showed that a restrictive RBC threshold was safe in hemodynamically stable critically ill children (Lacroix, 2007).
Recommendations for pediatrics:	**Valentine (2018): Consensus Recommendations for RBC Transfusion Practice in Critically Ill Children From the Pediatric Critical Care Transfusion and Anemia Expertise Initiative. Pediatric Critical Care Medicine (Doctor, 2018).** *AGREE II assessment: Domain 1 = 89%, Domain 2 = 44%, Domain 3 = 79%, Domain 4 = 78%, Domain 5 = 63%, Domain 6 = 92%, Overall Guideline Assessment: Score 5.* Recommendations for critically ill children according to Valentine (2018): - In critically ill children or those at risk for critical illness **an Hb threshold of 3.1 mmol/dL is advised**. Strong recommendation, Low quality pediatric evidence (1C), 100% Agreement, (n=35), Median 9, IQR 8-9. - Supporting arguments: Several descriptive studies have reported significantly adverse outcomes in hospitalized children with an Hb level of 3.1 mmol/dL. However, the study of Lackritzsuggests that RBC transfusion <3.1 mmol improves survival in patients. (English, 2002; Lackritz, 1992; Lackritz, 1997; Akech, 2008; Olupot-Olupot, 2014) - In critically ill children or those at risk for critical illness, who are hemodynamically stable, **an Hb threshold >4.3 mmol/dL is not advised**. Strong recommendation, Moderate quality pediatric evidence (1B), 97% Agreement, (n=29), Median 9, IQR 8-9. - Supporting arguments: The TRIPICU study showed that a restrictive RBC threshold was safe in hemodynamically stable critically ill children (Lacroix, 2007). - There is **insufficient evidence** to make a recommendation regarding transfusion thresholds for critically ill children who have **an Hb concentration between 3.1 and 4.3 mmol/dL**. However, it is reasonable to consider transfusion based on clinical judgment in these children. Consensus panel expertise, 100% Agreement, (n=29), Median 9, IQR 9-9 . - Supporting arguments: The TRIPICU study suggests that a RBC threshold of 4.3 mmol/dL is safe and Lackritzstate that a RBC transfusion should be given in patients with an Hb <3.1 mmol/dL. It is unknown whether a RBC transfusion should be given between 3.1 and 4.3 mmol/dL (Lackritz, 1997; Lacroix, 2007). - In critically ill children or those at risk for critical illness who are hemodynamically stable, it is **recommended** that the **post-transfusion goal is between 4.3 mmol/dL and 5.6 mmol/dL**. Weak recommendation, Low quality pediatric evidence (2C), 96% Agreement, (n=28), Median 8, IQR 8-9.

	- Supporting evidence: The TRIPICU study set the post-transfusion Hb goal between 4.3 and 5.6 mmol/dL, but not to increase the Hb to the normal range (>7.5 mmol/dL), which was safe (Lacroix, 2007).
	British Committee for Standards in Haematology (2016): Guidelines on transfusion for fetuses, neonates and older children. *AGREE II assessment: Domain 1 = 83%, Domain 2 = 55%, Domain 3 = 54%, Domain 4 = 83%, Domain 5 = 29%, Domain 6 = 50%, Overall Guideline Assessment: Score 4.* Recommendations according to New (2016): - **An Hb threshold <4.3 mmol/L is advised in stable non-cyanotic patients**. 1B recommendation. - **An Hb threshold >4.3 mmol/L may be considered in unstable patients or symptomatic anemia**. 2C recommendation. - Supporting arguments: Based on the TRIPICU study and others (Lacroix, 2007; Lacroix, 2012; Carson, 2012; BCSH, 2013; Hébert & Carson, 2014; NICE, 2015)
	NICE (2015): Blood transfusion. *AGREE II assessment: Domain 1 = 100%, Domain 2 = 89%, Domain 3 = 69%, Domain 4 = 94%, Domain 5 = 54%, Domain 6 = 92%, Overall Guideline Assessment: Score 5.* Recommendations according to the NICE (2015) blood transfusion guideline: - **Consider an Hb threshold of 4.3 mmol/dL** and a hemoglobin concentration target of 4.3–5.6 mmol/dL after transfusion. - Supporting arguments: This is based on 2 studies (Lacroix, 2007; Cholette, 2011).
Recommendations for adults with cancer	**CBO (2011): Guideline transfusions.** *AGREE II assessment: Domain 1 = 89%, Domain 2 = 94%, Domain 3 = 85%, Domain 4 = 61%, Domain 5 = 50%, Domain 6 = 0%, Overall Guideline Assessment: Score 5.* Recommendations according to CBO (2011): - **An Hb <3 mmol/L is an absolute indication** for a RBC transfusion. - Supporting arguments: Based on an old study in Jehovah's Witnesses stating that mortality rates increased with an Hb <3 mmol/dL (Viele & Weiskopf, 1994). - Prophylactic RBC transfusions may be indicated for asymptomatic chronic anemia in a **patient without cardiopulmonary limitations and an Hb <4 mmol/L**. - Supporting arguments: Recommendation is based on consensus. - Prophylactic RBC transfusions may be indicated with **limited cardiopulmonary compensation** options or risk factors according to the **4-5-6 rule**. - Supporting arguments: Recommendation is based on consensus. - When there are **no clear limited cardiopulmonary compensation option**s or risk factors, an Hb **threshold 3.5-4.5 mmol/dL** may be used for prophylactic RBC transfusions in children and adolescents <25 years. - Supporting arguments: Recommendation is based on consensus. - In case of **aplasia-inducing treatments** it has been shown that a **restrictive transfusion policy (4.4-5.5 mmol/L)** compared to a more liberal policy (6 mmol/L) did not lead to more adverse patient outcomes. - Supporting arguments: Based on one study (Jansen, 2004). - In case of **solid tumors**, cancer patients often receive transfusions at **Hb <6 mmol/L**. - Supporting arguments: Recommendation is based on consensus. - In case of **lymphatic and myeloid leukemias**, there are **no studies** on Hb thresholds for this condition. - Supporting arguments: none.
	JPAC (2013): Transfusion Handbook. *AGREE II assessment: Domain 1 = 94%, Domain 2 = 56%, Domain 3 = 35%, Domain 4 = 56%, Domain 5 = 58%, Domain 6 = 25%, Overall Guideline Assessment: Score 4.* Recommendation according to the Transfusion Handbook from the JPAC (2013): - Consider **an Hb threshold between 5.0 and 5.6 mmol/dL**. - Supporting arguments: this is what most units in the UK followed, but this is not based on evidence.

Supplemental materials 7: Evidence to Decision Framework & Overall conclusions - <3.1 mmol/L versus >3.1 mmol/L

Hb threshold <3.1 mmol/L versus an Hb threshold >3.1 mmol/L				
	Criteria	**Judgements**	**Research evidence**	**Additional considerations**
PROBLEM	Is the problem a priority?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ■ **Yes**	RBC transfusions are one of the backbones in the supportive care management of children with oncologic diagnoses and those who are undergoing hematopoietic stem cell transplants (HSCT). Children with cancer may require RBC transfusions due to the underlying oncologic disease or bone marrow suppression as a result of the anti-cancer treatment. This guideline is the first guideline to be established specifically for pediatric oncology.	
BENEFITS AND HARMS	What is the overall certainty of this evidence?	☐ No included studies ■ **Very low** ☐ Low ☐ Moderate ☐ High	Summary of findings: <u>Mortality</u> - Pediatric oncology: No studies included. - Pediatric: Lackritz (1997) reported significantly more mortality in the group with an Hb <3.1 mmol/L in comparison to the group with an Hb >3.1 (**<u>RR 1.93 (95% CI 1.36 - 2.74)</u>**). *Evidence cited in existing guidelines.* - Adult: Viele & Weiskopf (1994), Shander (2014), and Carson (2002) all reported significantly more mortality in the group with an Hb <3.1 mmol/L in comparison to the group with an Hb >3.1 mmol/L (**<u>23 of the 50 reported deaths were primarily due to anemia and died with Hb concentrations <or = 3.1 mmol/L, RR 3.87 (95% CI 1.56 - 9.58)</u>**, and **<u>RR 7.18 (95% CI 3.32 - 15.54)</u>**, respectively). *Evidence cited in existing guidelines.* *Pooled effect (Shander & Carson):* **<u>RR 5.50 (95% CI 3.08 - 9.83)</u>**	
	Is there important uncertainty about how much people value the main outcomes?	☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ■ **No important uncertainty or variability** ☐ No known undesirable outcomes		The relative importance of all outcomes was unanimously determined.
	Are the desirable anticipated effects large?	☐ No ☐ Probably no ■ **Uncertain** ☐ Probably yes ☐ Yes ☐ Varies		The desirable effects are unknown e.g. quality of life, hospital admission, costs.

	Are the undesirable anticipated effects small?	☐ No ■ **Probably no** ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies		The risk of mortality increases significantly in all studies. Therefore, the undesirable anticipated effects are not considered to be small. However, the evidence is mainly based on adult data, thus probably no.
	Are the desirable effects large relative to undesirable effects?	☐ No ■ **Probably no** ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies		Even though this is purely based on data in adults: the risk of mortality, and thus the most critical undesirable outcome, overrules the uncertain desirable effects. However, this is purely based on mainly adult data, thus probably no.
RESOURCE USE	Are the resources required small?	☐ No ☐ Probably no ☐ Uncertain ■ **Probably yes** ☐ Yes ☐ Varies		The guideline panel decided that the resources necessary are probably small.
	Is the incremental cost small relative to the net benefits?	☐ No ☐ Probably no ■ **Uncertain** ☐ Probably yes ☐ Yes ☐ Varies		There are costs involved (e.g., hospital admission costs). However, benefits are considered uncertain.
EQUITY	What would be the impact on health inequities?	☐ Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ■ **Varies**		The panel expected that implementing this option has no effect on health inequities, given the structure of the Dutch healthcare system. However, in other countries this may vary depending on their healthcare system.

ACCEPTABILITY	Is the option acceptable to key stakeholders?	■ **No** ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies		The panel considered the option of a transfusion threshold <3.1 mmol/L not acceptable for the key stakeholders, e.g., doctors and parents.
FEASIBILITY	Is the option feasible to implement?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ■ **Yes** ☐ Varies		The panel considered the option of a transfusion threshold <3.1 mol/l feasible to implement.

Balance of consequences – Hb threshold <3.1 mmol/L relative to an Hb threshold >3.1 mmol/L				
Undesirable consequences *clearly outweigh* desirable consequences in most settings ■	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐

Type of recommendation – Hb threshold <3.1 mmol/L relative to an Hb threshold >3.1 mmol/L			
We recommend against offering this option ■	We suggest not offering this option ☐	We suggest offering this option ☐	We recommend offering this option ☐
Recommendation (text)	We recommend *against* a hemoglobin (Hb) threshold of 3.1 mmol/L or lower for red blood cell (RBC) transfusion in children with cancer (Strong recommendation).		
Justification	Several descriptive studies have all reported significantly more mortality in hospitalised adults and children with an Hb level of 3.1 mmol/dL (Carson, 2002; Lackritz, 1997; Viele & Weiskopf, 1994; Shander, 2014). Although the level of evidence is low and from mainly adult studies, we recommend against offering this option considering the severe adverse event, death. There are		

	no studies reporting any potential benefit from an Hb threshold <3.1 mmol/L. In addition, this option is considered not acceptable for all stakeholders.
Subgroup considerations	No subgroup considerations were formulated.
Implementation considerations	No implementation considerations were formulated.
Monitoring and evaluation	Not applicable.
Research priorities	See chapter "Gaps in research".

Supplemental materials 8: Evidence to Decision Framework & Overall conclusions - <3.7 mmol/L versus >3.7 mmol/L

Hb threshold <3.7 mmol/L versus an Hb threshold >3.7 mmol/L				
	Criteria	**Judgements**	**Research evidence**	**Additional considerations**
PROBLEM	Is the problem a priority?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ■ **Yes**	RBC transfusions are one of the backbones in the supportive care management of children with oncologic diagnoses and those who are undergoing hematopoietic stem cell transplants (HSCT). Children with cancer may require RBC transfusions due to the underlying oncologic disease or bone marrow suppression as a result of the anti-cancer treatment. This guideline is the first guideline to be established specifically for pediatric oncology.	
BENEFITS AND HARMS	What is the overall certainty of this evidence?	☐ No included studies ■ **Very low** ☐ Low ☐ Moderate ☐ High	Summary of findings: <u>Mortality</u> - Pediatric oncology: No studies included. - Pediatric: No studies included. - Adults: Shander (2014) reported significantly more mortality in the group with an Hb threshold <3.1 mmol/L in comparison to the group with an Hb threshold >3.1 mmol/L, **<u>RR 5.46 (95% CI 1.81 - 16.46)</u>**. However, Carson (2002) reported no significant difference, RR 2.87 (95% CI 0.86 - 9.53). *Evidence cited in existing guidelines.* Pooled estimate: **<u>RR 4.01 (95% CI 1.80 - 8.95)</u>**	
	Is there important uncertainty about how much people value the main outcomes?	☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ■ **No important uncertainty or variability** ☐ No known undesirable outcomes		The relative importance of all outcomes was unanimously determined.
	Are the desirable anticipated effects large?	☐ No ☐ Probably no ■ **Uncertain** ☐ Probably yes ☐ Yes ☐ Varies		The desirable effects are unknown e.g., quality of life, hospital admission, costs.

	Are the undesirable anticipated effects small?	☐ No ■ **Probably no** ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies		The pooled risk of mortality was statistically different. Thus, the undesirable anticipated effects are not small. However, considering that this is based on adult data and on pooled data the risks are probably not small.
	Are the desirable effects large relative to undesirable effects?	☐ No ■ **Probably no** ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies		Even though this is purely based on data in adults: the risk of mortality, and thus the most critical undesirable outcome, overrules the uncertain desirable effects. However, this is purely based on pooled adult data, thus probably no.
RESOURCE USE	Are the resources required small?	☐ No ☐ Probably no ☐ Uncertain ■ **Probably yes** ☐ Yes ☐ Varies		The guideline panel decided that the resources necessary are probably small.
	Is the incremental cost small relative to the net benefits?	☐ No ☐ Probably no ■ **Uncertain** ☐ Probably yes ☐ Yes ☐ Varies		There are costs involved (e.g., hospital admission costs). However, benefits are considered uncertain.
EQUITY	What would be the impact on health inequities?	☐ Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ■ **Varies**		The panel expected that implementing this option has no effect on health inequities, given the structure of the Dutch healthcare system. However, in other countries this may vary depending on their healthcare system.

ACCEPTABILITY	Is the option acceptable to key stakeholders?	☐ No ■ **Probably no** ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies		The panel considered the option of a transfusion threshold <3.7 mmol/L probably not acceptable for the key stakeholders, e.g., doctors and parents. However, more acceptable than <3.1 mmol/L.
FEASIBILITY	Is the option feasible to implement?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ■ **Yes** ☐ Varies		The panel considered the option of a transfusion threshold <3.7 mol/l feasible to implement.

Balance of consequences – Hb threshold <3.7 mmol/L relative to an Hb threshold >3.7 mmol/L				
Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	**Undesirable consequences *probably outweigh* desirable consequences in most settings** ■	The balance between desirable and undesirable consequences *is uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐

Type of recommendation – Hb threshold <3.7 mmol/L relative to an Hb threshold >3.7 mmol/L			
We recommend against offering this option ☐	**We suggest not offering this option** ■	We suggest offering this option ☐	We recommend offering this option ☐
Recommendation (text)	We suggest *against* a hemoglobin (Hb) threshold of 3.7 mmol/L for red blood cell (RBC) transfusion in children with cancer (Weak recommendation).		
Justification	The pooled results report a significantly increased mortality risk with an Hb of 3.7 mmol/L in comparison to an Hb greater than 3.7 mmol/L in adult patients (Shander, 2014; Carson, 2002). Moreover, there are no studies reporting any potential benefit from an Hb of 3.7 mmol/L, and		

	thus the guideline panel decided that the risk of mortality, the most critical outcome, overrules the uncertain desirable effects. In addition, this option is considered probably not acceptable for all stakeholders. Therefore, the guideline panel decided against recommending an Hb threshold of 3.7 mmol/L in children with cancer.
Subgroup considerations	No subgroup considerations were formulated.
Implementation considerations	No implementation considerations were formulated.
Monitoring and evaluation	Not applicable.
Research priorities	See chapter "Gaps in research".

Supplemental materials 9: Evidence to Decision Framework & Overall conclusions - <4.3 mmol/L versus >4.3 mmol/L

Hb threshold <4.3 mmol/L versus an Hb threshold >4.3 mmol/L				
	Criteria	**Judgements**	**Research evidence**	**Additional considerations**
PROBLEM	Is the problem a priority?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ■ **Yes**	RBC transfusions are one of the backbones in the supportive care management of children with oncologic diagnoses and those who are undergoing hematopoietic stem cell transplants (HSCT). Children with cancer may require RBC transfusions due to the underlying oncologic disease or bone marrow suppression as a result of the anti-cancer treatment. This guideline is the first guideline to be established specifically for pediatric oncology.	
BENEFITS AND HARMS	What is the overall certainty of this evidence?	☐ No included studies ■ **Very low** ☐ Low ☐ Moderate ☐ High	Summary of findings: <u>Mortality</u> - Pediatric oncology: Lightdale (2012) reported no significant differences regarding mortality when comparing an Hb threshold <4.3 mmol/L with an Hb threshold <5.6 mmol/L, RR 0.67 (0.35 - 1.28). *Quality of evidence: Very low.* - Pediatric: Lacroix (2007) reported no significant differences regarding mortality when comparing an Hb threshold <4.3 mmol/L with an Hb threshold <5.0 mmol/L, RR 0.99 (95% CI 0.48 - 2.04). *Evidence cited in existing guidelines.* - Adult: Shander (2014) reported no significant difference regarding mortality when comparing an Hb threshold <4.3 mmol/L with an Hb threshold >4.3 mmol/L, RR 3.44 (95% CI 0.59 - 20.04). However, Carson (2002) reported more mortality in the group with an Hb <4.3 mmol/L in comparison to an Hb >4.3 mmol/L, **<u>RR 19.30 (95% CI 1.09 - 342.66)</u>**. However, Carson (2012) reported less mortality in the group with an Hb threshold <4.3 mmol/L in comparison to an Hb threshold <5.6 mmol/L, **<u>RR 0.75 (95% CI 0.59 - 0.96)</u>**. When comparing an Hb threshold <4.3 mmol/L with <6.2 mmol/L Hébert (1999) found no significant difference, RR 0.79 (95% CI 0.63 - 1.00). *Evidence cited in existing guidelines.* <u>Quality of life</u> - Pediatric oncology: no included studies. - Pediatric: no included studies.	The quality of the pediatric oncology studies was considered *very low*.
	Is there important uncertainty about how much people value the main outcomes?	☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ■ **No important uncertainty or variability** ☐ No known undesirable outcomes		The relative importance of all outcomes was unanimously determined.
	Are the desirable anticipated effects large?	☐ No ☐ Probably no ■ **Uncertain** ☐ Probably yes ☐ Yes ☐ Varies		There was no significant difference regarding quality of life and admission to hospital and there was a significant reduction of costs. However, these studies are of low quality. The expert panel decided that the benefits of an Hb threshold <4.3 mmol/L are uncertain considering the gap in evidence.

	Are the undesirable anticipated effects small?	☐ No ☐ Probably no ☐ Uncertain ■ **Probably yes** ☐ Yes ☐ Varies	- Adult: Carson (2012) reported no significant differences regarding quality of life when comparing an Hb threshold <4.3 mmol/L with <5.6 mmol/L. *Evidence cited in existing guidelines.* <u>Transfusion-related complications</u> - Pediatric oncology: Robitaille (2013) reported no significant differences regarding transfusion-related complications when comparing an Hb threshold <4.3 mmol/L with <7.5 mmol/L, RR 7.00 (95% CI 0.51 - 96.06). *Quality of evidence: Low.* - Pediatric: no included studies. - Adult: no included studies. <u>Morbidity</u> - Pediatric oncology: no included studies. - Pediatric: Lacroix (2007) reported no significant differences regarding morbidity when comparing an Hb threshold <4.3 mmol/L with an Hb threshold <5.0 mmol/L, RR 0.97 (95% CI 0.63 - 1.47). *Evidence cited in existing guidelines.* - Adult: Carson (2012) and Rohde (2014) reported significantly fewer infections when comparing an Hb threshold <4.3 mmol/L with an Hb threshold <5.6 mmol/L, **<u>RR 0.81 (95% CI 0.67 - 0.98)</u>** and **<u>RR 0.83 (95% CI 0.72 - 0.96)</u>**, other outcomes were not significant. Hébert (1999) reported no significant differences regarding morbidity when comparing an Hb threshold <4.3 mmol/L with an Hb threshold <6.2 mmol/L, RR 1.23 (95% CI 0.67 - 2.26). *Evidence cited in existing guidelines.* <u>Admission to hospital</u> - Pediatric oncology: Lightdale (2012) reported no significant differences regarding admission to hospital when comparing an Hb threshold <4.3 mmol/L with an Hb threshold <5.6 mmol/L. *Quality of evidence: Very low.* - Pediatric: Lacroix (2007) reported no significant differences regarding admission to hospital when comparing an Hb threshold <4.3 mmol/L with an Hb threshold <5.0 mmol/L, MD -0.46 (95% CI -0.70 - 1.70). *Evidence cited in existing guidelines.* - Adult: Carson (2012) reported no significant differences regarding admission to hospital when comparing an Hb threshold <4.3 mmol/L with an Hb threshold <5.6 mmol/L, MD 0.11 (95% CI -0.16 - 0.13). Hébert (1999) reported no significant differences regarding admission to hospital when comparing an Hb threshold <4.3 mmol/L with an Hb	There was no significant difference regarding mortality in most studies, except for 2 adult studies who showed contradictory results (Carson 2002; Carson 2012). There was no significant difference regarding morbidity except for 2 adult studies that reported a significant decrease in the risk of infections. There was no significant difference regarding transfusion-related complications (Robitaille, 2013), however this study was stopped prematurely considering that in the group with the higher Hb threshold three out of three children with cancer developed veno-occlusive disease.
	Are the desirable effects large relative to undesirable effects?	☐ No ☐ Probably no ☐ Uncertain ■ **Probably yes** ☐ Yes ☐ Varies		Desirable effects are uncertain except for costs and the undesirable effects are probably small. Therefore, the panel agreed that the desirable effects are probably large relative to the undesirable effects.

			threshold <6.2 mmol/L, MD -0.70 (95% CI -3.37 - 1.97). *Evidence cited in existing guidelines.* <u>Costs</u> - Pediatric oncology: Lightdale (2012) reported significantly less costs in the group with the Hb threshold <4.3 mmol/L in comparison to the group with an Hb threshold <5.6 mmol/L, ***p*=.004**. *Quality of evidence: Very low.* - Pediatric: no included studies. - Adult: no included studies.	
RESOURCE USE	Are the resources required small?	☐ No ☐ Probably no ☐ Uncertain ■ **Probably yes** ☐ Yes ☐ Varies		The guideline panel decided that the resources necessary are probably small.
	Is the incremental cost small relative to the net benefits?	☐ No ☐ Probably no ■ **Uncertain** ☐ Probably yes ☐ Yes ☐ Varies		There are costs involved (e.g., hospital admission costs). However, benefits are considered uncertain.
EQUITY	What would be the impact on health inequities?	☐ Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ■ **Varies**		The panel expected that implementing this option has no effect on health inequities, given the structure of the Dutch healthcare system. However, in other countries this may vary depending on their healthcare system.
ACCEPTABILITY	Is the option acceptable to key stakeholders?	☐ No ☐ Probably no ☐ Uncertain ■ **Probably yes** ☐ Yes ☐ Varies		The panel considered the option of a transfusion threshold <4.3 mmol/L acceptable for the key stakeholders, e.g., doctors and parents. However, it is unknown if some parties might find it not acceptable, thus probably yes.

FEASIBILITY	Is the option feasible to implement?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ■ **Yes** ☐ Varies		The panel considered the option of a transfusion threshold <4.3 mol/l feasible to implement.

Balance of consequences – Hb threshold <4.3 mmol/L relative to an Hb threshold >4.3 mmol/L				
Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced* ☐	**Desirable consequences *probably outweigh* undesirable consequences in most settings** ■	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐

Type of recommendation – Hb threshold <4.3 mmol/L relative to an Hb threshold >4.3 mmol/L			
We recommend against offering this option ☐	We suggest not offering this option ☐	**We suggest offering this option** ■	We recommend offering this option ☐
Recommendation (text)	We suggest a hemoglobin (Hb) threshold of 4.3 mmol/L for red blood cell (RBC) transfusion in children with cancer (Weak recommendation).		
Justification	Two pediatric oncology studies, one pediatric non-cancer study, and five adult non-cancer studies were identified. Based on the evidence, there is no significant increased risk for mortality, morbidity, and transfusion-related complications with an Hb of 4.3 mmol/L in comparison to an Hb greater than 4.3 mmol/L in children with cancer, children in general and adults in seven out of nine studies. However, one study did show significantly more mortality (Carson, 2002) and one study reported less mortality (Carson, 2012). The panel therefore concluded that likely there is no significant difference (Lightdale, 2012; Robitaille, 2013; Lacroix, 2007; Shander, 2014; Carson, 2002; Carson, 2012; Hébert, 1999; Rohde, 2014). And two studies reported less infections with an Hb of 4.3 mmol/L in comparison to an Hb greater than 4.3 mmol/L (Carson, 2012; Rohde, 2014). Moreover, there are no other studies reporting any significant potential		

	benefit from a higher Hb threshold (Rohde, 2014; Lightdale, 2012; Lacroix, 2007; Lacroix, 2012; Carson, 2012). In addition, all of these studies are considered of low quality. Based on this, the guideline panel decided that the benefits of attaining an Hb threshold of 4.3 mmol/L are probably large relative to an Hb threshold greater than 4.3 mmol/L. In addition, this option is considered probably acceptable for all stakeholders. Studies that included higher restrictive Hb thresholds than an Hb threshold of 4.3 mmol/L did not report significant outcomes regarding mortality, morbidity, quality of life, admission to hospital, and anti-cancer treatment-related complications (Jansen, 2004; Carson, 2011). Therefore, the guideline panel decided to suggest an Hb threshold of 4.3 mmol/L in children with cancer.
Subgroup considerations	However, it is reasonable to consider different transfusion thresholds based on clinical judgment in these children. For instance, in case of unstable children with cancer and sepsis, a higher Hb threshold should be maintained.
Implementation considerations	No implementation considerations were formulated.
Monitoring and evaluation	Not applicable.
Research priorities	See chapter "Gaps in research".

Module 1B: Red blood cell transfusions in neonates with cancer - English

A. Recommendations

Research question: What is the effect of prophylactic RBC transfusion on quality of life and other outcomes in neonates with cancer?

A1.1: Recommendations (English)

WEAK recommendation, VERY LOW QUALITY evidence[1]	We suggest a hemoglobin (Hb) threshold of 6.5 mmol/L for red blood cell (RBC) transfusion in neonates with cancer when they are less than 1 week old.

WEAK recommendation, VERY LOW QUALITY evidence[1]	We suggest a hemoglobin (Hb) threshold of 5.5 mmol/L for red blood cell (RBC) transfusion in neonates with cancer when they are between 1 and 3 weeks old.

WEAK recommendation, VERY LOW QUALITY evidence[1]	We suggest a hemoglobin (Hb) threshold of 4.5 mmol/L for red blood cell (RBC) transfusion in neonates with cancer when they are between 3 and 4 weeks old.

[1] No primary studies in childhood cancer patients, evidence derived from studies in the pediatric population.

B. Background, search and selection, relevant outcomes, and methods

B1: Background

The background of red blood cell (RBC) transfusions in pediatric oncology is discussed in the "Background section" of Research question 1A.

B2: Search and selection

In order to be able to answer the clinical question, a systematic literature analysis was carried out into the following search question:

What is the effect of prophylactic RBC transfusion on quality of life and other outcomes in neonates with cancer?

P = Neonates (aged 0-28 days) with cancer receiving anti-cancer treatment with curative intent*
I = Prophylactic RBC transfusion (at any threshold)
C = (No prophylactic RBC transfusion or transfusion at any other threshold)
O = Quality of life, transfusion-related complications, treatment-related complications, morbidity, mortality, admission to hospital, costs, late complications, event-free survival

* Excluding the subgroups defined by the authors (e.g. sepsis and cardiac and/or pulmonary comorbidities).

B3: Relevant outcomes

The importance of outcomes and their hierarchy are discussed in the method section "Research questions and outcomes measures".

B4: Methods

Evidence was searched in three electronic databases, in which (randomized) controlled trials including children and adolescents with cancer were eligible for inclusion. No pediatric oncology studies were included. Considering the scarcity of the primary evidence, the guideline panel decided that additional evidence ought to be sought in guidelines for general pediatric patients and for adults with cancer, reported in table 2 (Supplemental Materials).

C. Discussion of the literature

C1: Discussion of the evidence

C1.1: Evidence in pediatric oncology

No pediatric oncology studies were included.

C1.2: Recommendations and evidence derived from guidelines

Four out of seven guidelines included recommendations for neonates. The Dutch Association of Medical Specialists (FMS, 2019) has recommended a hemoglobin (Hb) threshold of 6.5 mmol/L in neonates less than 1 week old, between 2-3 weeks old an Hb threshold of 5.5 mmol/L and an Hb threshold of 4.5 mmol/L in neonates older than 3 weeks. This is based on the studies of Connelly (1999), Bell (2005), Whyte & Kirpalani (2006), Chen (2009), and Whyte & Kirpalani (2011). JPAC (2013) has based their recommendations on the British Committee for Standards in Haematology (BCSH) (2016) and has recommended Hb threshold of 6.2 mmol/L in neonates less than 1 week old. For neonates older than 2 weeks it is recommended to maintain the Hb between 4.7 and 5.3 mmol/L depending on their clinical situation based on Whyte & Kirpalani (2006); Chen (2009), Bell (2005), Whyte & Kirpalani (2011) and Venkatesh (2012).

C2: Description of the included studies

C2.1: Neonates with cancer

There were no primary pediatric oncology studies included from the systematic literature search.

C2.2: Neonates in general

There were six studies included from the additional literature review (Bell, 2005; Brooks, 1999; Chen, 2009; Mukhopadyay, 2004; Whyte & Kirpanali, 2006; Conelly, 1999).

The characteristics of the included studies are stated in the evidence table below. The studies differ from each other in patient population (gestational age and birth weight) and in methodology.

Table 1. Characteristics of the included studies regarding neonates with cancer.

Included studies				
Study	**Population**	**Liberal threshold**	**Restrictive threshold**	**Outcomes**
Bell (2005) *RCT*	103 neonates with very low birth weight (500 to 1300 grams)	- Neonates on ventilation 8.4 mmol/L - Neonates on oxygen/CPAP 6.9 mmol/L - Neonates without respiratory support 5.4 mmol/L	- Neonates on ventilation 6.2 mmol/L - Neonates on oxygen/CPAP 5.0 mmol/L - Neonates without respiratory support 4.4 mmol/L	- Mortality - Morbidity - Costs
Brooks (1999) *RCT*	50 neonates with very low birthweight (<1250 grams)	- Hematocrit of 0.40 L/L	- Asymptomatic: Hematocrit of 0.20 L/L + reticulocyte count 0.1x10e9/L - Symptomatic: Hematocrit of 0.30 L/L	- Mortality - Morbidity
Chen (2009) *RCT*	36 neonates with very low birth weight (<1500 grams)	- Neonates on ventilation 9.1 mmol/L - Neonates on CPAP 8.3 mmol/L - Neonates without respiratory support 6.2 mmol/L	- Neonates on ventilation 7.2 mmol/L - Neonates on CPAP 6.2 mmol/L - Neonates without respiratory support 4.5 mmol/L	- Mortality - Morbidity - Costs
Connelly (1999) *Prospective study*	24 neonates with very low birth weight (<1500 grams)	- First week of life 8.1 mmol/L - Second week of life with respiratory support 6.8 mmol/L - Third week of life 5.0 mmol/L	- First week of life 6.8 mmol/L - Second week of life with respiratory support 5.6 mmol/L - Third week of life 5.0 mmol/L	- Mortality - Morbidity - Costs
Mukhopadhyay (2004) *RCT*	38 preterm neonates weighing between 1000 and 1800 grams	- Hematocrit threshold of 0.40 L/L	- Hematocrit threshold of 0.30 L/L	- Mortality
Whyte & Kirpalani (2006) *RCT*	451 neonates with very low birth weight (<1000 gram)	- Neonates without respiratory support in week 1 7.5 mmol/L - Neonates without respiratory support in week 2 6.2 mmol/L - Neonates without respiratory support in week 3 5.3 mmol/L	- Neonates without respiratory support in week 1 6.2 mmol/L - Neonates without respiratory support in week 2 5.3 mmol/L - Neonates without respiratory support in week 3 4.7 mmol/L	- Mortality - Morbidity - Costs

		- Neonates on respiratory support in week 1 8.4 mmol/L - Neonates on respiratory support in week 2 7.5 mmol/L - Neonates on respiratory support in week 3 6.2 mmol/L	- Neonates on respiratory support in week 1 7.1 mmol/L - Neonates on respiratory support in week 2 6.2 mmol/L - Neonates on respiratory support in week 3 5.3 mmol/L	

C2.3: Excluded studies

Excluded studies	
Study	**Reasons for exclusion**
Whyte & Kirpalani (2011)	This was a review, including the following studies: Connelly (1999), Bell (2005), Chen (2009), and Whyte & Kirpalani (2006) and were all included.
Venkatesh (2012)	This was a review, including the following studies: Bell (2005), Chen (2009), Whyte & Kirpalani (2006), Brooks (1999), Mukhopadhya (2004), and Ransome (1989) and were all included except Ransome (1989) considering that this article was not found.

D. Results

D1: Neonates in general

D1.1: Hb of 4.3 mmol/L versus Hb greater than 4.3 mmol/L in neonates

Conclusion of evidence	**Effect**	**Level of evidence / studies**
Children with cancer – Systematic literature search		
No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
Mortality		
There was no significant difference regarding mortality when comparing an Hb of 4.3 mmol/L vs. greater than 4.3 mmol/L in neonates.	RR 0.52 (95% CI 0.05 - 5.56) None died (not estimable)	*Low** / Bell 2005 *Low** / Brooks 1999
Morbidity		
There was no significant difference regarding morbidity when comparing an Hb of 4.3 mmol/L vs. greater than 4.3 mmol/L in neonates.	Not significant (no effect measure reported) Not significant (no effect measure reported)	*Low** / Bell 2005 *Low** / Brooks 1999
Costs		
There was a significant difference regarding costs when comparing an Hb of 4.3 mmol/L vs. greater than 4.3 mmol/L in neonates.	**MD -1.10 (95% CI -2.10 - -0.10).**	*Low** / Bell 2005
Adults – Evidence cited in existing guidelines		
No studies	-	-

* The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

D.1.2: Hb of 5.0 mmol/L versus Hb greater than 5.0 mmol/L in neonates

Conclusion of evidence	**Effect**	**Level of evidence / studies**
Children with cancer – Systematic literature search		

No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
Mortality		
There was no significant difference regarding mortality when comparing an Hb of 5.0 mmol/L vs. greater than 5.0 mmol/L in neonates.	RR 1.79 (95% CI 0.18 - 18.02)	*Low** / Chen 2009
Morbidity		
There was no significant difference regarding morbidity when comparing an Hb of 5.0 mmol/L vs. greater than 5.0 mmol/L in neonates.	Not significant (no effect measure reported)	*Low** / Chen 2009
Costs		
There was a significant difference regarding costs when comparing an Hb of 5.0 mmol/L vs. greater than 5.0 mmol/L in neonates.	MD -1.00 (95% CI -2.49 - 0.49)	*Low** / Chen 2009
Adults – Evidence cited in existing guidelines		
No studies	-	-

* The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

D1.3: Hb of 6.2 mmol/L versus Hb greater than 6.2 mmol/L in neonates

Conclusion of evidence	Effect	Level of evidence / studies
Children with cancer – Systematic literature search		
No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
Mortality		
There was no significant difference regarding mortality when comparing an Hb of 6.2 mmol/L vs. greater than 6.2 mmol/L in neonates.	RR 3.50 (95% CI 0.62 - 1.18)	*Low** Mukhopadyay 2004
Adults – Evidence cited in existing guidelines		
No studies	-	-

* The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

D2: Neonates in first week of life

D2.1: Hb of 6.2 mmol/L versus Hb greater than 6.2 mmol/L in neonates in the first week of life

Conclusion of evidence	Effect	Level of evidence / studies
Children with cancer – Systematic literature search		
No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
Mortality		

There was no significant difference regarding mortality when comparing an Hb of 6.20 mmol/L vs. greater than 6.2 mmol/L in neonates in the first week of life.	RR 1.23 (95% CI 0.84 - 1.79)	*Low** / Whyte & Kirpalani 2006
Morbidity		
There was no significant difference regarding morbidity when comparing an Hb of 6.20 mmol/L vs. greater than 6.2 mmol/L in neonates in the first week of life. There was a significant difference regarding retinopathy of prematurity when comparing an Hb of 6.20 mmol/L vs. greater than 6.2 mmol/L in neonates in the first week of life.	Not significant (no effect measure reported) **RR 0.79 (95% CI 0.66 - 0.95)**	*Low** / Whyte & Kirpalani 2006 *Low** / Whyte & Kirpalani 2006
Costs		
There was no significant difference regarding costs when comparing an Hb of 6.20 mmol/L vs. greater than 6.2 mmol/L in neonates in the first week of life.	MD -0.80 (95% CI -1.65 - 0.05)	*Low** / Whyte & Kirpalani 2006
Adults – Evidence cited in existing guidelines		
No studies	-	-

* The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

D2.2: Hb of 6.8 mmol/L versus Hb greater than 6.8 mmol/L in neonates in the first week of life

Conclusion of evidence	Effect	Level of evidence / studies
Children with cancer – Systematic literature search		
No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
Mortality		
There was no significant difference regarding mortality when comparing an Hb of 6.8 mmol/L vs. greater than 6.8 mmol/L in neonates in the first week of life.	Not significant (no effect measure reported)	*Low** / Connelly 1999
Morbidity		
There was no significant difference regarding morbidity when comparing an Hb of 6.8 mmol/L vs. greater than 6.8 mmol/L in neonates in the first week of life.	Not significant (no effect measure reported)	*Low** / Connelly 1999
Costs		
There was a significant difference regarding costs when comparing an Hb of 6.8 mmol/L vs. greater than 6.8 mmol/L in neonates in the first week of life.	**MD -2.90 (95% CI -4.94 - -0.86)**	*Low** / Connelly 1999
Adults – Evidence cited in existing guidelines		
No studies	-	-

* The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

D3: Neonates on the second week of life
D3.1: Hb of 5.3 mmol/L versus Hb greater than 5.3 mmol/L in neonates in the second week of life

Conclusion of evidence	Effect	Level of evidence / studies
Children with cancer – Systematic literature search		
No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
Mortality		
There was no significant difference regarding mortality when comparing an Hb of 5.3 mmol/L vs. greater than 5.3 mmol/L in neonates in the second week of life.	RR 1.23 (95% CI 0.84 - 1.79)	*Low** / Whyte & Kirpalani 2006
Morbidity		
There was no significant difference regarding morbidity when comparing an Hb of 5.3 mmol/L vs. greater than 5.3 mmol/L in neonates in the second week of life. There was a significant difference regarding retinopathy of prematurity when comparing an Hb of 5.3 mmol/L vs. greater than 5.3 mmol/L in neonates in the second week of life.	Not significant (no effect measure reported) **RR 0.79 (95% CI 0.66 - 0.95)**	*Low** / Whyte & Kirpalani 2006 *Low** / Whyte & Kirpalani 2006
Costs		
There was no significant difference regarding costs when comparing an Hb of 5.3 mmol/L vs. greater than 5.3 mmol/L in neonates in the second week of life.	MD -0.80 (95% CI -1.65 - 0.05)	*Low** / Whyte & Kirpalani 2006
Adults – Evidence cited in existing guidelines		
No studies	-	-

* The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

D4. Neonates on the third week of life
D4.1: Hb of 4.7 mmol/L versus Hb greater than 4.7 mmol/L in the third week of life

Conclusion of evidence	Effect	Level of evidence / studies
Children with cancer – Systematic literature search		
No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
Mortality		
There was no significant difference regarding mortality when comparing an Hb of 4.7 mmol/L vs. greater than 4.7 mmol/L in neonates in the third week of life.	RR 1.23 (95% CI 0.84 - 1.79)	*Low** / Whyte & Kirpalani 2006
Morbidity		
There was no significant difference regarding morbidity when comparing an Hb of 4.7	Not significant (no effect measure reported)	*Low** / Whyte & Kirpalani 2006

mmol/L vs. greater than 4.7 mmol/L in neonates in the third week of life. There was a significant difference regarding retinopathy of prematurity when comparing an Hb of 4.7 mmol/L vs. greater than 4.7 mmol/L in neonates in the third week of life.	**RR 0.79 (95% CI 0.66 - 0.95)**	*Low** / Whyte & Kirpalani 2006
Costs		
There was no significant difference regarding costs when comparing an Hb of 4.7 mmol/L vs. greater than 4.7 mmol/L in neonates in the third week of life.	MD -0.80 (95% CI -1.65 - 0.05)	*Low** / Whyte & Kirpalani 2006
Adults – Evidence cited in existing guidelines		
No studies	-	-

* The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

E. Conclusions
No conclusions were formulated.

F. Considerations
The incidence of cancer in neonates is very low. Nevertheless, we deem it important to give a recommendation for this patient group as well. There were no pediatric oncology studies identified. The Dutch Association of Medical Specialists (FMS, 2019) developed a high-quality guideline addressing this matter with an AGREE II score of 6 out of 7. They based their recommendations on studies performed in very low birth-weight infants (birth weight of 1500 grams or less) and because of the lack of evidence regarding full term born neonates and late-premature born neonates and late-premature born neonates (gestational age ≥ 32 weeks), the FMS adopted these thresholds for neonates in general. Taking this into accound, the guideline panel decided to adopt the recommendations regarding neonates with cancer from the guideline of the FMS (2019).

Module 1B: Erytrocytentransfusies bij neonaten met kanker - Nederlands

G. Aanbevelingen (Nederlands)

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence[1]	Overweeg een hemoglobine (Hb) grens van 6.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker indien ze minder dan 1 week oud zijn.

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence[1]	Overweeg een hemoglobine (Hb) grens van 5.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker indien ze tussen de 1 en 3 weken oud zijn.

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence[1]	Overweeg een hemoglobine (Hb) grens van 4.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker indien ze tussen de 3 en 4 weken oud zijn.

[1] Geen primaire studies bij kinderen met kankerpatiënten, bewijs is afgeleid van onderzoek bij pediatrische populaties.

H. Overwegingen (Nederlands)

Er zijn zeer weinig neonaten die kanker krijgen en daarbij er zijn geen artikelen over neonaten met kanker geïncludeerd. De Nederlandse Federatie Medische Specialisten (FMS, 2019) heeft voor neonaten een hoogwaardige richtlijn ontwikkeld met een AGREE II-score van 6 uit de 7. Zij baseerden hun aanbevelingen op onderzoeken die uitgevoerd waren bij neonaten met een zeer laag geboortegewicht (geboortegewicht onder 1500 gram) en vanwege het gebrek aan studies met betrekking tot à terme geboren neonaten en laat-prematuur geboren neonaten (zwangerschapsduur ≥ 32 weken), nam de FMS deze grens voor neonaten in het algemeen over. Hiermee rekening houdend heeft de werkgroep besloten de aanbevelingen over te nemen betreffende neonaten met kanker uit de richtlijn van de FMS (2019).

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Module 1B: Supplemental materials

Supplemental materials 1: Additional guidelines

The full description of the additional guidelines and the AGREE II-scores are presented in Addendum 5.

Research question 1B - The effect of prophylactic RBC transfusion in neonates with cancer	
Recommendations for neonates	**Federation of Medical Specialists (2019): Blood transfusion policy.** *AGREE II assessment: Domain 1 = 94%, Domain 2 = 100%, Domain 3 = 71%, Domain 4 = 89%, Domain 5 = 13%, Domain 6 = 100%, Overall Guideline Assessment: Score 6.* Recommendations according to the Federation of Medical Specialists (2019): - That very low birth weight infants (birth weight <1500 grams) should receive these restrictive RBC transfusions thresholds and in absence of studies with regard to full term neonates and late preterm infants (gestational age>32 weeks), these recommendations are also applying to these groups: - Maintain **an Hb >6.5 mmol/L in neonates <1 week old**. - Maintain **an Hb >5.5 mmol/L in neonates between 2 and 3 weeks old**. - Maintain **an Hb >4.5 mmol/L in neonates >3 weeks old**. - Supporting arguments: Based on 4 studies and 1 Cochrane-analysis (Connelly, 1999; Bell, 2005; Kirpalani, 2006; Chen, 2009; Whyte & Kirpalani, 2011).
	JPAC (2013): Transfusion Handbook *AGREE II assessment: Domain 1 = 94%, Domain 2 = 56%, Domain 3 = 35%, Domain 4 = 56%, Domain 5 = 58%, Domain 6 = 25%, Overall Guideline Assessment: Score 4.* The Transfusion Handbook from the JPAC (2013) advises a neonatal top-up transfusion threshold: - In case of neonates without oxygen: - Maintain **an Hb >6.2 mmol/L in neonates <24 hours old**. - Maintain **an Hb >6.2 mmol/L in neonates <1 week old**. - Maintain **an Hb >4.65 - 5.28 mmol/L depending on clinical situation in neonates between 2-3 weeks old**. - Maintain **an Hb >4.65 - 5.28 mmol/L depending on clinical situation in neonates >4 weeks old**. - Supporting arguments: Based on the British Committee for Standards in Haematology Transfusion Guidelines for Neonates and Older Children (New, 2016).
	British Committee for Standards in Haematology (2016): Guidelines on transfusion for fetuses, neonates and older children. *AGREE II assessment: Domain 1 = 83%, Domain 2 = 55%, Domain 3 = 54%, Domain 4 = 83%, Domain 5 = 29%, Domain 6 = 50%, Overall Guideline Assessment: Score 4.* New (2016) advises a neonatal top-up transfusion threshold: - In case of neonates without oxygen: - Maintain **an Hb >6.2 mmol/L in neonates <24 hours old**. - Maintain **an Hb >6.2 mmol/L in neonates <1 week old**. - Maintain **an Hb >4.65 - 5.28 mmol/L depending on clinical situation in neonates between 2-3 weeks old**. - Maintain **an Hb >4.65 - 5.28 mmol/L depending on clinical situation in neonates >4 weeks old**. - Supporting arguments: Based on studies (Whyte & Kirpalani, 2006; Chen, 2009, Bell, 2005; Whyte & Kirpalani, 2011; Venkatesh, 2012).

Module 2A: Red blood cell transfusions in children with cancer and sepsis - English

A. Recommendations

Research question: What is the effect of prophylactic RBC transfusion on quality of life and other outcomes in children with cancer who suffer from sepsis (author-defined)?

A1.1: Recommendations (English)

WEAK recommendation, VERY LOW QUALITY evidence[1]	We suggest a hemoglobin (Hb) threshold of 4.3 mmol/L for red blood cell (RBC) transfusion in children with cancer and sepsis who are hemodynamically stable.

WEAK recommendation, EXPERT EVIDENCE[2]	We believe that for hemodynamically unstable children with cancer and sepsis and evidence of oxygen deficiency (e.g., use of inotropes, elevated lactate), it is recommended to consider an Hb threshold that ranges between 4.3 mmol/L and 6.2 mmol/L.

[1] No primary studies in childhood cancer patients, evidence derived from studies in the pediatric and adult population.
[2] No primary studies in childhood cancer patients, no evidence derived from studies from existing clinical practice guidelines.

B. Background, search and selection, relevant outcomes, and methods

B1: Background
The background of red blood cell (RBC) transfusions in pediatric oncology is discussed in the "Background section" of Research question 1A.

B2: Search and selection
In order to be able to answer the clinical question, a systematic literature analysis was carried out into the following search question:

What is the effect of prophylactic RBC transfusion on quality of life and other outcomes in children with cancer who suffer from sepsis (author-defined)?

P = Children (aged 28 days-18 years) with cancer with curative intent who suffer from sepsis (author-defined)
I = Prophylactic RBC transfusion (at any threshold)
C = (No prophylactic RBC transfusion or transfusion at any other threshold)
O = Quality of life, transfusion-related complications, treatment-related complications, morbidity, mortality, admission to hospital, costs, late complications, event-free survival

B3: Relevant outcomes
The importance of outcomes and their hierarchy are discussed in the method section "Research questions and outcomes measures".

B4: Methods
Evidence was searched in three electronic databases, in which (randomized) controlled trials including children and adolescents with cancer were eligible for inclusion. There were no pediatric oncology studies included. Considering the scarcity of the primary evidence, the guideline panel decided that additional evidence ought to be sought in guidelines for general pediatric patients and for adults with cancer, reported in Supplemental Materials 1. The full evidence to decision framework and the overall conclusions are stated in Supplemental Materials 2.

C. Discussion of the literature

C1: Discussion of the evidence
C1.1: Evidence in pediatric oncology
No pediatric oncology studies included children with sepsis.

C1.2: Recommendations and evidence derived from guidelines
Only one out of seven guidelines formulated recommendations for children with sepsis stating that a hemoglobin (Hb) threshold of 4.3 mmol/L can be safely applied in clinically stable children; however, in clinically unstable

children a higher threshold may be suggested (Valentine, 2018). This was based on Lacroix (2007) and Holst (2014).

C2: Description of the included studies
C2.1: Pediatric oncology
There were no primary pediatric oncology studies included from the systematic literature search.

C2.2: Children in general
One pediatric study was included from the additional literature review (Lacroix, 2012).

The characteristics of the included study are stated in the evidence table below.

Table 1. Characteristics of the included studies regarding children.

Included studies				
Study	**Population**	**Liberal threshold**	**Restrictive threshold**	**Outcomes**
Lacroix (2012) RCT	137 stable critically ill children with sepsis	- 5.0 mmol/L	- 4.3 mmol/L	- Mortality - Morbidity - Admission to hospital

C2.3: Adults
One adult study was included from the additional literature review (Holst, 2014).

The characteristics of the included study are stated in the evidence table below.

Table 2. Characteristics of the included studies regarding adults.

Included studies				
Study	**Population**	**Liberal threshold**	**Restrictive threshold**	**Outcomes**
Holst (2014) RCT	998 adult patients with sepsis	- 5.6 mmol/L	- 4.3 mmol/L	- Mortality - Morbidity

C2.4: Excluded studies

Excluded studies	
Study	**Reasons for exclusion**
Lacroix (2007)	This study included children in general. For this section the subanalysis of Lacroix (2012) was included.

D. Results

D1.1: Hb of 4.3 mmol/L versus Hb greater than 4.3

Conclusion of evidence	**Effect**	**Level of evidence / studies**
Children with cancer – Systematic literature search		
No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
Mortality		
No significant differences in group with an Hb of 4.3 mmol/L vs. greater than 4.3 mmol/L.	RR 3.45 (95% CI 0.74 - 16.02)	*Low** / Lacroix 2012
Morbidity		

No significant differences in group with an Hb of 4.3 mmol/L vs. greater than 4.3 mmol/L.	RR 0.99 (95% CI 0.49-1.97)	*Low** / Lacroix 2012
Hospital admission		
No significant differences in group with an Hb of 4.3 mmol/L vs. greater than 4.3 mmol/L.	Not significant (no effect measure reported)	*Low** / Lacroix 2012
Adults with sepsis – Evidence cited in existing guidelines		
Mortality		
No significant differences in group with an Hb of 4.3 mmol/L vs. greater than 4.3 mmol/L.	RR 0.96 (95% CI 0.83 - 1.10)	*Very low** / Holst 2014
Morbidity		
No significant differences in group with an Hb of 4.3 mmol/L vs. greater than 4.3 mmol/L.	RR 0.33 (95% CI 0.01 - 8.18)	*Very low** / Holst 2014

* The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

E. Conclusions

VERY LOW QUALITY OF EVIDENCE (GRADE)	There were no significant differences regarding mortality, morbidity, and admission to hospital with *a hemoglobin (Hb) of 4.3 mmol/L versus a hemoglobin (Hb) greater than 4.3 mmol/L* in 2 studies. Sources (*Lacroix, 2012; Holst, 2014*)

F. Considerations

Regarding the comparison of an Hb threshold of 4.3 mmol/L to an Hb threshold greater than 4.3 mmol/L in children with cancer and sepsis who are hemodynamically stable, one pediatric non-cancer study and one adult non-cancer study were identified. Based on this limited evidence there is no increased risk for mortality or morbidity with an Hb of 4.3 mmol/L in comparison to an Hb greater than 4.3 mmol/L in children and adults with sepsis who are clinically stable (Lacroix, 2012; Holst, 2014). In addition, there are no studies reporting any significant potential benefit from an Hb greater than 4.3 mmol/L (Lacroix, 2012). Thus the guideline panel decided that the benefits of an Hb threshold greater than 4.3 mmol/L are probably not large relative to an Hb threshold of 4.3 mmol/L. In addition, this option of an Hb threshold of 4.3 mmol/L is considered probably acceptable for all stakeholders. Moreover, the guideline panel considered that a higher Hb threshold might lead to more iron overload and costs. Therefore, we suggest against the option of an Hb threshold greater than 4.3 mmol/L. However, in hemodynamically unstable children with cancer and sepsis and evidence of oxygen deficiency (e.g., use of inotropes, elevated lactate) without ongoing blood loss, it is recommended to consider an Hb threshold that ranges between 4.3 mmol/L and 6.2 mmol/L as part of a comprehensive approach to improve oxygen delivery for children with unstable non hemorrhagic shock and evidence of oxygen debt (based on Muszynski, 2018).

Module 2A: Erytrocytentransfusies bij kinderen met kanker en sepsis - Nederlands

G. Aanbevelingen (Nederlands)

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence[1]	Overweeg een hemoglobine (Hb) grens van 4.3 mmol/L voor erytrocytentransfusies bij stabiele kinderen met kanker en sepsis.

ZWAKKE aanbeveling, EXPERT EVIDENCE[2]	De werkgroep is van mening dat het aanbevolen wordt om voor hemodynamisch onstabiele kinderen met kanker en sepsis en tekenen van zuurstoftekort (bijv. gebruik van inotropen, verhoogd lactaatgehaalte) een Hb grens te overwegen die varieert tussen 4.3 mmol/L en 6.2 mmol/L.

[1] Geen primaire studies bij kinderen met kankerpatiënten, bewijs is afgeleid van onderzoek bij pediatrische en volwassen populaties.
[2] Geen primaire studies bij kinderen met kankerpatiënten, geen bewijs afgeleid van onderzoek bij pediatrische en volwassen populaties.

H. Overwegingen (Nederlands)

Voor de vergelijking van een Hb grens van 4.3 mmol/L met een Hb grens hoger dan 4.3 mmol/L bij kinderen met sepsis die hemodynamisch stabiel zijn werd één studie bij kinderen zonder kanker en één studie bij volwassenen zonder kanker geïdentificeerd. Op basis van beperkt bewijs is er geen verhoogd risico op mortaliteit of morbiditeit bij een Hb van 4.3 mmol/L in vergelijking met een Hb hoger dan 4.3 mmol/L (Lacroix, 2012; Holst, 2014). Bovendien zijn er geen studies die een significant potentieel voordeel van een Hb hoger dan 4.3 mmol/L melden (Lacroix, 2012). Daarom besloot de werkgroep dat de voordelen van een Hb grens hoger dan 4.3 mmol/L waarschijnlijk niet groot zijn ten opzichte van een Hb grens van 4.3 mmol/L. Daarbij wordt de optie van een Hb grens van 4.3 mmol/L waarschijnlijk acceptabel geacht voor alle belanghebbenden. Daarnaast was de werkgroep van mening dat een hogere Hb grens zou kunnen leiden tot meer ijzerstapeling en kosten. Daarom raden we de optie van een Hb grens hoger dan 4.3 mmol/L af. Bij hemodynamisch instabiele kinderen met kanker en bloedvergiftiging en tekenen van zuurstoftekort (bijv. gebruik van inotropica, verhoogd lactaatgehalte) zonder aanhoudend bloedverlies, wordt echter aanbevolen om een Hb grens te overwegen die varieert tussen 4.3 mmol/L en 6.2 mmol/L als onderdeel van een alomvattende benadering om zuurstoftoevoer te verbeteren bij kinderen met een onstabiele niet-hemorragische shock en tekenen van zuurstoftekort (gebaseerd op Muszynski, 2018).

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Module 2A: Supplemental materials

Supplemental materials 1: Additional guidelines

The full description of the additional guidelines and the AGREE II-scores are presented in Addendum 5.

Research question 2A - The effect of prophylactic RBC transfusion in children with cancer who suffer from sepsis	
Recommendations for children with sepsis	**Valentine (2018): Consensus Recommendations for RBC Transfusion Practice in Critically Ill Children From the Pediatric Critical Care Transfusion and Anemia Expertise Initiative. Pediatric Critical Care Medicine (Muszynski, 2018).** *AGREE II assessment: Domain 1 = 89%, Domain 2 = 44%, Domain 3 = 79%, Domain 4 = 78%, Domain 5 = 63%, Domain 6 = 92%, Overall Guideline Assessment: Score 5.* Recommendations for critically ill children with a non-hemorrhagic shock, such as a septic shock according to Valentine (2018): - In **hemodynamically stable** critically ill children with a diagnosis of severe sepsis or septic shock, they **recommended not administering a RBC transfusion if the Hb concentration is ≥ 4.3 mmol/dL.** - Weak recommendation, Low quality pediatric evidence, 96% Agreement, (n=29), Median 8, IQR 8-9. - Supporting arguments: The recommendation is based on the TRIPICU study and the adult study TRISS stating that an Hb threshold of 4.3 mmol/dL is safe (Lacroix, 2007; Holst, 2014) - In **hemodynamically unstable** critically ill children with a diagnosis of severe sepsis or septic shock and evidence of oxygen deficiency, they suggest **an Hb threshold between 4.3 mmol/dL and 6.2 mmol/dL**. Consensus panel expertise, 100% Agreement, Median 9, IQR 8-9 - Supporting arguments: The recommendation is based on consensus, due to lack of evidence.

Supplemental materials 2: Evidence to Decision Framework & Overall conclusions - >4.3 mmol/L versus <4.3 mmol/L

Hemoglobin (Hb) threshold >4.3 mmol/L versus a hemoglobin (Hb) threshold of 4.3 mmol/L				
	Criteria	**Judgements**	**Research evidence**	**Additional considerations**
PROBLEM	Is the problem a priority?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ■ **Yes**	RBC transfusions are one of the backbones in the supportive care management of children with oncologic diagnoses and those who are undergoing hematopoietic stem cell transplants (HSCT). Children with cancer may require RBC transfusions due to the underlying oncologic disease or bone marrow suppression as a result of the anti-cancer treatment. This guideline is the first guideline to be established specifically for children with cancer and sepsis.	
BENEFITS AND HARMS	What is the overall certainty of this evidence?	☐ No included studies ■ **Very low** ☐ Low ☐ Moderate ☐ High	Summary of findings: <u>Mortality</u> - Pediatric oncology: no studies included. - Pediatric: Lacroix (2012) reported no significant differences regarding mortality when comparing an Hb threshold <4.3 mmol/L versus an Hb threshold <5.0 mmol/L, RR 3.45 (95% CI 0.74 - 16.02). - Adult: Holst (2014) reported no significant differences regarding mortality when comparing an Hb threshold <4.3 mmol/L versus an Hb threshold <5.6 mmol/L, RR 0.96 (95% CI 0.83 - 1.10). <u>Morbidity</u> - Pediatric oncology: no included studies. - Pediatric: Lacroix (2012) reported no significant differences regarding morbidity when comparing an Hb threshold <4.3 mmol/L versus an Hb threshold <5.0 mmol/L RR 0.99 (95% CI 0.49 - 1.97). - Adult: Holst (2014) reported no significant differences regarding morbidity when comparing an Hb threshold <4.3 mmol/L versus an Hb threshold <5.6 mmol/L, RR 0.33 (95% CI 0.01 - 8.18). <u>Admission to hospital</u> - Pediatric oncology: no included studies. - Pediatric: Lacroix (2012) reported no significant differences regarding admission to hospital when comparing an Hb threshold <4.3 mmol/L versus an Hb threshold <5.0 mmol/L. - Adult: No pediatric oncology: no included studies.	
	Is there important uncertainty about how much people value the main outcomes?	☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ■ **No important uncertainty or variability** ☐ No known undesirable outcomes		The relative importance of all outcomes was unanimously determined.
	Are the desirable anticipated effects large?	☐ No ■ **Probably no** ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies		There is no significant difference regarding mortality and morbidity. Thus, the undesirable anticipated effects are probably not large.

	Are the undesirable anticipated effects small?	☐ No ☐ Probably no ■ **Uncertain** ☐ Probably yes ☐ Yes ☐ Varies		Apart from admission to hospital, there are no other desirable anticipated effects included, thus uncertain.
	Are the desirable effects large relative to undesirable effects?	☐ No ■ **Probably no** ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies		Considering that there is no significant difference regarding mortality, morbidity, and admission to hospital. The desirable anticipated effects are probably not large relative to the undesirable effects.
RESOURCE USE	Are the resources required small?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ■ **Yes** ☐ Varies		The guideline panel decided that the resources necessary are probably small.
	Is the incremental cost small relative to the net benefits?	☐ No ☐ Probably no ☐ Uncertain ■ **Probably yes** ☐ Yes ☐ Varies		There are costs involved. However, benefits are considered uncertain.
EQUITY	What would be the impact on health inequities?	☐ Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ■ **Varies**		The panel expected that implementing this option has no effect on health inequities, given the structure of the Dutch healthcare system. However, in other countries this may vary depending on their healthcare system.

ACCEPTABILITY	Is the option acceptable to key stakeholders?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ■ **Yes** ☐ Varies		The guideline panel considered the option for an Hb threshold >4.3 mmol/L acceptable to the key stakeholders.
FEASIBILITY	Is the option feasible to implement?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ■ **Yes** ☐ Varies		The panel considered the option of a transfusion threshold >4.3 mol/l feasible to implement.

Balance of consequences – Hb threshold >4.3 mmol/L relative to an Hb threshold <4.3 mmol/L				
Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	**The balance between desirable and undesirable consequences *is closely balanced*** ■	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐

Type of recommendation – Hb threshold >4.3 mmol/L relative to an Hb threshold <4.3 mmol/L			
We recommend against offering this option ☐	**We suggest not offering this option** ■	We suggest offering this option ☐	We recommend offering this option ☐
Recommendation (text)	We suggest a hemoglobin (Hb) threshold <4.3 mmol/L for RBC transfusion in children with cancer and sepsis (Weak recommendation).		
Justification	Based on limited evidence there is a suggestion that there is no increased risk for mortality or morbidity with an Hb threshold for RBC transfusion <4.3 mmol/L in comparison to an Hb threshold >4.3 mmol/L in children and adults with sepsis (Lacroix, 2012; Holst, 2014). In addition, there are no studies reporting any significant potential benefit from an Hb threshold >4.3 mmol/L (Lacroix, 2012). In addition, this option of an Hb threshold <4.3 mmol/L is considered probably acceptable for all stakeholders. In addition, the		

	expert panel considered that a higher Hb threshold might lead to more iron overload. Therefore, we suggest not offering the option of an Hb threshold >4.3 mmol/L.
Subgroup considerations	In hemodynamically unstable children with cancer and sepsis and evidence of oxygen deficiency without ongoing blood loss, it is recommended to consider an Hb threshold that ranges between <4.3 mmol/L and <6.2 mmol/L as part of a comprehensive approach to improve oxygen delivery for children with unstable non hemorrhagic shock and evidence of oxygen debt (based on Muszynski, 2018).
Implementation considerations	No implementation considerations were formulated.
Monitoring and evaluation	Not applicable.
Research priorities	See chapter "Gaps in research".

Module 2B: Red blood cell transfusions in neonates with cancer and sepsis - English

A. Recommendations

Research question: What is the effect of prophylactic RBC transfusion on quality of life and other outcomes in neonates with cancer who suffer from sepsis (author-defined)?

A1.1: Recommendations (English)

WEAK recommendation, VERY LOW QUALITY evidence[1]	We suggest a hemoglobin (Hb) threshold of 6.5 mmol/L for red blood cell (RBC) transfusion in neonates with cancer and sepsis when they are less than 1 week old.

WEAK recommendation, VERY LOW QUALITY evidence[1]	We suggest a hemoglobin (Hb) threshold for red blood cell (RBC) transfusion of 5.5 mmol/L in neonates with cancer and sepsis when they are between 1 and 3 weeks old.

WEAK recommendation, VERY LOW QUALITY evidence[1]	We suggest a hemoglobin (Hb) threshold for red blood cell (RBC) transfusion of 4.5 mmol/L in neonates with cancer and sepsis when they are between 3 and 4 weeks old.

[1] No primary studies in childhood cancer patients, evidence derived from studies in the pediatric population.

B. Background, search and selection, relevant outcomes, and methods

B1: Background

The background of red blood cell (RBC) transfusions in pediatric oncology is discussed in the "Background section" of Research question 1A.

B2: Search and selection

In order to be able to answer the clinical question, a systematic literature analysis was carried out into the following search question:

What is the effect of prophylactic RBC transfusion on quality of life and other outcomes in neonates with cancer who suffer from sepsis (author-defined)?

P = Neonates (aged 0-28 days) with cancer with curative intent who suffer from sepsis (author-defined)
I = Prophylactic RBC transfusion (at any threshold)
C = (No prophylactic RBC transfusion or transfusion at any other threshold)
O = Quality of life, transfusion-related complications, treatment-related complications, morbidity, mortality, admission to hospital, costs, late complications, event-free survival

B3: Relevant outcomes

The importance of outcomes and their hierarchy are discussed in the method section "Research questions and outcomes measures".

B4: Methods

Evidence was searched in three electronic databases, in which (randomized) controlled trials including children and adolescents with cancer were eligible for inclusion. There were no pediatric oncology studies included. Considering the scarcity of the primary evidence, the guideline panel decided that additional evidence ought to be sought in guidelines for general pediatric patients and for adults with cancer. However, no guidelines were found.

C: Discussion of the literature

C1: Discussion of the evidence

C1.1: Evidence in pediatric oncology

No pediatric oncology studies included neonates.

C1.2: Recommendations and evidence derived from guidelines
No guidelines included neonates.

C2: Description of the included studies
There were no primary pediatric oncology studies included from the systematic literature search and no additional studies from the additional literature review.

D. Results
As no studies were included, no results were presented.

E. Conclusions
As no studies were included, no conclusions were formulated.

F. Considerations
There was no increased risk for mortality and morbidity in children and adults with sepsis with a hemoglobin (Hb) threshold of 4.3 mmol/L in comparison to an Hb threshold greater than 4.3 mmol/L (see Chapter “Children with cancer and sepsis”). This suggests that children with sepsis do not benefit from a higher Hb in comparison to children in general and thus do not differ from each other. Considering this, the guideline panel decided that a neonate with cancer and sepsis does not differ from a neonate with cancer in general and suggested the recommendations for neonates with cancer for neonates with cancer and sepsis (see Chapter “Neonates with cancer”).

Module 2B: Erytrocytentransfusies bij neonaten met kanker en sepsis - Nederlands

G. Aanbevelingen (Nederlands)

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence[1]	Overweeg een hemoglobine (Hb) grens van 6.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker en sepsis indien ze minder dan 1 week oud zijn.

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence[1]	Overweeg een hemoglobine (Hb) grens van 5.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker en sepsis indien ze tussen de 1 en 3 weken oud zijn.

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence[1]	Overweeg een hemoglobine (Hb) grens van 4.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker en sepsis indien ze tussen de 3 en 4 weken oud zijn.

[1] Geen primaire studies bij kinderen met kankerpatiënten, bewijs is afgeleid van onderzoek bij pediatrische populaties.

H. Overwegingen (Nederlands)

Er was geen verhoogd risico op mortaliteit en morbiditeit bij kinderen en volwassenen met sepsis bij een Hb grens voor erytrocytentransfusie van 4.3 mmol/L in vergelijking met een Hb grens hoger dan 4.3 mmol/L (zie hoofdstuk “Kinderen met kanker en sepsis”). Dit suggereert dat kinderen met sepsis geen baat hebben bij een hoger Hb gehalte in vergelijking met kinderen in algemeen en dat deze groepen dus niet van elkaar verschillen. De werkgroep besloot daarom dat een neonaat met kanker en sepsis niet verschilt van een neonaat met kanker in algemeen en daarom werden de aanbevelingen voor neonaten met kanker overgenomen voor neonaten met kanker en sepsis (zie hoofdstuk “Neonaten met kanker”).

Referenties

None.

Module 3A: Red blood cell transfusions in children with cancer who undergo radiotherapy - English

A. Recommendations

Research question: What is the effect of prophylactic RBC transfusion on quality of life and other outcomes in children with cancer who undergo radiotherapy?

A1.1: Recommendations (English)

WEAK recommendation, EXPERT EVIDENCE[1]	We believe a hemoglobin (Hb) threshold of 4.3 mmol/L for red blood cell (RBC) transfusion should be maintained in children with cancer who undergo radiotherapy.

[1] No primary studies in childhood cancer patients, no evidence derived from studies from existing clinical practice guidelines.

B. Background, search and selection, relevant outcomes, and methods

B1: Background

The background of red blood cell (RBC) transfusions in pediatric oncology is discussed in the "Background section" of Research question 1A.

B2: Search and selection

In order to be able to answer the clinical question, a systematic literature analysis was carried out into the following search question:

What is the effect of prophylactic RBC transfusion on quality of life and other outcomes in children with cancer who undergo radiotherapy?

P = Children (aged 28 days-18 years) with cancer who undergo radiotherapy with curative intent
I = Prophylactic RBC transfusion (at any threshold)
C = (No prophylactic RBC transfusion or transfusion at any other threshold)
O = Quality of life, transfusion-related complications, treatment-related complications, morbidity, mortality, admission to hospital, costs, late complications, event-free survival

B3: Relevant outcomes

The importance of outcomes and their hierarchy are discussed in the method section "Research questions and outcomes measures".

B4: Methods

Evidence was searched in three electronic databases, in which (randomized) controlled trials including children and adolescents with cancer were eligible for inclusion. No pediatric oncology studies were included. Considering the scarcity of the primary evidence, the guideline panel decided that additional evidence ought to be sought in guidelines for general pediatric patients and for adults with cancer, reported in table 2 (Supplemental Materials).

C. Discussion of the literature

C1: Discussion of the evidence

C1.1: Evidence in pediatric oncology

No pediatric oncology studies included children with cancer who undergo radiotherapy.

C1.2: Recommendations and evidence derived from guidelines

One guideline was found from the National Blood Authority (2012) in which it was stated that the same hemoglobin (Hb) threshold should be used in patients with cancer who undergo radiotherapy (not further specified). This was based on consensus.

C2: Description of the included studies
There were no primary pediatric oncology studies included from the systematic literature search and no additional studies from the additional literature review.

D. Results
As no studies were included, no results were presented.

E. Conclusions
As no studies were included, no conclusions were formulated.

F. Considerations
There are no studies regarding children with cancer who undergo radiotherapy. However, there are studies that have showed that low pretreatment Hb levels are a strong prognostic factor of poor disease control and survival (Hoff, 2011; Henke, 2004). On the contrary, there is one study in 414 adult patients with Head and Neck Squamous Cell Carcinoma (HNSCC) in which patients with “low” pre-irradiation Hb values (females Hb of 8.07 mmol/L, males Hb of 9.0 mmol/L) were randomized in receiving a RBC transfusion with the aim to achieve an Hb level in the “high” value range or no transfusion. The study showed that the transfusions prior to and during the radiotherapy treatment did not improve the poor prognosis in patients with low Hb values (Hoff, 2011). In addition, other RCTs have also failed to show the effectiveness of transfusion strategies, and the use of erythropoietin was even counterproductive (Janssens, 2014). The study of Janssens (2014) does show that ARCON (briefly administering a gas mixture carbogen and taking nicotinamide pills) has potential to correct the poor outcome of cancer patients and anemia. The study tried to explain why transfusions do not influence the outcome. It is thought that RBC transfusions stimulate inflammatory and immunosuppressive pathways. Erythropoietin was thought to decrease tissue oxygenation caused by increased viscosity with the increased Hb and the presence of erythropoietin receptors on the tumor cell membranes to stimulate tumor growth. A study in animals showed that the correction of the anemia by blood transfusions produced an increased tumor radiosensitivity, possibly by the improved oxygenation of the tumor cells. However, this effect was transient and lost within 24 hours. It is thought that tumors which are chronically exposed to higher oxygen levels (e.g., normal Hb levels) will eventually adapt and will proliferate more actively and outgrow their oxygen supply. With ARCON, the increase of oxygenation is too short (10-15 minutes) and the adaptation will not happen (Janssens, 2014). In conclusion, a higher Hb threshold for RBC transfusion does not lead to better outcomes in adults. Therefore, the guideline panel decided to adopt the recommendations for children with cancer (see chapter “Children with cancer”).

Module 3A: Erytrocytentransfusies bij kinderen met kanker die radiotherapie ondergaan - Nederlands

G. Aanbevelingen (Nederlands)

ZWAKKE aanbeveling, EXPERT EVIDENCE[1]	De werkgroep is van mening dat een hemoglobine (Hb) grens van 4.3 mmol/L voor erytrocytentransfusie moet worden gehandhaafd bij kinderen met kanker die radiotherapie ondergaan.

[1] Geen primaire studies bij kinderen met kankerpatiënten, geen bewijs afgeleid van onderzoeken uit bestaande klinische praktijkrichtlijnen.

H. Overwegingen (Nederlands)

Er zijn geen studies over kinderen met kanker die radiotherapie ondergaan. Er zijn echter wel onderzoeken die aantonen dat een laag Hb waarde vóór de behandeling een sterke prognostische factor zou zijn voor slechte controle van de kanker en overleving (Hoff, 2011; Henke, 2004). Echter, er is een studie van 414 volwassen patiënten met een hoofd-hals plaveiselcelcarcinomen (HNSCC) waarbij patiënten met een “laag Hb-waarde vóór bestraling (vrouwen Hb lager dan 8.07 mmol/L, mannen Hb lager dan 9.0 mmol/L) werden gerandomiseerd in het krijgen van een erytrocytentransfusie met als doel het bereiken van een “hoog” Hb-waarde of in het krijgen van geen transfusie. Uit het onderzoek blijkt dat de transfusies vóór en tijdens de bestraling de slechte prognose bij patiënten met een laag Hb-waarde niet verbeterden (Hoff, 2011). Daarnaast hebben ook andere RCT’s de effectiviteit van van transfusiestrategieën niet aangetoond en was het gebruik van erytropoëtine zelfs contraproductief. Uit de studie van Janssens (2014) blijkt wel dat ARCON (het kortstondig toedienen van het gasmengsel carbogen en het slikken van nicotinamide pillen) de slechte uitkomst van kankerpatiënten en bloedarmoede kan corrigeren. Het artikel heeft geprobeerd uit te leggen waarom transfusies geen effect hebben op de uitkomst. Men denkt dat erytrocytentransfusies inflammatoire en immunosuppressieve *pathways* stimuleren. Van erytropoëtine wordt gedacht dat het de weefseloxygenatie vermindert door de verhoogde viscositeit als gevolg van het verhoogde Hb en de aanwezigheid van erytropoëtinereceptoren op de tumor celmembranen stimuleren de tumorgroei. Een studie uitgevoerd bij dieren toonde aan dat de correctie van de bloedarmoede door bloedtransfusies een verhoogde stralingsgevoeligheid van de tumor veroorzaakte, mogelijk door de verbeterde oxygenatie van de tumorcellen. Dit effect was echter van tijdelijke aard en verdween binnen 24 uur. Men denkt dat tumoren die chronisch worden blootgesteld aan hogere zuurstofgehaltes (bijvoorbeeld bij normale Hb-waarden) zich uiteindelijk zullen aanpassen en actiever zullen profileren en hun zuurstofvoorziening uiteindelijk ontgroeien. Bij ARCON is de toename van de oxygenatie te kort (10-15 minuten) en daarom zal deze aanpassing niet plaatsvinden (Janssens, 2014). Concluderend leidt dus een hogere Hb grens niet tot betere uitkomsten voor de volwassen patiënt. Dit in acht nemend heeft de werkgroep daarom besloten de aanbevelingen voor kinderen met kanker over te nemen (zie hoofdstuk “Kinderen met kanker”).

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Module 3A: Supplemental materials

Supplemental materials 1: additional guidelines

The full description of the additional guidelines and the AGREE II-scores are presented in Addendum 5.

Research question 3A - The effect of prophylactic RBC transfusion in children with cancer who undergo radiotherapy	
Recommendations for adults who undergo radiotherapy	**National Blood Authority (2012): Patient Blood Management Guidelines module 3.** *AGREE II assessment: Domain 1 = 89%, Domain 2 = 44%, Domain 3 = 67%, Domain 4 = 89%, Domain 5 = 29%, Domain 6 = 58%, Overall Guideline Assessment: Score 4.* Recommendations according to the Patient Blood Management Guidelines National Blood Authority (2012): - The **same hemoglobin (Hb) thresholds as other patients with cancer**. - Supporting arguments: Based on a review stating that the correction of anemia by RBC transfusions led to adverse effects (Varlotto & Stevenson, 2005).

Module 3B: Red blood cell transfusions in neonates with cancer who undergo radiotherapy - English

A. Recommendations

Research question: What is the effect of prophylactic RBC transfusion on quality of life and other outcomes in neonates with cancer who undergo radiotherapy?

A1.1: Recommendations (English)

WEAK recommendation, EXPERT EVIDENCE[1]	We believe a hemoglobin (Hb) threshold of 6.5 mmol/L for red blood cell (RBC) transfusion should be maintained in neonates with cancer who undergo radiotherapy when they are less than 1 week old.

WEAK recommendation, EXPERT EVIDENCE[1]	We believe a hemoglobin (Hb) threshold for red blood cell (RBC) transfusion of 5.5 mmol/L should be maintained in neonates with cancer who undergo radiotherapy when they are between 1 and 3 weeks old.

WEAK recommendation, EXPERT EVIDENCE[1]	We believe a hemoglobin (Hb) threshold for red blood cell (RBC) transfusion of 4.5 mmol/L should be maintained in neonates with cancer who undergo radiotherapy when they are between 3 and 4 weeks old.

[1] No primary studies in childhood cancer patients, no evidence derived from studies from existing clinical practice guidelines.

B. Background, search and selection, relevant outcomes, and methods

B1: Background

The background of red blood cell (RBC) transfusions in pediatric oncology is discussed in the "Background section" of Research question 1A.

B2: Search and selection

In order to be able to answer the clinical question, a systematic literature analysis was carried out into the following search question:

What is the effect of prophylactic RBC transfusion on quality of life and other outcomes in neonates with cancer who undergo radiotherapy?

P = Neonates (aged 0-28 days) with cancer who undergo radiotherapy with curative intent
I = Prophylactic RBC transfusion (at any threshold)
C = (No prophylactic RBC transfusion or transfusion at any other threshold)
O = Quality of life, transfusion-related complications, treatment-related complications, morbidity, mortality, admission to hospital, costs, late complications, event-free survival

B3: Relevant outcomes

The importance of outcomes and their hierarchy are discussed in the method section "Research questions and outcomes measures".

B4: Methods

Evidence was searched in three electronic databases, in which (randomized) controlled trials including children and adolescents with cancer were eligible for inclusion. No pediatric oncology studies were included. Considering the scarcity of the primary evidence, the guideline panel decided that additional evidence ought to be sought in guidelines for general pediatric patients and for adults with cancer, reported in table 2 (Supplemental Materials).

C. Discussion of the literature

C1: Discussion of the evidence

C1.1: Evidence in pediatric oncology

No pediatric oncology studies included neonates.

C1.2: Recommendations and evidence derived from guidelines

One guideline was found from the National Blood Authority (2012) and they state that the same hemoglobin (Hb) threshold should be used in patients with cancer who undergo radiotherapy (not further specified). This was

based on consensus.

C2: Description of the included studies
There were no primary pediatric oncology studies included from the systematic literature search and no additional studies from the additional literature review.

D. Results
As no studies were included, no results were presented.

E. Conclusions
As no studies were included, no conclusions were formulated.

F. Considerations
For the considerations of the recommendations “Neonates with cancer who undergo radiotherapy” reference is made to the chapter “Children with cancer who undergo radiotherapy”.

Module 3B: Erytrocytentransfusies bij neonaten met kanker die radiotherapie ondergaan - Nederlands

G. Aanbevelingen (Nederlands)

ZWAKKE aanbeveling, EXPERT EVIDENCE[1]	De werkgroep is van mening dat een hemoglobine (Hb) grens van 6.5 mmol/L voor erytrocytentransfusie moet worden gehandhaafd bij neonaten met kanker die radiotherapie ondergaan indien ze minder dan 1 week oud zijn.

ZWAKKE aanbeveling, EXPERT EVIDENCE[1]	De werkgroep is van mening dat een hemoglobine (Hb) grens van 5.5 mmol/L voor erytrocytentransfusie moet worden gehandhaafd bij neonaten met kanker die radiotherapie ondergaan indien ze tussen de 1 en 3 weken oud zijn.

ZWAKKE aanbeveling, EXPERT EVIDENCE[1]	De werkgroep is van mening dat een hemoglobine (Hb) grens van 4.5 mmol/L voor erytrocytentransfusie moet worden gehandhaafd bij neonaten met kanker die radiotherapie ondergaan indien ze tussen de 3 en 4 weken oud zijn.

[1] Geen primaire studies bij kinderen met kankerpatiënten, geen bewijs afgeleid van onderzoeken uit bestaande klinische praktijkrichtlijnen.

H. Overwegingen (Nederlands)

Voor de overwegingen van de aanbevelingen “Neonaten met kanker die radiotherapie ondergaan” wordt verwezen naar het hoofdstuk “Kinderen met kanker die radiotherapie ondergaan”.

Referenties

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Hoff, C. M., Hansen, H. S., Overgaard, M., Grau, C., Johansen, J., Bentzen, J., & Overgaard, J. (2011). The importance of haemoglobin level and effect of transfusion in HNSCC patients treated with radiotherapy – Results from the randomized DAHANCA 5 study. *Radiotherapy and Oncology*, *98*(1), 28–33. https://doi.org/10.1016/j.radonc.2010.09.024

Hoff, C. M., Lassen, P., Eriksen, J. G., Hansen, H. S., Specht, L., Overgaard, M., Grau, C., Johansen, J. Bentzen, J., Andersen, L., Evensen, J. F., & Overgaard, J. (2011). Does transfusion improve the outcome for HNSCC patients treated with radiotherapy? – Results from the randomized DAHANCA 5 and 7 trials. *Acta Oncologica*, *50*(7), 1006–1014. https://doi.org/10.3109/0284186x.2011.592650

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Module 3B: Supplemental materials

Supplemental materials 1: additional guidelines

The full description of the additional guidelines and the AGREE II-scores are presented in Addendum 5.

Research question 3B - The effect of prophylactic RBC transfusion in children with cancer who undergo radiotherapy	
Recommendations for adults who undergo radiotherapy	**National Blood Authority (2012): Patient Blood Management Guidelines module 3.** *AGREE II assessment: Domain 1 = 89%, Domain 2 = 44%, Domain 3 = 67%, Domain 4 = 89%, Domain 5 = 29%, Domain 6 = 58%, Overall Guideline Assessment: Score 4.* Recommendations according to the Patient Blood Management Guidelines National Blood Authority (2012): - The **same Hb thresholds as other patients with cancer**. - Supporting arguments: Based on a review stating that the correction of anemia by RBC transfusions led to adverse effects (Varlotto & Stevenson, 2005).

Module 4A: Red blood cell transfusions in children with cancer with cardiac and pulmonary comorbidities - English

A. Recommendations

Research question: What is the effect of prophylactic RBC transfusion on patient-related and other outcomes in children with cancer with cardiac and pulmonary comorbidity?

A1.1: Recommendations (English)

WEAK recommendation, VERY LOW QUALITY evidence[1]	We suggest a hemoglobin (Hb) threshold of 4.3 mmol/L for red blood cell (RBC) transfusion in children with cancer and cardiac and pulmonary comorbidities.

WEAK recommendation, VERY LOW QUALITY evidence[2]	We believe that in case of a hemodynamically unstable child with cancer and pulmonary and/or cardiac comorbidities (e.g., use of inotropes, elevated lactate) a higher Hb threshold can be considered.

WEAK recommendation, EXPERT EVIDENCE[1]	For children on ECMO: - In critically ill children on ECMO, we recommend taking measures to minimize the number of donor exposures. - In critically ill children on ECMO, we recommend using physiologic metrics and biomarkers of oxygen delivery in addition to Hb concentration to guide RBC transfusion. Administration of a RBC transfusion should be based on evidence of inadequate cardiorespiratory support or decreased systemic and/or regional oxygen delivery. - In critically ill children on ECMO, there is insufficient evidence to recommend a specific RBC transfusion decision-making strategy using physiologic-based metrics and biomarkers.

[1] No primary studies in childhood cancer patients, evidence derived from studies in the pediatric and adult population.
[2] No primary studies in childhood cancer patients, no evidence derived from studies from existing clinical practice guidelines.

B. Background, search and selection, relevant outcomes, and methods

B1: Background

The background of red blood cell (RBC) transfusions in pediatric oncology is discussed in the “Background section” of Research question 1A.

B2: Search and selection

In order to be able to answer the clinical question, a systematic literature analysis was carried out into the following search question:

<u>What is the effect of prophylactic RBC transfusion on patient-related and other outcomes in children with cancer with cardiac and pulmonary comorbidity?</u>

P = Children (aged 28 days-18 years) with cancer with curative intent and cardiac and/or pulmonary comorbidity (ASA equal to or bigger than 3)
I = Prophylactic RBC transfusion (at any threshold)
C = (No prophylactic RBC transfusion or transfusion at any other threshold)
O = Quality of life, transfusion-related complications, treatment-related complications, morbidity, mortality, admission to hospital, costs, late complications, event-free survival

B3: Relevant outcomes

The importance of outcomes and their hierarchy are discussed in the method section “Research questions and outcomes measures”.

B4: Methods

Evidence was searched in three electronic databases, in which (randomized) controlled trials including children and adolescents with cancer were eligible for inclusion. There were no pediatric oncology studies included. Considering the scarcity of the primary evidence, the guideline panel decided that additional evidence ought to be

sought in guidelines for general pediatric patients and for adults with cancer, reported in Supplemental Materials 1. The full evidence to decision framework and the overall conclusions are stated in Supplemental Materials 2.

C. Discussion of the literature

C1: Discussion of the evidence

C1.1: Evidence in pediatric oncology

No pediatric oncology studies were included.

C1.2: Recommendations and evidence derived from guidelines

Three out of seven guidelines included recommendations for children with cardiac and pulmonary comorbidities. These recommendations are distinguished in children with acute respiratory failure and children with acquired and congenital heart disease.

Only Valentine (2018) included recommendations for children with respiratory failure, advising a hemoglobin (Hb) threshold of 3.1 mmol/L. They do not advise an Hb threshold higher than 4.3 mmol/L in critically ill children with respiratory failure without severe acute hypoxemia, chronic cyanotic conditions, or hemolytic anemia. There was not enough evidence to create a recommendation regarding RBC transfusion thresholds between 3.1 and 4.3 mmol/L. A recommendation could not be made for critically ill children with respiratory failure and severe hypoxemia. These recommendations were based on 7 studies in both children and adults (Marsh, 1995; English, 2002; Lackritz, 1992; Viele & Weiskopf, 1994; Carson, 2002; Shander, 2014; Lacroix, 2007).

Valentine (2018) and the BCSH (2016) included recommendations for children with acquired and congenital heart disease. Valentine (2018) advises in hemodynamically stable critically ill children with uncorrected congenital heart disease an Hb threshold between 4.3 mmol/L and 5.6 mmol/L depending on the cardiopulmonary reserve. There is not enough evidence to create recommendations for children with right or left ventricular myocardial dysfunction (acquired or congenital) or for children with a structurally normal heart and idiopathic or acquired pulmonary hypertension (mean pulmonary arterial pressure >25 mmHg with normal pulmonary capillary wedge pressure). This was based on Lacroix (2007). The BCSH (2016) advises an Hb threshold of 4.3 mmol/L in stable children with non-cyanotic heart disease. There is insufficient evidence to make a recommendation for pre-transfusion Hb thresholds in pediatric hematology/oncology patients and those undergoing stem cell transplantation and for children with cyanotic heart disease (Lacroix, 2007; Lacroix, 2012; Carson, 2012; Retter, 2013; Hébert, 1999; Carson, 2011; NICE, 2015).

C2: Description of the included studies

C2.1: Pediatric oncology

There were no primary pediatric oncology studies included from the systematic literature search.

C2.2: Children in general

Five pediatric studies were included from the additional literature review (Lacroix, 2012; Cholette, 2011; Willems, 2010; English, 2002; Marsh, 1995).

The characteristics of the included studies are stated in the evidence table below. The studies differ from each other in patient population and in methodology.

Table 1. Characteristics of the included studies regarding children.

Included studies				
Study	**Population**	**Liberal threshold**	**Restrictive threshold**	**Outcomes**
Lacroix (2012) Subananalysis of Lacroix (2007)	400 stable critically ill children with respiratory distress	- 5.0 mmol/L	- 4.3 mmol/L	- Mortality - Morbidity - Admission to hospital
Cholette (2011) RCT	60 infants and children with variations of single-ventricle physiology presenting for cavopulmonary connection	- 8.1 mmol/L	- 5.6 mmol/L	- Mortality - Admission to hospital
Willems (2010) Subananalysis of Lacroix (2007)	125 stable critically ill children post cardiac surgery (noncyanotic)	- 5.0 mmol/L	- 4.3 mmol/L	- Mortality - Morbidity - Admission to hospital
Marsh (1995) Prospective study	1844 children with malaria and an Hb below 3.1 mmol/L with respiratory distress	-	-	- Mortality

English (2002) Retrospective and prospective cohort study	1516 severely anemic children divided into 1185 children who had malaria and 331 children with other diagnoses in Kenya	- 3.1 mmol/L	- 2.5 mmol/L - 3.1 mmol/L with respiratory distress	- Mortality - Morbidity - Admission to hospital

C2.3: Adults

Three adult studies were included from the additional literature review (Carson, 2002; Hajjar, 2010; Carson, 2011).

The characteristics of the included studies are stated in the evidence table below. The studies differ from each other in patient population and in methodology.

Table 2. Characteristics of the included studies regarding adults.

Included studies				
Study	**Population**	**Liberal threshold**	**Restrictive threshold**	**Outcomes**
Carson (2002) Retrospective study	300 adults with a postoperative Hb of 5.0 with cardiovasculair comorbidities	Different Hb levels		- Mortality
Hajjar (2010) RCT	RCT including 512 adults undergoing elective cardiac surgery	- Hematocrit 0.30 L/L	- Hematocrit 0.24 L/L	- Mortality - Morbidity - Admission to hospital
Carson (2011) RCT	2016 adults with either a history of or risk factors for cardiovascular disease and whose Hb level was of 6.2 mmol/L after hip-fracture surgery	- 6.2 mmol/L	- 5.0 mmol/L	- Mortality - Morbidity - Admission to hospital - Quality of life

C2.4: Excluded studies

Excluded studies	
Study	**Reasons for exclusion**
Lacroix (2007)	This study included children in general. For this section the subanalysis of Lacroix (2012) was included.
Lackritz (1992)	This study included children in general and was included in the section “Children with cancer”.
Viele & Weiskopf (1994)	This study included adults in general and was included in the section “Children with cancer”.
Carson (2002)	This study included adults in general and was included in the section “Children with cancer”.
Shander (2014)	This study included adults in general and was included in the section “Children with cancer”.
Carson (2012)	This study included adults in general and was included in the section “Children with cancer”.
BCSH (2013)	This is a former guideline from the BCSH group and was thus not included.
Hébert (1999)	This study included adults in general and was included in the section “Children with cancer”.

D. Results

D1.1: Hb of 4.3 mmol/L versus Hb greater than 4.3 mmol/L

Conclusion of evidence	Effect	Level of evidence / studies
Children with cancer – Systematic literature search		
No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
Mortality		
No significant differences regarding mortality when comparing an Hb of 4.3 mmol/L with 5.0 mmol/L.	RR 0.98 (95% CI 0.14 - 6.77)*	*Very low*** / Willems 2010
Morbidity		
No significant differences regarding morbidity when comparing an Hb of 4.3 mmol/L with 5.0 mmol/L.	RR 0.99 (95% CI 0.64 - 1.54) RR 1.97 (95% CI 0.62 - 6.20)	*Very low*** / Lacroix 2012 (respiratory distress) *Very low*** / Willems 2010
Admission to hospital		
No significant differences regarding admission to hospital when comparing an Hb of 4.3 mmol/L with 5.0 mmol/L.	MD 0.10 (95% CI -0.78 - 0.98) MD -0.40 (95% CI -2.42 - 1.62)*	*Very low*** / Lacroix 2012 *Very low*** / Willems 2010
Adults – Evidence cited in existing guidelines		
Mortality		
No significant differences regarding mortality when comparing an Hb of 4.3 mmol/L with 5.0 mmol/L.	None died (not estimable)	*Very low*** / Carson 2002

* Results could not be pooled due to different study populations or outcome measures.
** The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

D1.2: Hb of 5.0 mmol/L versus Hb greater than 5.0 mmol/L

Conclusion of evidence	Effect	Level of evidence / studies
Children with cancer – Systematic literature search		
No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
No studies	-	-
Adults – Evidence cited in existing guidelines		
Mortality		
No significant differences regarding mortality when comparing an Hb of 5.0 mmol/L with 6.2 mmol/L.	RR 1.16 (95% CI 0.56 - 2.39) RR 0.87 (95% CI 0.63 - 1.19)*	*Moderate*** / Hajjar 2010 *Very low*** / Carson 2011
Morbidity		
No significant differences regarding morbidity when comparing an Hb of 5.0 mmol/L with 6.2 mmol/L.	Not significant (no effect measure reported)	*Moderate*** / Hajjar 2010 *Very low*** / Carson 2011
Quality of life		

No significant differences regarding quality of life when comparing an Hb of 5.0 mmol/L with 6.2 mmol/L.	Not significant (no effect measure reported)	*Very low*** / Carson 2011
Admission to hospital		
No significant differences regarding admission to hospital when comparing an Hb of 5.0 mmol/L with 6.2 mmol/L.	Not significant (no effect measure reported) MD 0.30 (95% CI -0.11 - 0.71)	*Moderate*** / Hajjar 2011 *Very low*** / Carson 2011

* Results could not be pooled due to different study populations or oucome measures.
** The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

D1.3: Hb of 5.6 mmol/L versus Hb greater than 5.6 mmol/L

Conclusion of evidence	Effect	Level of evidence / studies
Children with cancer – Systematic literature search		
No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
Mortality		
No significant differences regarding mortality when comparing an Hb of 5.6 mmol/L with 8.07 mmol/L.	RR 0.33 (95% CI 0.01 - 7.87)	*Very low*** / Cholette 2011
Admission to hospital		
No significant differences regarding admission to hospital when comparing an Hb of 5.6 mmol/L with 8.07 mmol/L.	Not significant (no effect measure reported)	*Very low*** / Cholette 2011
Adults – Evidence cited in existing guidelines		
No studies	-	-

** The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

E. Conclusions

VERY LOW QUALITY OF EVIDENCE (GRADE)	No significant difference regarding mortality, morbidity, and admission to hospital in both children and adults with cardiac and pulmonary comorbidities with *a hemoglobin (Hb) of 4.3 mmol/L versus a hemoglobin (Hb) greater than 4.3 mmol/L* in 3 studies. Sources (*Lacroix, 2012; Carson, 2002; Willems, 2010*)

F. Considerations

Regarding the comparison of an Hb threshold of 4.3 mmol/L to an Hb threshold greater than 4.3 mmol/L in children with cancer with cardiac and pulmonary comorbidities, two pediatric non-cancer studies, and one adult non-cancer study were identified. Based on the evidence there is no increased risk for mortality, morbidity and hospital admission with an Hb of 4.3 mmol/L in comparison to an Hb greater than 4.3 mmol/L in children and adults with cardiac and pulmonary comorbidities (Lacroix, 2012; Carson, 2002; Willems, 2010), thus the guideline panel decided that the benefits of an Hb threshold greater than 4.3 mmol/L are probably not large in comparison to an Hb threshold of 4.3 mmol/L. In addition, this option is considered probably acceptable for all stakeholders. Studies that included higher restrictive Hb thresholds (such as 5.0 mmol/L and 5.6 mmol/L) also did not report significant outcomes regarding mortality, morbidity, quality of life, and admission to hospital (Hajjar, 2010; Carson, 2011; Cholette, 2011). Therefore, the guideline panel decided to suggest an Hb threshold of 4.3 mmol/L in children with cancer and cardiac and pulmonary comorbidities. It is reasonable to consider transfusion based on clinical judgment in these children. In case of a hemodynamically unstable child with cancer and pulmonary and/or cardiac comorbidities (e.g., use of inotropes, elevated lactate) a higher Hb threshold can be considered.

For children on Extracorporeal Membrane Oxygenation (ECMO) the guideline panel decided to adopt the following recommendations from the Valentine (2018) guideline:

- In critically ill children on ECMO, we recommend taking measures to minimize the number of donor exposures. *Consensus panel expertise.*
- In critically ill children on ECMO, we recommend using physiologic metrics and biomarkers of oxygen delivery in addition to Hb concentration to guide RBC transfusion. Administration of a RBC transfusion should be based on evidence of inadequate cardiorespiratory support or decreased systemic and/or regional oxygen delivery. *Weak recommendation*.
- In critically ill children on ECMO, there is insufficient evidence to recommend a specific RBC transfusion decision-making strategy using physiologic-based metrics and biomarkers. *Consensus panel expertise*.

Module 4A: Erytrocytentransfusies bij kinderen met kanker en cardiale en/of pulmonale comorbiditeiten - Nederlands

G. Aanbevelingen (Nederlands)

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence[1]	Overweeg een hemoglobine (Hb) grens van 4.3 mmol/L voor erytrocytentransfusies bij kinderen met kanker en cardiale en pulmonale comorbiditeiten.

ZWAKKE aanbeveling, EXPERT EVIDENCE[2]	De werkgroep is van mening dat bij een hemodynamisch instabiel kind met kanker en pulmonale en/of cardiale comorbiditeiten (bijv. gebruik van inotropica, verhoogd lactaatgehalte) een hogere Hb grens worden kan overwogen.

ZWAKKE aanbeveling, EXPERT EVIDENCE[1]	Voor kinderen aan de ECMO: - Bij ernstig zieke kinderen aan ECMO raden we aan maatregelen te nemen om het aantal blootstellingen van donoren te minimaliseren. - Bij ernstig zieke kinderen aan ECMO raden we aan om naast de Hb concentratie ook fysiologische meetwaarden en biomarkers voor zuurstoftoevoer te gebruiken om een erytrocytentransfusie te geven. Toediening van een erytrocytentransfusie moet gebaseerd zijn op tekenen van onvoldoende cardiorespiratoire ondersteuning of verminderde systemische en/of regionale zuurstoftoediening. - Bij ernstig zieke kinderen aan ECMO is er onvoldoende bewijs om een specifieke strategie aan te bevelen over het nemen van beslissingen over erytrocytentransfusies met behulp van fysiologische metrieken en biomarkers.

[1] Geen primaire studies bij kinderen met kankerpatiënten, bewijs is afgeleid van onderzoek bij pediatrische en volwassen populaties.
[2] Geen primaire studies bij kinderen met kankerpatiënten, geen bewijs afgeleid van onderzoek bij pediatrische en volwassen populaties.

H. Overwegingen (Nederlands)

Voor de vergelijking van een Hb grens van 4.3 mmol/L met een Hb grens hoger dan 4.3 mmol/L voor kinderen met kanker en cardiale en/of pulmonale comorbiditeiten werden twee onderzoeken bij kinderen zonder kanker en één onderzoek bij volwassenen zonder kanker geïdentificeerd. Op basis van deze literatuur is geen verhoogd risico op mortaliteit, morbiditeit en ziekenhuisopname met een Hb lager dan 4.3 mmol/L in vergelijking met een Hb hoger dan 4.3 mmol/L bij kinderen en volwassenen met cardiale en pulmonale comorbiditeiten (Lacroix, 2012; Carson, 2002; Willems, 2010), waardoor de werkgroep besloot dat de voordelen van een Hb grens hoger dan 4.3 mmol/L waarschijnlijk niet groot zijn ten opzichte van een Hb grens van 4.3 mmol/L. Bovendien wordt deze optie waarschijnlijk aanvaardbaar geacht voor alle belanghebbenden. Studies met hogere restrictieve Hb grenzen (zoals 5.0 mmol/L en 5.6 mmol/L) rapporteren ook geen significante uitkomsten met betrekking tot mortaliteit, morbiditeit, kwaliteit van leven en ziekenhuisopnames (Hajjar, 2010; Carson, 2011; Cholette, 2011). Daarom besloot de werkgroep om een Hb grens van 4.3 mmol/L voor te stellen bij kinderen met kanker en cardiale en pulmonale comorbiditeiten. Redelijkerwijs mag overwogen worden om een hogere Hb grens aan te houden op basis van klinisch oordeel bij deze kinderen. Bij een hemodynamisch instabiel kind met kanker en pulmonale en/of cardiale comorbiditeiten (bijv. gebruik van inotropica, verhoogd lactaatgehalte) kan een hogere Hb grens worden overwogen.

Voor kinderen aan Extracorporele Membraan Oxygenatie (ECMO) heeft de werkgroep besloten de volgende aanbevelingen uit de richtlijn van Valentine (2018) over te nemen:

- Bij ernstig zieke kinderen aan ECMO raden we aan maatregelen te nemen om het aantal blootstellingen van donoren te minimaliseren. *Expertise van het consensus panel.*
- Bij ernstig zieke kinderen aan ECMO raden we aan om naast de Hb concentratie ook fysiologische meetwaarden en biomarkers voor zuurstoftoevoer te gebruiken om een erytrocytentransfusie te geven. Toediening van een erytrocytentransfusie moet gebaseerd zijn op tekenen van onvoldoende cardiorespiratoire ondersteuning of verminderde systemische en/of regionale zuurstoftoediening. *Zwakke aanbeveling.*
- Bij ernstig zieke kinderen aan ECMO is er onvoldoende bewijs om een specifieke strategie aan te bevelen over het nemen van beslissingen over erytrocytentransfusies met behulp van fysiologische metrieken en biomarkers. *Expertise van het consensus panel.*

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Module 4A: Supplemental materials

Supplemental materials 1: Additional guidelines

The full description of the additional guidelines and the AGREE II-scores are presented in Addendum 5.

Research question 4A - The effect of prophylactic RBC transfusion in children with cancer with cardiac and pulmonary comorbidity	
Recommendations for children with acute respiratory failure	**Valentine (2018): Consensus Recommendations for RBC Transfusion Practice in Critically Ill Children From the Pediatric Critical Care Transfusion and Anemia Expertise Initiative. Pediatric Critical Care Medicine (Demaret, 2018).** *AGREE II assessment: Domain 1 = 89%, Domain 2 = 44%, Domain 3 = 79%, Domain 4 = 78%, Domain 5 = 63%, Domain 6 = 92%, Overall Guideline Assessment: Score 5.* Recommendations for critically ill children with acute respiratory failure according to Valentine (2018): - In case of a critically ill **child with respiratory failure an Hb threshold of 3.1 mmol/L is recommended**. Strong recommendation, Low quality pediatric evidence (1C), 100% Agreement, (n=35), Median 9 IQR 8-9. - Supporting arguments: The recommendation is based on several studies in children and adults stating that an Hb <3.1 mmol/dL is associated with adverse patient outcomes (Marsh, 1995; English, 2002; Lackritz, 1992; Viele & Weiskopf, 1994; Carson, 2002; Shander, 2014). - In critically ill children with **respiratory failure without severe acute hypoxemia, a chronic cyanotic condition or hemolytic anemia, and with a stable hemodynamic situation a RBC transfusion >4.3 mmol/L is not recommended**. Strong recommendation, Moderate quality pediatric evidence (1B), 100% Agreement, (n=29), Median 8.5, IQR 8-9. - Supporting arguments: This recommendation is based on the TRIPICU study stating that an Hb >4.3 mmol/dL is safe (Lacroix, 2007). - In critically ill children with **respiratory failure and severe hypoxemia a recommendation could not be made**. Consensus panel expertise, 97% Agreement, (n=29), Median 8, IQR 8-9. - Supporting arguments: The recommendation is based on consensus, due to lack of evidence. - There was **not enough evidence to create a recommendation regarding RBC transfusion thresholds between 3.1 - 4.3 mmol/L**, but the clinical judgements should be considered. Consensus panel expertise, 97% Agreement, (n=35), Median 9 IQR 8-9. - Supporting arguments: The recommendation is based on consensus, due to lack of evidence.
Recommendations for children with acquired and congenital heart disease	**Valentine (2018): Consensus Recommendations for RBC Transfusion Practice in Critically Ill Children From the Pediatric Critical Care Transfusion and Anemia Expertise Initiative. Pediatric Critical Care Medicine (Cholette, 2018).** *AGREE II assessment: Domain 1 = 89%, Domain 2 = 44%, Domain 3 = 79%, Domain 4 = 78%, Domain 5 = 63%, Domain 6 = 92%, Overall Guideline Assessment: Score 5.* Recommendations for critically ill children with acquired and congenital heart disease according to Valentine (2018): - Children with **right or left ventricular myocardial dysfunction, acquired or congenital: there is insufficient evidence to support RBC transfusion thresholds. There is no evidence that an Hb level >6.2 mmol/dL is beneficial**. Consensus panel expertise, 83% Agreement, (n=30), Median 8 IQR 7.25-8.75. - Supporting arguments: The recommendation is based on consensus, due to lack of evidence. - Children with a **structurally normal heart and idiopathic or acquired pulmonary hypertension (mean pulmonary arterial pressure >25 mmHg with normal pulmonary capillary wedge pressure): There is insufficient evidence to support RBC transfusion thresholds. There is no evidence that an Hb level >6.2 mmol/dL is beneficial**. Consensus panel expertise, 97% Agreement, (n=35), Median 9, IQR 8-9. - Supporting arguments: The recommendation is based on consensus, due to lack of evidence. - In a hemodynamically stable critically ill child with **uncorrected congenital heart disease an Hb threshold between 4.3 mmol/dL and 5.6 mmol/dL is advised, depending on the degree of cardiopulmonary reserve**. Weak recommendation, Low quality pediatric evidence (2C), 81% Agreement, (n=35), Median 8, IQR 7-8. - Supporting arguments: This recommendation is based on the TRIPICU study stating that an Hb >4.3 mmol/dL is safe (Lacroix, 2007). However, there is no evidence that transfusion to the Hb >5.6 mmol/dL is beneficial and might be of some risk.

	British Committee for Standards in Haematology (2016): Guidelines on transfusion for fetuses, neonates, and older children. *AGREE II assessment: Domain 1 = 83%, Domain 2 = 55%, Domain 3 = 54%, Domain 4 = 83%, Domain 5 = 29%, Domain 6 = 50%, Overall Guideline Assessment: Score 4.* Recommendations according to New (2016): - **An Hb threshold <4.3 mmol/L is advised in stable children with non-cyanotic heart disease**. 2B recommendation. - Supporting arguments: Based on the TRIPICU study and others (Lacroix, 2007; Lacroix, 2012; Carson, 2012; Retter, 2013; Hébert, 1999; Hajjar, 2010; Carson, 2011; NICE, 2015) - There is **insufficient evidence to make a recommendation for children with cyanotic heart disease**. 2C recommendation. - There is **insufficient evidence to make recommendations for pre-transfusion Hb thresholds in pediatric hematology/oncology patients and those undergoing stem cell transplantation.** 2C recommendation.

Supplemental materials 2: Evidence to Decision Framework & Overall conclusions - <4.3 mmol/L versus >4.3 mmol/L

Hb threshold >4.3 mmol/L (intervention) versus an Hb threshold <4.3 mmol/L (control)				
	Criteria	**Judgements**	**Research evidence**	**Additional considerations**
PROBLEM	Is the problem a priority?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ■ **Yes**	RBC transfusions are one of the backbones in the supportive care management of children with oncologic diagnoses and those who are undergoing hematopoietic stem cell transplants (HSCT). Children with cancer may require RBC transfusions due to the underlying oncologic disease or bone marrow suppression as a result of the anti-cancer treatment. This guideline is the first guideline to be established specifically for pediatric oncology.	
BENEFITS AND HARMS	What is the overall certainty of this evidence?	☐ No included studies ■ **Very low** ☐ Low ☐ Moderate ☐ High	Summary of findings: <u>1. Mortality</u> - Pediatric oncology: no included studies. - Pediatric: Willems (2010) reported no significant difference regarding mortality when comparing an Hb threshold <4.3 mmol/L versus <5.0 mmol/L, RR 0.98 (95% CI 0.14 - 6.77). *Evidence cited in existing guidelines.* - Adult: The results from Carson (2002) were not estimable considering that no one died when comparing an Hb threshold <4.3 mmol/L versus <5.0 mmol/L. *Evidence cited in existing guidelines.* <u>5. Morbidity</u> - Pediatric oncology: no included studies. - Pediatric: Willems (2010), and Lacroix (2012) both reported no significant differences regarding morbidity when comparing an Hb threshold <4.3 mmol/L with <5.0 mmol/L, RR 1.97 (95% CI 0.62 - 6.20, RR 0.99 (95% CI 0.64 - 1.54) respectively. *Evidence cited in existing guidelines.* - Adult: no included studies. <u>7. Admission to hospital</u> - Pediatric oncology: no included studies. - Pediatric: Willems (2010), and Lacroix (2012) reported no significant	
	Are the desirable anticipated effects large?	☐ No ■ **Probably no** ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies		There is no significant difference regarding mortality and morbidity. Thus the desirable effects are probably small.
	Are the undesirable anticipated effects small?	☐ No ☐ Probably no ■ **Uncertain** ☐ Probably yes ☐ Yes ☐ Varies		Apart from admission to hospital, no other undesirable effects are included, thus uncertain.

	Are the desirable effects large relative to undesirable effects?	☐ No ■ **Probably no** ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies	differences regarding admission to hospital when comparing an Hb threshold <4.3 mmol/L with <5.0 mmol/L, MD -0.40 (95% CI -2.42 - 1.62), and MD 0.10 (95% CI -.78 - 0.98) respectively. *Evidence cited in existing guidelines.*	Considering that there is no significant difference regarding mortality or morbidity and there is no significant difference regarding admission to hospital, the desirable effects are probably not large relative to the undesirable effects.
RESOURCE USE	Are the resources required small?	☐ No ■ **Probably no** ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies		The guideline panel decided that the resources necessary are probably not small, e.g., hospital admission costs.
	Is the incremental cost small relative to the net benefits?	☐ No ■ **Probably no** ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies		There are costs involved (e.g., hospital admission costs). However, benefits are considered probably not large
EQUITY	What would be the impact on health inequities?	☐ Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ■ **Varies**		The panel expected that implementing this option has no effect on health inequities, given the structure of the Dutch healthcare system. However, in other countries this may vary depending on their healthcare system.
ACCEPTABILITY	Is the option acceptable to key stakeholders?	☐ No ☐ Probably no ☐ Uncertain ■ **Probably yes** ☐ Yes ☐ Varies		The panel considered the option of a transfusion threshold <4.3 mmol/L acceptable for the key stakeholders, e.g., doctors and parents. However, it is unknown if some parties might find it not acceptable, thus probably yes.
FEASIBILITY	Is the option feasible to implement?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ■ **Yes** ☐ Varies		The panel considered the option of a transfusion threshold <4.3 mol/l feasible to implement.

Balance of consequences – Hb threshold >4.3 mmol/L relative to an Hb threshold <4.3 mmol/L				
Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	**Undesirable consequences *probably outweigh* desirable consequences in most settings** ■	The balance between desirable and undesirable consequences *is closely balanced* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐

Type of recommendation – Hb threshold >4.3 mmol/L relative to an Hb threshold <4.3 mmol/L			
We recommend against offering this option ☐	**We suggest not offering this option** ■	We suggest offering this option ☐	We recommend offering this option ☐
Recommendation (text)	We suggest a hemoglobin (Hb) threshold <4.3 mmol/L for RBC transfusion in children with cancer and cardiac and pulmonary comorbidities (weak recommendation).		
Justification	Regarding the comparison of an Hb threshold <4.3 mmol/L to an Hb threshold >4.3 mmol/L, 3 pediatric non-cancer studies and 1 adult non-cancer study were identified. Based on the evidence there is a suggestion that there is no increased risk for mortality, morbidity, and hospital admission with an Hb threshold for RBC transfusion <4.3 mmol/L in comparison to an Hb >4.3 mmol/L in children and adults with cardiac and pulmonary comorbidities (Lacroix, 2012; Carson, 2002; Willems, 2010). In addition, this option is considered probably acceptable for all stakeholders. Studies that included higher restrictive Hb thresholds (such as <5.0 mmol/L and 5.6 mmol/L) also did not report significant outcomes regarding mortality, morbidity, quality of life, and admission to hospital (Hajjar, 2010; Carson, 2011; Cholette, 2011). Therefore, the guideline panel decided to suggest an Hb threshold <4.3 mmol/L in clinically stable children with cancer and cardiac and pulmonary comorbidities.		
Subgroup considerations	It is reasonable to consider transfusion based on clinical judgment in these children. In case of a hemodynamically unstable child with cancer and pulmonary and/or cardiac comorbidities (e.g., use of inotropes, elevated lactate) a higher Hb threshold can be considered.		

Implementation considerations	No implementation considerations were formulated.
Monitoring and evaluation	Not applicable
Research priorities	See chapter "Gaps in research".

Module 4B: Red blood cell transfusions in neonates with cancer with cardiac and pulmonary comorbidities - English

A. Recommendations

Research question: What is the effect of prophylactic RBC transfusion on patient-related and other outcomes in neonates with cancer with cardiac and pulmonary comorbidity?

A1.1: Recommendations (English)

WEAK recommendation, VERY LOW QUALITY evidence[1]	We suggest a hemoglobin (Hb) threshold of 7.5 mmol/L for red blood cell (RBC) transfusion in neonates with cancer and cardiac and pulmonary comorbidities when they are less than 1 week old.

WEAK recommendation, VERY LOW QUALITY evidence[1]	We suggest a hemoglobin (Hb) threshold of 6.5 mmol/L for red blood cell (RBC) transfusion in neonates with cancer and cardiac and pulmonary comorbidities when they are between 2 and 3 weeks old.

WEAK recommendation, VERY LOW QUALITY evidence	We suggest a hemoglobin (Hb) threshold of 5.5 mmol/L for red blood cell (RBC) transfusion in neonates with cancer and cardiac and pulmonary comorbidities when they are between 3 and 4 weeks old.

[1] No primary studies in childhood cancer patients, evidence derived from studies in the pediatric population.

B. Background, search and selection, relevant outcomes, and methods

B1: Background

The background of red blood cell (RBC) transfusions in pediatric oncology is discussed in the "Background section" of Research question 1A.

B2: Search and selection

In order to be able to answer the clinical question, a systematic literature analysis was carried out into the following search question:

What is the effect of prophylactic RBC transfusion on patient-related and other outcomes in neonates with cancer with cardiac and pulmonary comorbidity?

P = Neonates (aged 0-28 days) with cancer with curative intent and cardiac and/or pulmonary comorbidity (ASA equal to or bigger than 3)
I = Prophylactic RBC transfusion (at any threshold)
C = (No prophylactic RBC transfusion or transfusion at any other threshold)
O = Quality of life, transfusion-related complications, treatment-related complications, morbidity, mortality, admission to hospital, costs, late complications, event-free survival

B3: Relevant outcomes

The importance of outcomes and their hierarchy are discussed in the method section "Research questions and outcomes measures".

B4: Methods

Evidence was searched in three electronic databases, in which (randomized) controlled trials including children and adolescents with cancer were eligible for inclusion. No pediatric oncology studies were included. Considering the scarcity of the primary evidence, the guideline panel decided that additional evidence ought to be sought in guidelines for general pediatric patients and for adults with cancer, reported in table 2 (Supplemental Materials).

C. Discussion of the literature

C1: Discussion of the evidence

C1.1: Evidence in pediatric oncology

No pediatric oncology studies included neonates.

C1.2: Recommendations and evidence derived from guidelines

Four out of seven guidelines included recommendations for neonates with cardiac and/or pulmonary comorbidities. The Dutch Association of Medical Specialists (FMS, 2019) have recommended a hemoglobin (Hb) threshold of 7.5 mmol/L in neonates less than 1 week old, between weeks 2-3 an Hb threshold of 6.5 and to maintain an Hb threshold of 5.5 mmol/L in neonates older than 3 weeks. This was based on Connelly (1999), Bell (2005), Whyte & Kirpalani (2006), Chen (2009), Whyte & Kirpalani (2011). JPAC (2013) have based their recommendations on the BCSH (2016). BCSH (2016) have distinguished their recommendations between neonates on ventilation and neonates on oxygen or CPAP. In case of neonates on ventilation, their advice is to maintain an Hb greater than 7.5 mmol/L in neonates younger than 1 week old. In case of neonates older than 2 weeks old maintain the Hb greater than 6.2 mmol/L. In case of neonates on oxygen or CPAP, their advice is to maintain the Hb greater than 7.5 mmol/L in neonates less then 24 hours old. In case of neonates less than 1 week maintain an Hb greater than 6.2 mmol/L. Between 2 and 3 weeks old maintain the Hb greater than 5.9 mmol/L. In case of neonates older than 4 weeks old, maintain an Hb greater than 5.3 mmol/L. Based on studies of Whyte & Kirpalani (2006), Chen (2009), Bell (2005), Whyte & Kirpalani (2011), and Venkatesh (2012). Valentine (2018) have advised in hemodynamically stable infants with uncorrected congenital heart disease an Hb threshold between 4.3 mmol/L and 5.6 mmol/L, depending on the degree of cardiopulmonary reserve. This recommendation is based on the TRIPICU study stating that an Hb greater than 4.3 mmol/dL is safe (Lacroix, 2007). However, there is no evidence that transfusion to the Hb greater than 5.6 mmol/dL is beneficial and might be of some risk.

C2: Description of the included studies

C2.1: Pediatric oncology

There were no primary pediatric oncology studies included from the systematic literature search.

C2.2: Neonates in general

There were four studies included from the additional literature review (Bell, 2005; Chen, 2009; Whyte & Kirpanali, 2006; Conelly, 1999).

The characteristics of the included studies are stated in the evidence table below. The studies differ from each other in patient population (gestational age and birth weight) and in methodology.

Table 1. Characteristics of the included studies regarding neonates with cancer with cardiac and/or pulmonary comorbidities.

Included studies				
Study	Population	Liberal threshold	Restrictive threshold	Outcomes
Bell (2005) *RCT*	103 neonates with very low birth weight (500 to 1300 grams)	- Neonates on ventilation 8.4 mmol/L - Neonates on oxygen/CPAP 6.9 mmol/L - Neonates without respiratory support 5.4 mmol/L	- Neonates on ventilation 6.2 mmol/L - Neonates on oxygen/CPAP 5.0 mmol/L - Neonates without respiratory support 4.4 mmol/L	- Mortality - Morbidity - Costs
Chen (2009) *RCT*	36 neonates with very low birth weight (<1500 grams)	- Neonates on ventilation 9.1 mmol/L - Neonates on CPAP 8.3 mmol/L - Neonates without respiratory support 6.2 mmol/L	- Neonates on ventilation 7.2 mmol/L - Neonates on CPAP 6.2 mmol/L - Neonates without respiratory support 4.5 mmol/L	- Mortality - Morbidity - Costs
Connelly (1999) *Prospective study*	24 neonates with very low birth weight (<1500 grams)	- First week of life 8.1 mmol/L - Second week of life with respiratory support 6.8 mmol/L - Third week of life 5.0 mmol/L	- First week of life 6.8 mmol/L - Second week of life with respiratory support 5.6 mmol/L - Third week of life 5.0 mmol/L	- Mortality - Morbidity - Costs
Whyte & Kirpalani (2006) *RCT*	451 neonates with very low birth weight (<1000 gram)	- Neonates without respiratory support in week 1 7.5 mmol/L - Neonates without respiratory support in week 2 6.2 mmol/L - Neonates without respiratory support in week 3 5.3 mmol/L - Neonates on respiratory support in week 1 8.4 mmol/L - Neonates on respiratory support in week 2 7.5 mmol/L - Neonates on respiratory support in week 3 6.2 mmol/L	- Neonates without respiratory support in week 1 6.2 mmol/L - Neonates without respiratory support in week 2 5.3 mmol/L - Neonates without respiratory support in week 3 4.7 mmol/L - Neonates on respiratory support in week 1 7.1 mmol/L - Neonates on respiratory support in week 2 6.2 mmol/L - Neonates on respiratory support in week 3 5.3 mmol/L	- Mortality - Morbidity - Costs

C2.3: Excluded studies

Excluded studies	
Study	**Reasons for exclusion**
Whyte & Kirpalani (2011)	This was a review, including the following studies: Connelly (1999), Bell (2005), Chen (2009), and Whyte & Kirpalani (2006) and were all included.
Venkatesh (2012)	This was a review, including the following studies: Bell (2005), Chen (2009), Whyte & Kirpalani (2006), Brooks (1999), Mukhopadhya (2004), and Ransome (1989) and were all included except Ransome (1989) considering that this article was not found.
Lacroix (2007)	This study included children in general and was thus included in the section “Children with cancer”.

D. Results

D1: Neonates on oxygen/CPAP

D1.1: Hb of 5.0 mmol/L versus Hb greater than 5.0 mmol/L in neonates on oxygen/CPAP

Conclusion of evidence	Effect	Level of evidence / studies
Children with cancer – Systematic literature search		
No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
Mortality		
There was no significant difference regarding mortality when comparing an Hb of 5.6 mmol/L vs. greater than 5.6 mmol/L in neonates.	RR 0.52 (95% CI 0.05 - 5.56).	*Low** / Bell 2005
Morbidity		
There was no significant difference regarding morbidity when comparing an Hb of 5.6 mmol/L vs. greater than 5.6 mmol/L in neonates.	Not significant (no effect measure reported)	*Low** / Bell 2005
Costs		
There was a significant reduction regarding costs when comparing an Hb of 5.6 mmol/L vs. greater than 5.6 mmol/L in neonates.	**MD -1.10 (95% CI -2.10 - -0.10)**	*Low** / Bell 2005
Adults – Evidence cited in existing guidelines		
No studies	-	-

* The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

D1.2: Hb of 6.2 mmol/L versus Hb greater than 6.2 mmol/L in neonates on oxygen/CPAP

Conclusion of evidence	Effect	Level of evidence / studies
Children with cancer – Systematic literature search		
No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
Mortality		

There was no significant difference regarding mortality when comparing an Hb of 6.2 mmol/L vs. greater than 6.2 mmol/L in neonates.	RR 1.79 (95% CI 0.18 - 18.02)	*Low** / Chen 2009
Morbidity		
There was no significant difference regarding morbidity when comparing an Hb of 6.2 mmol/L vs. greater than 6.2 mmol/L in neonates.	Not significant (no effect measure reported)	*Low** / Chen 2009
Costs		
There was no significant reduction regarding costs when comparing an Hb of 6.2 mmol/L vs. greater than 6.2 mmol/L in neonates.	MD -1.00 (95% CI -2.49 - 0.49)	*Low** / Chen 2009
Adults – Evidence cited in existing guidelines		
No studies	-	-

* The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

D2: Neonates on ventilation

D2.1: Hb of 6.2 mmol/L versus Hb greater than 6.2 mmol/L in neonates on ventilation

Conclusion of evidence	Effect	Level of evidence / studies
Children with cancer – Systematic literature search		
No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
Mortality		
There was no significant difference regarding mortality when comparing an Hb of 6.2 mmol/L vs. greater than 6.2 mmol/L in neonates.	RR 0.52 (95% CI 0.05 - 5.56)	*Low** / Bell 2005
Morbidity		
There was no significant difference regarding morbidity when comparing an Hb of 6.2 mmol/L vs. greater than 6.2 mmol/L in neonates.	Not significant (no effect measure reported)	*Low** / Bell 2005
Costs		
There was a significant reduction regarding costs when comparing an Hb of 6.2 mmol/L vs. greater than 6.2 mmol/L in neonates.	**MD -1.10 (95% CI -2.10 - -0.10)**	*Low** / Bell 2005
Adults – Evidence cited in existing guidelines		
No studies	-	-

* The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

D2.2: Hb of 7.5 mmol/L versus Hb greater than 7.5 mmol/L in neonates on ventilation

Conclusion of evidence	Effect	Level of evidence / studies
Children with cancer – Systematic literature search		
No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		

Mortality		
There was no significant difference regarding mortality when comparing an Hb of 7.5 mmol/L vs. greater than 7.5 mmol/L in neonates.	RR 1.79 (95% CI 0.18 - 18.02)	*Low** / Chen 2009
Morbidity		
There was no significant difference regarding morbidity when comparing an Hb of 7.5 mmol/L vs. greater than 7.5 mmol/L in neonates.	Not significant (no effect measure reported)	*Low** / Chen 2009
Costs		
There was no significant reduction regarding costs when comparing an Hb of 7.5 mmol/L vs. greater than 7.5 mmol/L in neonates.	MD -1.00 (95% CI -2.49 - 0.49)	*Low** / Chen 2009
Adults – Evidence cited in existing guidelines		
No studies	-	-

* The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

D3: Neonates in the first week of life

D3.1: Hb of 7.5 mmol/L versus Hb greater than 7.5 mmol/L in neonates in the first week of life

Conclusion of evidence	**Effect**	**Level of evidence / studies**
Children with cancer – Systematic literature search		
No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
Mortality		
There was no significant difference regarding mortality when comparing an Hb of 7.5 mmol/L vs. greater than 7.5 mmol/L in neonates in the first week of life.	RR 1.23 (95% CI 0.84 - 1.79)	*Low** / Whyte & Kirpalani 2006
Morbidity		
There was no significant difference regarding morbidity when comparing an Hb of 7.5 mmol/L vs. greater than 7.5 mmol/L in neonates in the first week of life. There was a significant difference regarding retinopathy of prematurity when comparing an Hb of 7.5 mmol/L vs. greater than 7.5 mmol/L in neonates in the first week of life.	Not significant (no effect measure reported) **RR 0.79 (95% CI 0.66 - 0.95)**	*Low** / Whyte & Kirpalani 2006
Costs		
There was no significant difference regarding costs when comparing an Hb of 7.5 mmol/L vs. greater than 7.5 mmol/L in neonates in the first week of life.	MD -0.80 (95% CI -1.65 - 0.05)	*Low** / Whyte & Kirpalani 2006
Adults – Evidence cited in existing guidelines		
No studies	-	-

* The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

D4: Neonates in the second week of life

D4.1: Hb of 5.6 mmol/L versus Hb greater than 5.6 mmol/L in neonates on respiratory support in the second week of life

Conclusion of evidence	Effect	Level of evidence / studies
Children with cancer – Systematic literature search		
No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
Mortality		
There was no significant difference regarding mortality when comparing an Hb of 5.6 mmol/L vs. greater than 5.6 mmol/L in neonates in the second week of life.	None died (not estimable)	*Low** / Connelly 1999
Morbidity		
There was no significant difference regarding morbidity when comparing an Hb of 5.6 mmol/L vs. greater than 5.6 mmol/L in neonates in the second week of life.	Not significant (no effect measure reported)	*Low** / Connelly 1999
Costs		
There was a significant reduction regarding costs when comparing an Hb of 5.6 mmol/L vs. greater than 5.6 mmol/L in neonates in the second week of life.	**MD -2.90 (95% CI -4.94 - -0.86)**	*Low** / Connelly 1999
Adults – Evidence cited in existing guidelines		
No studies	-	-

* The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

D4.2: Hb of 6.2 mmol/L versus Hb greater than 6.2 mmol/L in neonates in the second week of life

Conclusion of evidence	Effect	Level of evidence / studies
Children with cancer – Systematic literature search		
No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
Mortality		
There was no significant difference regarding mortality when comparing an Hb of 6.2 mmol/L vs. greater than 6.2 mmol/L in neonates in the second week of life.	RR 1.23 (95% CI 0.84 - 1.79)	*Low** / Whyte & Kirpalani 2006
Morbidity		
There was no significant difference regarding morbidity when comparing an Hb of 6.2 mmol/L vs. greater than 6.2 mmol/L in neonates in the second week of life. There was a significant difference regarding retinopathy of prematurity when comparing an	Not significant (no effect measure reported) **RR 0.79 (95% CI 0.66 - 0.95)**	*Low** / Whyte & Kirpalani 2006

Hb of 6.2 mmol/L vs. greater than 6.2 mmol/L in neonates in the second week of life.		
Costs		
There was no significant difference regarding costs when comparing an Hb of 6.2 mmol/L vs. greater than 6.2 mmol/L in neonates in the second week of life.	MD -0.80 (95% CI -1.65 - 0.05)	*Low** / Whyte & Kirpalani 2006
Adults – Evidence cited in existing guidelines		
No studies	-	-

* The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

D5: Neonates in the third week of life

D5.1: Hb of 5.6 mmol/L versus Hb greater than 5.6 mmol/L in neonates on respiratory support in the third week of life

Conclusion of evidence	Effect	Level of evidence / studies
Children with cancer – Systematic literature search		
No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
Mortality		
There was no significant difference regarding mortality when comparing an Hb of 5.6 mmol/L vs. greater than 5.6 mmol/L in neonates in the third week of life.	RR 1.23 (95% CI 0.84 - 1.79)	*Low** / Whyte & Kirpalani 2006
Morbidity		
There was no significant difference regarding morbidity when comparing an Hb of 5.6 mmol/L vs. greater than 5.6 mmol/L in neonates in the third week of life. There was a significant difference regarding retinopathy of prematurity when comparing an Hb of 5.6 mmol/L vs. greater than 5.6 mmol/L in neonates in the third week of life.	Not significant (no effect measure reported) **RR 0.79 (95% CI 0.66 - 0.95)**	*Low** / Whyte & Kirpalani 2006
Costs		
There was no significant difference regarding costs when comparing an Hb of 5.6 mmol/L vs. greater than 5.6 mmol/L in neonates in the third week of life.	MD -0.80 (95% CI - 1.65 - 0.05)	*Low** / Whyte & Kirpalani 2006
Adults – Evidence cited in existing guidelines		
No studies	-	-

* The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

E. Conclusions

No conclusions were formulated.

F. Considerations

There are very few neonates that develop cancer and have pulmonary and/or cardiac comorbidities. Concerning this clinical question, no pediatric oncology studies were identified. The Dutch Association of Medical Specialists

(FMS, 2019) developed a high-quality guideline addressing this matter with an AGREE II-score of 6 out of 7. They based their recommendations on studies performed in very low birth-weight infants (birth weight of 1500 grams or less) with respiratory support. Because of the lack of evidence regarding full term born neonates and late-premature born neonates (gestational age ≥ 32 weeks), the FMS adopted these thresholds for neonates with respiratory support. Taking this into account, the guideline panel decided to adopt the recommendations regarding neonates with cancer and pulmonary and/or cardiac comorbidities from the guideline of the FMS (2019).

Module 4B: Erytrocytentransfusies bij neonaten met kanker en cardiale en/of pulmonale comorbiditeiten - Nederlands

G. Aanbevelingen (Nederlands)

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence[1]	Overweeg een hemoglobine (Hb) grens van 7.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker en cardiale en pulmonale comorbiditeiten indien ze minder dan 1 week oud zijn.

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence[1]	Overweeg een hemoglobine (Hb) grens van 6.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker en cardiale en pulmonale comorbiditeiten indien ze tussen de 1 en 3 weken oud zijn.

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence[1]	Overweeg een hemoglobine (Hb) grens van 5.5 mmol/L voor erytrocytentransfusie bij neonaten met kanker en cardiale en pulmonale comorbiditeiten indien ze tussen de 3 en 4 weken oud zijn.

[1] Geen primaire studies bij kinderen met kankerpatiënten, bewijs is afgeleid van onderzoek bij pediatrische populaties.

H. Overwegingen (Nederlands)

Er zijn zeer weinig neonaten die kanker krijgen en daarbij pulmonale en/of cardiale comorbiditeiten hebben. Daarbij zijn er geen artikelen over neonaten met kanker geïncludeerd. De FMS (2019) heeft echter voor neonaten met pulmonale en cardiale comorbiditeiten een hoogwaardige richtlijn ontwikkeld met een AGREE II-score van 6 uit de 7. Zij baseerden hun aanbevelingen op onderzoeken uitgevoerd bij neonaten met een zeer laag geboortegewicht (geboortegewicht lager dan 1500 gram) met ademhalingsondersteuning en vanwege het gebrek aan studies met betrekking tot à terme geboren neonaten en laat-prematuur geboren neonaten (zwangerschapsduur ≥ 32 weken), nam de FMS deze grenzen over voor neonaten met ademhalingsondersteuning. Hiermee rekening houdend heeft de werkgroep besloten de aanbevelingen over te nemen betreffende neonaten met kanker en pulmonale en/of cardiale comorbiditeiten uit de richtlijn van de FMS (2019).

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Module 4B: Supplemental materials

Supplemental materials 1: Additional guidelines

The full description of the additional guidelines and the AGREE II-scores are presented in Addendum 5.

Research question 4B - The effect of prophylactic RBC transfusion in neonates with cancer with cardiac and pulmonary comorbidities	
Recommendations for neonates with cardiac and pulmonary comorbidities	**Federation of Medical Specialists (2019): Blood transfusion policy.** *AGREE II assessment: Domain 1 = 94%, Domain 2 = 100%, Domain 3 = 71%, Domain 4 = 89%, Domain 5 = 13%, Domain 6 = 100%, Overall Guideline Assessment: Score 6.* Recommendations according to the Federation of Medical Specialists (2019): - That very low birth weight infants (birth weight <1500 grams) should receive restrictive RBC transfusions in infants with cardiac and or pulmonary comorbidity and in absence of studies about full term neonates and late preterm infants (gestational age>32 weeks), these recommendations are also applied to these groups: - Maintain **an Hb >7.5 mmol/L in neonates <1 week old**. - Maintain **an Hb >6.5 mmol/L in neonates between 2 and 3 weeks old**. - Maintain **an Hb >5.5 mmol/L in neonates >3 weeks old**. - Supporting arguments: Based on 4 studies and 1 Cochrane-analyses (Connelly, 1999; Bell, 2005; Kirpalani, 2006; Chen, 2009; Whyte & Kirpalani, 2011).
	Valentine (2018): Consensus Recommendations for RBC Transfusion Practice in Critically Ill Children From the Pediatric Critical Care Transfusion and Anemia Expertise Initiative. Pediatric Critical Care Medicine. *AGREE II assessment: Domain 1 = 89%, Domain 2 = 44%, Domain 3 = 79%, Domain 4 = 78%, Domain 5 = 63%, Domain 6 = 92%, Overall Guideline Assessment: Score 5.* Recommendations for critically ill neonates with acquired and congenital heart disease according to Valentine (2018): - In a **hemodynamically stable** critically ill infant with uncorrected congenital heart disease **an Hb threshold between 4.3 mmol/dL and 5.6 mmol/dL is advised**, depending on the degree of cardiopulmonary reserve. Weak recommendation, low quality pediatric evidence (2C), 81% Agreement, (n=35), Median 8, IQR 7-8. - Supporting arguments: This recommendation is based on the TRIPICU study stating that an Hb >4.3 mmol/dL is safe (Lacroix, 2007). However, there is no evidence that transfusion to the Hb >5.6 mmol/dL is beneficial and might be of some risk.
	JPAC (2013): Transfusion Handbook *AGREE II assessment: Domain 1 = 94%, Domain 2 = 56%, Domain 3 = 35%, Domain 4 = 56%, Domain 5 = 58%, Domain 6 = 25%, Overall Guideline Assessment: Score 4.* The Transfusion Handbook from the JPAC (2013) advises a neonatal top-up transfusion threshold: - In case of ventilated neonates: - Maintain **an Hb >7.5 mmol/L in neonates <24 hours old**. - Maintain **an Hb >7.5 mmol/L in neonates <1 week old**. - Maintain **an Hb >6.2 mmol/L in neonates between 2-3 weeks old**. - Maintain **an Hb >6.2 mmol/L in neonates >4 weeks old**. - Supporting arguments: Based on the British Committee for Standards in Haematology Transfusion Guidelines for Neonates and Older Children (New, 2016). - In case of neonates on oxygen/CPAP: - Maintain **an Hb >7.5 mmol/L in neonates <24 hours old**. - Maintain **an Hb >6.2 mmol/L in neonates <1 week old**. - Maintain **an Hb >5.9 mmol/L in neonates between 2-3 weeks old**. - Maintain **an Hb >5.3 mmol/L in neonates >4 weeks old**. - Supporting arguments: Based on the British Committee for Standards in Haematology Transfusion Guidelines for Neonates and Older Children (New, 2016).
	British Committee for Standards in Haematology (2016): Guidelines on transfusion for fetuses, neonates and older children. *AGREE II assessment: Domain 1 = 83%, Domain 2 = 55%, Domain 3 = 54%, Domain 4 = 83%, Domain 5 = 29%, Domain 6 = 50%, Overall Guideline Assessment: Score 4.* Recommendations according to New (2016): - In case of ventilated neonates:

	- Maintain **an Hb >7.5 mmol/L in neonates <24 hours old**. - Maintain **an Hb >7.5 mmol/L in neonates <1 week old**. - Maintain **an Hb >6.2 mmol/L in neonates between 2-3 weeks old**. - Maintain **an Hb >6.2 mmol/L in neonates >4 weeks old**. - Supporting arguments: Based on studies (Whyte & Kirpalani, 2006; Chen, 2009, Bell, 2005; Whyte & Kirpalani, 2011; Venkatesh, 2012; Brooks 1999; Mukhopadhyay, 2004; Ransome, 1989) - In case of neonates on oxygen/CPAP: - Maintain **an Hb >7.5 mmol/L in neonates <24 hours old**. - Maintain **an Hb >6.2 mmol/L in neonates <1 week old**. - Maintain **an Hb >5.9 mmol/L in neonates between 2-3 weeks old**. - Maintain **an Hb >5.3 mmol/L in neonates >4 weeks old**. - Supporting arguments: Based on studies (Whyte & Kirpalani, 2006; Chen, 2009, Bell, 2005; Whyte & Kirpalani, 2011; Venkatesh, 2012).

Module 5A/B: Red blood cell transfusions in children and neonates with cancer and hyperleukocytosis - English

A. Recommendations

Research question:
1. What is the effect of prophylactic RBC transfusion on quality of life and other outcomes in children with cancer and hyper leukocytosis (author-defined)?
2. What is the effect of prophylactic RBC transfusion on quality of life and other outcomes in neonates with cancer and hyper leukocytosis (author-defined)?

A1.1: Recommendations (English)

WEAK recommendation, EXPERT EVIDENCE[1]	In children and neonates with cancer and hyperleukocytosis, we believe that a red blood cell (RBC) transfusion should given with restraint until the number of leukocytes has fallen below 100 x 10^9/L, unless there are severe clinical signs of anemia or in case of an Hb below 3.1 mmol/L. If needed, only transfuse with a maximum of 5 ml/kg/3-4 hours.

[1] No primary studies in childhood cancer patients, no evidence derived from studies from existing clinical practice guidelines.

B. Background, search and selection, relevant outcomes, and methods

B1: Background
The background of red blood cell (RBC) transfusions in pediatric oncology is discussed in the "Background section" of Research question 1A.

B2: Search and selection
In order to be able to answer the clinical question, a systematic literature analysis was carried out into the following search question:

<u>What is the effect of prophylactic RBC transfusion on quality of life and other outcomes in children with cancer and hyper leukocytosis (author-defined)?</u>

P = Children with cancer (aged 28 days-18 years) with curative intent and hyperleukocytosis (author-defined)
I = Prophylactic RBC transfusion (at any threshold)
C = No prophylactic RBC transfusion or transfusion at any other threshold
O = Quality of life, transfusion-related complications, treatment-related complications, morbidity, mortality, admission to hospital, costs, late complications

<u>What is the effect of prophylactic RBC transfusion on quality of life and other outcomes in neonates with cancer and hyper leukocytosis (author-defined)?</u>

P = Neonates with cancer (aged 0-28 days) with curative intent and hyperleukocytosis (author-defined)
I = Prophylactic RBC transfusion (at any threshold)
C = No prophylactic RBC transfusion or transfusion at any other threshold
O = Quality of life, transfusion-related complications, treatment-related complications, morbidity, mortality, admission to hospital, costs, late complications

B3: Relevant outcomes
The importance of outcomes and their hierarchy are discussed in the method section "Research questions and outcomes measures".

B4: Methods
Evidence was searched in three electronic databases, in which (randomized) controlled trials including children and adolescents with cancer were eligible for inclusion. There were no pediatric oncology studies included. Considering the scarcity of the primary evidence, the guideline panel decided that additional evidence ought to be sought in guidelines for general pediatric patients and for adults with cancer. However, no guidelines were found.

C. Discussion of the literature

C1: Discussion of the evidence
<u>C1.1: Evidence in pediatric oncology</u>
No pediatric oncology studies included children or neonates with cancer and hyperleukocytosis.

<u>C1.2: Recommendations and evidence derived from guidelines</u>

No guidelines included children or neonates with cancer and hyperleukocytosis.

C2: Description of the included studies
There were no primary pediatric oncology studies included from the systematic literature search and no additional studies from the additional literature review.

D. Results
As no studies were included, no results were presented.

E. Conclusions
As no studies were included, no conclusions were formulated.

F. Considerations
There are no studies regarding RBC transfusions in children nor neonates with cancer and hyperleukocytosis. A study on the management of hyperleukocytosis stated that RBC transfusion should be avoided as it increases the viscosity of the blood and can lead to the development or worsening of the leukostasis, unless the patient has symptoms of anemia (Giammarco, 2017). The guideline panel decided to adopt this recommendation based on expert evidence. In case of a clinically relevant hyperleukocytosis and a leukocytapheresis is necessary, a RBC transfusion can be used as replacement fluid to correct the anemia isovolemic and dosed (Padmanabhan, 2019).

Module 5A/B: Erytrocytentransfusies bij kinderen en neonaten met kanker en hyperleukocytose - Nederlands

G. Aanbevelingen (Nederlands)

ZWAKKE aanbeveling, EXPERT EVIDENCE[1]	Bij kinderen en neonaten met kanker en hyperleukocytose, zijn wij van mening dat een erytrocytentransfusie terughoudend moet worden gegeven tot het aantal leukocyten gedaald is tot 100 x 10^9/L of lager, tenzij er klinische tekenen zijn van een ernstige anemie of in geval van een Hb lager dan 3.1 mmol/L. Indien nodig, alleen transfunderen met maximaal 5 ml/kg/3-4 uur.

[1] Geen primaire studies bij kinderen met kankerpatiënten, geen bewijs afgeleid van onderzoeken uit bestaande klinische praktijkrichtlijnen.

F. Overwegingen (Nederlands)

Er zijn geen studies over erytrocytentransfusies bij kinderen noch neonaten met kanker en hyperleukocytose. In een artikel over de behandeling van hyperleukocytose staat dat erytrocytentransfusies vermeden moeten worden aangezien het de viscositeit van het bloed verhoogt en daardoor kan leiden tot de ontwikkeling of verergering van de leukostase, tenzij de patiënt symptomen heeft (Giammarco, 2017). De werkgroep heeft op basis van *expert evidence* besloten dit advies over te nemen. In geval van een klinisch relevante hyperleukocytose en een leukocytaferese noodzakelijk is, kan een erytrocytentransfusie worden gebruikt als vervangingsvloeistof om de anemie isovolemisch en gedoseerd te corrigeren (Padmanabhan, 2019).

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Module 6A/B: Irradiated red blood cell transfusions in children and neonates with cancer - English

A. Recommendations

Research question:
1. What is the effect of irradiated RBC products on complications and other outcomes in children with cancer who need to undergo a RBC transfusion?
2. What is the effect of irradiated RBC products on complications and other outcomes in neonates with cancer who need to undergo a RBC transfusion?

A1.1: Recommendations (English)

WEAK recommendation, EXPERT EVIDENCE[1]	We believe that irradiated blood products should be used in case of an HLA related product and donor: a) Transfusion between 1st to 3rd degree relatives of cell-containing blood products; b) HLA-compatible platelet concentrates.
WEAK recommendation, EXPERT EVIDENCE[1]	We believe that the granulocyte transfusionproduct should be irradiated.
WEAK recommendation, EXPERT EVIDENCE[1]	We believe that irradiated blood products should be used depending on the patient's immune status: a) During intrauterine transfusions until 6 months after the due date; b) Children with congenital combined immune deficiencies (e.g. SCID); c) Acquired immune deficiencies such as: - Allogeneic stem cell transplantations up to 1 year after transplantation; - Autologous stem cell transplantations up to 6 months after transplantation; - After application of donor lymphocyte infusion (DLI) or infusion of cytotoxic T lymphocytes (CTL) up to 1 year after transfusion.
WEAK recommendation, EXPERT EVIDENCE[1]	We believe that irradiated blood products should be used in case of patients with prolonged T-cell depletion after medication: a) Fludarabine or other T-cell depleting therapy as indicated by the pharmacotherapeutic compass (up to 6 months after discontinuation of the therapy); b) Medications that, in combination with the disease, cause long-term T-cell depletion, such as anti-CD52 treatment in hematological diseases and ATG treatment in aplastic anemia from the initiation to 6 months after completion of the treatment.
WEAK recommendation, EXPERT EVIDENCE[2]	We believe that irradiated blood products should be used in case of patients that receive CAR-T cell therapy from 4 weeks before the leukapheresis until 1 year after the infusion. Unless otherwise described in the study protocol.

[1] No primary studies in childhood cancer patients, evidence derived from existing clinical practice guidelines.
[2] No primary studies in childhood cancer patients, no evidence derived from existing clinical practice guidelines.

B. Background, search and selection, relevant outcomes, and methods

B1: Background
The background of red blood cell (RBC) transfusions in pediatric oncology is discussed in the “Background section” of Research question 1A.

B2: Search and selection
In order to be able to answer the clinical question, a systematic literature analysis was carried out into the following search questions:

<u>What is the effect of irradiated RBC products on complications and other outcomes in children with cancer who need to undergo a RBC transfusion?</u>

P = Children with cancer (aged 28 days-18 years) with curative intent who need to undergo a RBC transfusion for any indication
I = Irradiated RBC products
C = Non irradiated RBC products
O = Quality of life, transfusion-related complications, treatment-related complications, morbidity, mortality, admission to hospital, costs, late complications

What is the effect of irradiated RBC products on complications and other outcomes in neonates with cancer who need to undergo a RBC transfusion?

P = Neonates with cancer (aged 0-28 days) with curative intent who need to undergo a RBC transfusion for any indication
I = Irradiated RBC products
C = Non irradiated RBC products
O = Quality of life, transfusion-related complications, treatment-related complications, morbidity, mortality, admission to hospital, costs, late complications

B3: Relevant outcomes
The importance of outcomes and their hierarchy are discussed in the method section "Research questions and outcomes measures".

B4: Methods
Evidence was searched in three electronic databases, in which (randomized) controlled trials including children and adolescents with cancer were eligible for inclusion. No pediatric oncology studies were included. Considering the scarcity of the primary evidence, the guideline panel decided that additional evidence ought to be sought in guidelines for general pediatric patients and for adults with cancer, reported in Supplemental Materials 1.

C. Discussion of the literature

C1: Discussion of the evidence
C1.1: Evidence in pediatric oncology
No pediatric oncology studies were included.

C1.2: Recommendations and evidence derived from guidelines
The only guideline that included recommendations for irradiated RBC products was the Dutch Association of Medical Specialists (FMS, 2019) based on one study (Kopolovic, 2015; a review cased on 348 case studies) and a survey under hemovigilance organisations worldwide:

- In case of HLA related products and donors:
    a) Transfusion between 1st to 3rd degree relatives of cell-containing blood products;
    b) HLA-compatible plated concentrates.
- In case of granulocyte transfusions
- Depending on the patient's immune status:
    a) During intrauterine transfusions until 6 months after the due date;
    b) Children with congenital combined immune deficiencies (e.g., SCID);
    c) Acquired immune deficiencies such as:
        - Allogeneic stem cell transplantations up to 1 year after transplantation;
        - Autologous stem cell transplantations up to 6 months after transplantation;
        - After application of donor lymphocyte infusion (DLI) or infusion of cytotoxic T lymphocytes (CTL) up to 1 year after transfusion.
- In case of patients with prolonged T-cell depletion after medication:
    a) Fludarabine or other T-cell depleting therapy or indicated by the pharmacotherapeutic compass (up to 6 months after discontinuation of the therapy);
    b) Medications that, in combination with the disease, cause long-term T-cell depletions, such as anti-CD52 treatments in hematological diseases and ATG treatment in aplastic anemia from the initiation to 6 months after completion of the treatment.

C2: Description of the included studies
There were no primary pediatric oncology studies included from the systematic literature search and no additional studies from the additional literature review.

D. Results

As no studies were included, no results were presented.

E. Conclusions

As no studies were included, no conclusions were formulated.

F. Considerations

There were no pediatric oncology studies identified. The Dutch Association of Medical Specialists (FMS, 2019) developed a high-quality guideline addressing this matter with an AGREE II score of 6 out of 7. They based their recommendations on a study of Kopolovic (2015) and a survey amongst hemovigilance organisations worldwide. Therefore, the guideline panel decided to adopt the recommendations regarding irradiated blood products from the guideline of the FMS (2019). The guideline panel added the indication for the use of CAR-T cells, based on the recommendations in the current study protocol (the pharmaceutical company that creates the CAR-T cells prescribes this period of irradiated bloodproducts in a research context).

Module 6A/B: Bestraalde erytrocytentransfusies bij kinderen en neonaten met kanker - Nederlands

G. Aanbevelingen (Nederlands)

ZWAKKE aanbeveling, EXPERT EVIDENCE[1]	De werkgroep is van mening dat bestraalde bloedproducten moeten worden gebruikt in het geval van een HLA-gelijkenis tussen donor (product) en ontvanger: a) Transfusie tussen 1e tot en met 3e graads verwanten van cel houdende bloedproducten; b) HLA compatibele trombocytenconcentraten.
ZWAKKE aanbeveling, EXPERT EVIDENCE[1]	De werkgroep is van mening dat het granulocyten transfusieproduct bestraald moeten worden.
ZWAKKE aanbeveling, EXPERT EVIDENCE[1]	De werkgroep is van mening dat bestraalde bloedproducten moeten worden gebruikt afhankelijk van de immuunstatus van de patiënt: a) Tijdens intra-uteriene transfusies, daarna tot en met 6 maanden na de à terme datum; b) Kinderen met aangeboren gecombineerde immuundeficiëntie (bijv. SCID); c) Verworven immuundeficiëntie zoals bij: - Allogene stamceltransplantatie tot 1 jaar na transplantatie; - Autologe stamceltransplantatie tot 6 maanden na transplantatie; - Na toepassing van donor lymfocyten infusie (DLI) of infusie van cytotoxische T-lymfocyten (CTL) tot 1 jaar na transfusie.
ZWAKKE aanbeveling, EXPERT EVIDENCE[1]	De werkgroep is van mening dat bestraalde bloedproducten moeten worden gebruikt in geval van patiënten met een langdurige T-cel depletie na medicatie: a) Fludarabine of andere T-cel depleterende therapie zoals het farmacotherapeutisch kompas dat aangeeft (tot 6 maanden na staken therapie); b) Medicatie die in combinatie met de ziekte een langdurige T-cel depletie geven, zoals anti-CD52 behandeling bij hematologische ziekten en ATG-behandeling bij aplastische anemie vanaf de instelling van de toediening tot 6 maanden na het voltooien van de behandeling.
ZWAKKE aanbeveling, EXPERT EVIDENCE[2]	De werkgroep is van mening dat bestraalde bloedproducten moeten worden gebruikt in patiënten die CAR-T celtherapie krijgen vanaf 4 weken voor de leukaferese tot 1 jaar na de infusie. Tenzij anders beschreven in het onderzoeksprotocol.

[1] Geen primaire studies bij kinderen met kankerpatiënten, bewijs afgeleid van onderzoeken uit bestaande klinische praktijkrichtlijnen.
[2] Geen primaire studies bij kinderen met kankerpatiënten, geen bewijs afgeleid van onderzoeken uit bestaande klinische praktijkrichtlijnen.

H. Overwegingen (Nederlands)

Er waren geen pediatrische oncologische artikelen geïdentificeerd. De FMS (2019) heeft hierover een hoogwaardige richtlijn ontwikkeld met een AGREE II-score van 6 uit de 7. Zij baseren hun advies op een studie van Kopolovic (2015) en een enquete onder hemovigilantie-organisaties wereldwijd. Daarom heeft de werkgroep besloten de aanbevelingen met betrekking tot bestraalde bloedproducten uit de richtlijn van de FMS (2019) over te nemen. Enkel de indicatie voor het gebruik van CAR-T-cellen is toegevoegd, gebaseerd op de adviezen uit het huidige studieprotocol (het farmaceutische bedrijf dat de CAR-T cellen ontwikkelt, schrijft deze periode van bestraalde bloedproducten voor in studieverband).

Referenties

Federation of Medical Specialists. (2019). Startpagina - Bloedtransfusiebeleid - Richtlijn - Richtlijnendatabase. Federation of Medical Specialists. https://richtlijnendatabase.nl/richtlijn/bloedtransfusiebeleid/startpagina_-_bloedtransfusiebeleid.html

Kopolovic, I., Ostro, J., Tsubota, H., Lin, Y., Cserti-Gazdewich, C. M., Messner, H. A., Keir, A. K., DenHollander, N., Dzik, W. S., & Callum, J. (2015). A systematic review of transfusion-associated graft-versus-host disease. *Blood*, *126*(3), 406–414. https://doi.org/10.1182/blood-2015-01-620872

Module 6A/B: Supplemental materials

Supplemental materials 1: Additional guidelines

The full description of the additional guidelines and the AGREE II-scores are presented in Addendum 5.

Research question 6A/B - The effect of irradiated RBC products in children and neonates with cancer	
Recommendations for children	**Federation of Medical Specialists (2019): Blood transfusion policy.** *AGREE II assessment: Domain 1 = 94%, Domain 2 = 100%, Domain 3 = 71%, Domain 4 = 89%, Domain 5 = 13%, Domain 6 = 100%, Overall Guideline Assessment: Score 6.* Recommendations for irradiated RBC products according to Dutch Association of Medical Specialists (FMS, 2019): a) In case of HLA related products and donors: b) Transfusion between 1st to 3rd degree relatives of cell-containing blood products; c) HLA-compatible plated concentrates. - In case of granulocyte transfusions - Depending on the patient's immune status: a) During intrauterine transfusions until 6 months after the due date; b) Children with congenital combined immune deficiencies (e.g. SCID); c) Acquired immune deficiencies such as: - Allogeneic stem cell transplantations up to 1 year after transplantation; - Autologous stem cell transplantations up to 6 months after transplantation; - After application of donor lymphocyte infusion (DLI) or infusion of cytotoxic T lymphocytes (CTL) up to 1 year after transfusion. - In case of patients with prolonged T-cell depletion after medication: a) Fludarabine or other T-cell depleting therapy or indicated by the pharmacotherapeutic compass (up to 6 months after discontinuation of the therapy); b) Medications that, in combination with the disease, cause long-term T-cell depletions, such as anti-CD52 treatments in hematological diseases and ATG treatment in aplastic anemia from the initiation to 6 months after completion of the treatment.

Module 7A: Low or high-volume red blood cell transfusions in children with cancer - English

A. Recommendations

Research question: What is the effect of low-volume prophylactic RBC transfusion compared to high-volume RBC transfusion on quality of life and other outcomes in children with cancer?

A1.1: Recommendations (English)

WEAK recommendation, VERY LOW QUALITY evidence[1]	We suggest a transfusion volume of 10-15 ml/kg in children with cancer.

WEAK recommendation, EXPERT EVIDENCE[2]	We suggest a transfusion volume with a maximum of 2 donorunits (between 500-600 ml).

WEAK recommendation VERY LOW QUALITY evidence[1]	We suggest *against* a transfusion volume of 20 ml/kg or higher in children with cancer.

[1] No primary studies in childhood cancer patients, evidence derived from studies in the pediatric population.
[2] No primary studies in childhood cancer patients, no evidence derived from studies in the pediatric population.

B. Background, search and selection, relevant outcomes, and methods

B1: Background

The background of red blood cell (RBC) transfusions in pediatric oncology is discussed in the "Background section" of Research question 1A.

B2: Search and selection

In order to be able to answer the clinical question, a systematic literature analysis was carried out into the following search question:

What is the effect of low-volume prophylactic RBC transfusion compared to high-volume RBC transfusion on quality of life and other outcomes in children with cancer?

P = Children with cancer (aged 28 days-18 years) with curative intent
I = Low-volume RBC transfusion (at any threshold)
C = High-volume RBC transfusion
O = Quality of life, transfusion-related complications, treatment-related complications, morbidity, mortality, admission to hospital, costs, late complications

B3: Relevant outcomes

The importance of outcomes and their hierarchy are discussed in the method section "Research questions and outcomes measures".

B4: Methods

Evidence was searched in three electronic databases, in which (randomized) controlled trials including children and adolescents with cancer were eligible for inclusion. There were no pediatric oncology studies included. Considering the scarcity of the primary evidence, the guideline panel decided that additional evidence ought to be sought in guidelines for general pediatric patients and for adults with cancer. However, no guidelines were found, but one study was included. The full evidence to decision frameworks and overall conclusions are stated in Supplemental Materials 1.

C. Discussion of the literature

C1: Discussion of the evidence

C1.1: Evidence in pediatric oncology

No pediatric oncology studies included RBC volumes in children.

C1.2: Recommendations and evidence derived from guidelines
No guidelines included RBC volumes in children.

C2: Description of the included studies
C2.1: Pediatric oncology
There were no primary pediatric oncology studies included from the systematic literature search.

C2.2: Children in general
One pediatric study was included from the additional literature review (Olupot-Olupot, 2014).

The characteristics of the included study are stated in the evidence table below.

Table 1. Characteristics of the included studies regarding children.

Included studies				
Study	**Population**	**Liberal volume**	**Restrictive volume**	**Outcomes**
Olupot-Olupot (2014) *RCT*	160 children with severe anemia (Hb of 3.7 mmol/L)	- 30 ml/kg	- 20 ml/kg	- Mortality - Morbidity - Costs

D. Results

D1.1 Prophylactic RBC transfusion volume 20 ml/kg versus >20 ml/kg

Conclusion of evidence	**Effect**	**Level of evidence / studies**
Children with cancer – Systematic literature search		
No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
Mortality		
No significant differences in group with volume of 20 ml/kg vs. higher than 20 ml/kg	RR 5.71 (95% CI 0.70 - 46.34)	*Very low** / Olupot-Olupot 2014
Morbidity		
No significant differences in group with volume of 20 ml/kg vs. higher than 20 ml/kg	RR 2.85 (95% CI 0.59 - 13.72)	*Very low** / Olupot-Olupot 2014
Costs		
No significant differences in group with volume of 20 ml/kg vs. higher than 20 ml/kg	RR 2.85 (95% CI 0.96 - 8.47)	*Very low** / Olupot-Olupot 2014
Adults with cancer – Evidence cited in existing guidelines		
No studies	-	-

* The level of evidence is taken directly from the concerned guidelines *minus* 1 level for indirectness in this guideline.

E. Conclusions

VERY LOW QUALITY OF EVIDENCE (GRADE)	No significant difference regarding mortality, morbidity and costs with a *volume of 20 ml/kg versus higher than 20 ml/kg* in 1 study. Sources (*Olupot-Olupot, 2014*)

F. Considerations

Regarding the comparison of a volume of 20 ml/kg to a volume higher than 20 ml/kg, one study with children without cancer was identified. Based on limited evidence, a RBC transfusion volume of 20 ml/kg in comparison to a RBC transfusion volume of higher than 20 ml/kg does not lead to more mortality or morbidity (Olupot-Olupot, 2014).

Moreover, there are no studies included that report any potential benefit from a RBC transfusion volume higher than 20 ml/kg, apart from no significant difference regarding costs (Olupot-Olupot, 2014), thus the guideline panel decided that the benefits of a volume higher than 20 ml/kg are uncertain relative to a volume of 20 ml/kg. This option is considered probably acceptable for all stakeholders. However, there are no other studies regarding volumes of RBC transfusions in children with cancer. Considering that there was no increased risk for mortality or morbidity in neonates that were transfused with a volume of 10-15 ml/kg in comparison to a higher transfusion volume and the consideration that a volume of 20 ml/kg leads to more exposure (see next chapter “Low or high-volume RBC transfusion in neonates with cancer”). The expert panel decided that a lower transfusion volume leads to less exposure. Therefore, we suggest against the option 20 ml/kg and the guideline panel decided to adopt the recommendations regarding transfusion volume for neonates with cancer to children with cancer. The expert panel advises, based on *expert evidence,* to transfuse with a maximum of 2 donorunits (volume between 500-600 ml).

Module 7A: Laag- of hoogvolume erytrocytentransfusies bij kinderen met kanker - Nederlands

G. Aanbevelingen (Nederlands)

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence[1]	Overweeg een transfusievolume van 10-15 ml/kg bij kinderen met kanker.

ZWAKKE aanbeveling, EXPERT EVIDENCE[2]	Overweeg een transfusievolume van maximaal 2 donoreenheden (volume tussen 500-600 ml).

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence[1]	Wij adviseren *tegen* een transfusievolume van 20 ml/kg of hoger bij kinderen met kanker.

[1] Geen primaire studies bij kinderen met kankerpatiënten, bewijs is afgeleid van onderzoek bij pediatrische populaties.
[2] Geen primaire studies bij kinderen met kankerpatiënten, geen bewijs afgeleid van onderzoek bij pediatrische populaties.

H. Overwegingen (Nederlands)

Voor de vergelijking van een volume van 20 ml/kg met een volume meer dan 20 ml/kg, werd één studie met kinderen zonder kanker geïdentificeerd. Op basis van beperkt bewijs leidt een erytrocytentransfusievolume van 20 ml/kg in vergelijking met een erytrocytentransfusievolume van meer dan 20 ml/kg niet tot meer mortaliteit of morbiditeit (Olupot-Olupot, 2014). Bovendien zijn er geen studies geïncludeerd die een mogelijk voordeel rapporteren van een erytrocytentransfusievolume van meer dan 20 ml/kg, afgezien van geen significant verschil in kosten (Olupot-Olupot, 2014), waardoor de werkgroep oordeelde dat de voordelen van een volume meer dan 20 ml/kg onzeker zijn ten opzichte van een volume van 20 ml/kg. Deze optie wordt waarschijnlijk aanvaardbaar geacht voor alle belanghebbenden. Echter, zijn er geen andere studies met betrekking tot volumes van erytrocytentransfusies bij kinderen met kanker. Er was geen verhoogd risico op mortaliteit of morbiditeit bij neonaten die een transfusievolume van 10-15 ml/kg kregen in vergelijking met een hoger transfusievolume en de overweging dat een volume van 20 ml/kg leidt tot meer blootstelling (Zie het volgende hoofdstuk “Laag of hoog volume erytrocytentransfusie bij neonaten met kanker”). De werkgroep oordeelde echter dat een lager transfusievolume leidt tot minder blootstelling. Daarom raden we de optie 20 ml/kg af en heeft de werkgroep besloten de aanbevelingen met betrekking tot het transfusievolume voor neonaten met kanker over te nemen op kinderen met kanker. De werkgroep adviseert op basis van *expert evidence* om te transfunderen met maximaal 2 donoreenheden (volume tussen 500-600 ml).

Referenties

Olupot-Olupot, P., Engoru, C., Thompson, J., Nteziyaremye, J., Chebet, M., Ssenyondo, T., Dambisya, C. M., Okuuny, V., Wokulira, R., Amorut, D., Ongodia, P., Mpoya, A., Williams, T. N., Uyoga, S., Macharia, A., Gibb, D. M., Walker, A. S., & Maitland, K. (2014). Phase II trial of standard versus increased transfusion volume in Ugandan children with acute severe anemia. BMC Medicine, 12(1), 67. https://doi.org/10.1186/1741-7015-12-67

Module 7A: Supplemental materials

Supplemental materials 1: Evidence to Decision Framework & Overall conclusions - <20 ml/kg versus >20 ml/kg

Prophylactic RBC transfusion volume 20 ml/kg versus >20 ml/kg				
	Criteria	**Judgements**	**Research evidence**	**Additional considerations**
PROBLEM	Is the problem a priority?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ■ **Yes**	RBC transfusions are one of the backbones in the supportive care management of children with oncologic diagnoses and those who are undergoing hematopoietic stem cell transplants (HSCT). Children with cancer may require RBC transfusions due to the underlying oncologic disease or bone marrow suppression as a result of the anti-cancer treatment. This guideline is the first guideline to be established specifically for RBC transfusion volumes in children with cancer.	
BENEFITS AND HARMS	What is the overall certainty of this evidence?	☐ No included studies ■ **Very low** ☐ Low ☐ Moderate ☐ High	Summary of findings: <u>Mortality</u> - Pediatric oncology: no included studies. - Pediatric: Olupot-Olupot (2014) reported no significant differences regarding mortality when comparing a volume of 20 ml/kg with 30 ml/kg, RR 5.71 (95% CI 0.70 - 46.34). - Adult: no included studies. <u>Morbidity</u> - Pediatric oncology: no included studies. - Pediatric: Olupot-Olupot (2014) reported no significant differences regarding morbidity when comparing a volume of 20 ml/kg with 30 ml/kg, RR 2.85 (95% CI 0.59 - 13.72). - Adult: no included studies. <u>Costs</u> - Pediatric oncology: no included studies.	
	Is there important uncertainty about how much people value the main outcomes?	☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ■ **No important uncertainty or variability** ☐ No known undesirable outcomes		The relative importance of all outcomes was unanimously determined.

	Are the desirable anticipated effects large?	☐ No ☐ Probably no ■ **Uncertain** ☐ Probably yes ☐ Yes ☐ Varies	- Pediatric: Olupot-Olupot (2014) reported no significant differences regarding costs when comparing a volume of 20 ml/kg with 30 ml/kg, RR 2.85 (95% CI 0.96 - 8.47). - Adult: no included studies.	The desirable effects are unknown e.g., quality of life, hospital admission, costs.
	Are the undesirable anticipated effects small?	☐ No ☐ Probably no ☐ Uncertain ■ **Probably yes** ☐ Yes ☐ Varies		There is no significant difference regarding mortality and morbidity. Thus the undesirable effects are probably small.
	Are the desirable effects large relative to undesirable effects?	☐ No ☐ Probably no ■ **Uncertain** ☐ Probably yes ☐ Yes ☐ Varies		Considering that there are probably no large, anticipated effects and the undesirable effects are uncertain. Thus, the desirable effects are uncertain relative to the undesirable effects.
RESOURCE USE	Are the resources required small?	☐ No ☐ Probably no ☐ Uncertain ■ **Probably yes** ☐ Yes ☐ Varies		The guideline panel decided that the resources necessary are probably small.
	Is the incremental cost small relative to the net benefits?	☐ No ☐ Probably no ■ **Uncertain** ☐ Probably yes ☐ Yes ☐ Varies		There are costs involved (e.g., hospital admission costs). However, benefits are considered uncertain.

EQUITY	What would be the impact on health inequities?	☐ Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ■ **Varies**		The panel expected that implementing this option has no effect on health inequities, given the structure of the Dutch healthcare system. However, considering the different healthcare structures in the world the impact may vary per country.
ACCEPTABILITY	Is the option acceptable to key stakeholders?	☐ No ☐ Probably no ☐ Uncertain ■ **Probably yes** ☐ Yes ☐ Varies		The panel considered the option of a transfusion volume of 20 ml/kg probably acceptable for the key stakeholders, e.g. doctors and parents.
FEASIBILITY	Is the option feasible to implement?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ■ **Yes** ☐ Varies		The panel considered the option of a transfusion volume of 20 ml/kg feasible to implement.

Balance of consequences – Prophylactic RBC transfusion volume 20 ml/kg versus >20 ml/kg				
Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	**The balance between desirable and undesirable consequences *is closely balanced*** ■	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐

Type of recommendation – Prophylactic RBC transfusion volume 20 ml/kg versus >20 ml/kg			
We recommend against offering this option ☐	**We suggest not offering this option** ■	We suggest offering this option ☐	We recommend offering this option ☐
Recommendation (text)	We suggest not offering a transfusion volume of 20 ml/kg or higher in neonates with cancer (Weak recommendation).		
Justification	Based on limited evidence there is a suggestion that a RBC transfusion volume of 20 ml/kg in comparison to a RBC transfusion volume of >20 ml/kg does not lead to more mortality or morbidity (Olupot-Olupot, 2014). Moreover, there are no studies included that report any potential benefit from a RBC transfusion volume >20 ml/kg, apart from no significant difference regarding costs (Olupot-Olupot, 2014). In addition, the expert panel decided that a lower transfusion volume leads to less exposure and this option is considered probably acceptable for all stakeholders. Therefore we suggest not offering this option.		
Subgroup considerations	No subgroup considerations were formulated.		
Implementation considerations	No implementation considerations were formulated.		
Monitoring and evaluation	Not applicable		
Research priorities	See chapter "Gaps in research".		

Module 7B: Low or high-volume red blood cell transfusions in neonates with cancer - English

A. Recommendations

Research question: What is the effect of low-volume prophylactic RBC transfusion compared to high-volume RBC transfusion on quality of life and other outcomes in neonates with cancer?

A1.1: Recommendations (English)

WEAK recommendation, VERY LOW QUALITY evidence[1]	We suggest a transfusion volume of 10-15 ml/kg in neonates with cancer.

WEAK recommendation VERY LOW QUALITY evidence[1]	We suggest *against* a transfusion volume of 20 ml/kg or higher in neonates with cancer.

[1] No primary studies in childhood cancer patients, evidence derived from studies in the pediatric population.

B. Background, search and selection, relevant outcomes, and methods

B1: Background

The background of red blood cell (RBC) transfusions in pediatric oncology is discussed in the "Background section" of Research question 1A.

B2: Search and selection

In order to be able to answer the clinical question, a systematic literature analysis was carried out into the following search question:

What is the effect of low-volume prophylactic RBC transfusion compared to high-volume RBC transfusion on quality of life and other outcomes in neonates with cancer?

P = Neonates with cancer (aged 0-28 days) with curative intent
I = Low-volume prophylactic RBC transfusion (at any threshold)
C = High-volume prophylactic RBC transfusion
O = Quality of life, transfusion-related complications, treatment-related complications, morbidity, mortality, admission to hospital, costs, late complications

B3: Relevant outcomes

The importance of outcomes and their hierarchy are discussed in the method section "Research questions and outcomes measures".

B4: Methods

Evidence was searched in three electronic databases, in which (randomized) controlled trials including children and adolescents with cancer were eligible for inclusion. The complete inclusion process is shown in Figure 1 (Supplemental Materials). There were no pediatric oncology studies included. Considering the scarcity of the primary evidence, the guideline panel decided that additional evidence ought to be sought in guidelines for general pediatric patients and for adults with cancer, reported in table 2 (Supplemental Materials). The full evidence to decision frameworks and overall conclusions are stated in Supplemental Materials 2 to 4.

C. Discussion of the literature

C1: Discussion of the evidence

C1.1: Evidence in pediatric oncology

No pediatric oncology studies included low or high-volume prophylactic RBC transfusions

C1.2: Recommendations and evidence derived from guidelines

Two out of seven guidelines included recommendations regarding the volume of the prophylactic RBC transfusion. All (FMS, 2019; New, 2016) recommend a volume of 15 ml/kg in neonates. These recommendations were based on 4 studies (Paul, 2002; Wong 2005; Khodabux, 2009; Olupot-Olupot, 2014).

C2: Description of the included studies
C2.1: Pediatric oncology
There were no primary pediatric oncology studies included from the systematic literature search.

C2.2: Children in general
Four pediatric studies were included from the additional literature review (Paul, 2002; Wong, 2005; Khodabux, 2009).

The characteristics of the included studies are stated in the evidence table below. The studies differ from each other in patient population and in methodology.

Table 1. Characteristics of the included studies regarding children.

Included studies				
Study	**Population**	**Liberal volume**	**Restrictive volume**	**Outcomes**
Paul (2002) RCT	13 neonates with a very low birthweight (<1500 grams)	- 20 ml/kg	- 10 ml/kg	- Mortality
Wong (2005) RCT	20 neonates with a very low birthweight (<1500 grams)	- 20 ml/kg	- 15 ml/kg	- Mortality
Khodabux (2009) Observational study	459 premature born neonates with a gestational age between 24+0 and 31+6 weeks	- 20 ml/kg	- 15 ml/kg	- Mortality - Morbidity

C2.3: Excluded studies

Excluded studies	
Study	**Reasons for exclusion**
Olupot-Olupot (2014)	This study included children and was thus included in the section “Low or high-volume transfusion in children”.

D. Results

D1.1: Prophylactic RBC transfusion volume 10 ml/kg versus higher than 10 ml/kg

Conclusion of evidence	**Effect**	**Level of evidence / studies**
Children with cancer – Systematic literature search		
No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
Morbidity		
No significant differences in group with volume of 10 ml/kg vs. higher than 10 ml/kg	Not significant (no effect measure reported)	*Very low*** / Paul 2002
Adults with cancer – Evidence cited in existing guidelines		
No studies	-	-

** The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

D1.2: Prophylactic RBC transfusion volume 15 ml/kg versus >15 ml/kg

Conclusion of evidence	**Effect**	**Level of evidence / studies**
Children with cancer – Systematic literature search		

No studies	-	-
Children non-cancer – Evidence cited in existing guidelines		
<u>Mortality</u>		
No significant differences in group with volume of 15 ml/kg vs. higher than 15 ml/kg	RR 1.00 (95% CI 0.07 - 13.87) RR 0.94 (95% CI 0.43 - 2.04)*	*Very low*** / Wong 2005 *Very low*** / Khodabux 2009
<u>Morbidity</u>		
No significant differences in group with volume of 15 ml/kg vs. higher than 15 ml/kg	Not significant (no effect measure reported)	*Very low*** / Wong 2005 *Very low*** / Khodabux 2009
Adults with cancer – Evidence cited in existing guidelines		
No studies	-	-

* Results could not be pooled due to different study populations or outcome measures.
** The level of evidence is taken directly from the relevant guidelines *minus* 1 level for indirectness in this guideline.

E. Conclusions

VERY LOW QUALITY OF EVIDENCE (GRADE)	No significant difference regarding morbidity with a *volume of 10 ml/kg versus higher than 10 ml/kg* in 1 study. Sources (*Paul, 2002*)

VERY LOW QUALITY OF EVIDENCE (GRADE)	No significant difference regarding mortality and morbidity with a *volume of 15 ml/kg versus higher than 15 ml/kg* in 2 studies. Sources (*Khodabux, 2009; Wong, 2005*)

F. Considerations

Regarding the comparison of a volume of 10 ml/kg to a volume higher than 10 ml/kg, one study with neonates without cancer was identified. Based on limited evidence, a RBC transfusion volume of 10 ml/kg in comparison to a RBC transfusion volume of higher than 10 ml/kg does not lead to more morbidity (Paul, 2002). However, other outcomes were not included. Moreover, there are no studies included that report any potential benefit from a RBC transfusion volume higher than 10 ml/kg, thus the guideline panel decided that the benefits of a volume higher than 10ml/kg are uncertain relative to a volume of 10 ml/kg. In addition, the expert panel decided that a lower transfusion volume leads to less exposure and this option is considered probably acceptable for all stakeholders. Therefore, we suggest this option.

Regarding the comparison of a volume of 15 ml/kg to a volume higher than 15 ml/kg, two studies with neonates without cancer were identified. Based on limited evidence, a RBC transfusion volume of 15 ml/kg in comparison to a RBC transfusion volume of higher than 15 ml/kg does not lead to more mortality or morbidity (Khodabux, 2009; Wong 2005). Moreover, there are no studies included that report any potential benefit from a RBC transfusion volume higher than 15 ml/kg, thus the guideline panel decided that the benefits of a volume higher than 15 ml/kg are uncertain relative to a volume of 15 ml/kg. In addition, the expert panel decided that a lower transfusion volume leads to less exposure and this option is considered probably acceptable for all stakeholders. Therefore, we suggest this option.

Module 7B: Laag- of hoogvolume erytrocytentransfusies bij neonaten met kanker - Nederlands

G. Aanbevelingen (Nederlands)

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence[1]	Overweeg een transfusievolume van 10-15 ml/kg bij neonaten met kanker.

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence[1]	Wij adviseren *tegen* een transfusievolume van 20 ml/kg of hoger bij neonaten met kanker.

[1] Geen primaire studies bij kinderen met kankerpatiënten, bewijs is afgeleid van onderzoek bij pediatrische populaties.

H. Overwegingen (Nederlands)

Voor de vergelijking van een volume van 10 ml/kg met een volume meer dan 10 ml/kg, werd één studie met neonaten zonder kanker geïdentificeerd. Op basis van beperkt bewijs, leidt een erytrocytentransfusievolume van 10 ml/kg in vergelijking met een erytrocytentransfusievolume van meer dan 10 ml/kg niet tot meer morbiditeit (Paul, 2002). Andere uitkomsten zijn echter niet meegenomen. Bovendien zijn er geen studies geïncludeerd die een mogelijk voordeel rapporteren van een erytrocytentransfusievolume van meer dan 10 ml/kg, waardoor de werkgroep oordeelde dat de voordelen van een volume meer dan 10 ml/kg onzeker zijn ten opzichte van een volume van 10 ml/kg. Daarnaast heeft de werkgroep geconcludeerd dat een lager transfusievolume leidt tot minder blootstelling en deze optie wordt waarschijnlijk acceptabel geacht voor alle belanghebbenden. Daarom raden we deze optie aan.

Voor de vergelijking van een volume van 15 ml/kg met een volume meer dan 15 ml/kg, werden twee studies met neonaten zonder kanker geïdentificeerd. Op basis van beperkt bewijs leidt een erytrocytentransfusievolume van 15 ml/kg in vergelijking met een erytrocytentransfusievolume van meer dan 15 ml/kg niet tot meer mortaliteit of morbiditeit (Khodabux, 2009; Wong 2005). Bovendien zijn er geen studies geïncludeerd die een mogelijk voordeel rapporteren van een erytrocytentransfusievolume van meer dan 15 ml/kg, waardoor de werkgroep oordeelde dat de voordelen van een volume meer dan 15 ml/kg onzeker zijn ten opzichte van een volume van 15 ml/kg. Daarnaast heeft de werkgroep geconcludeerd dat een lager transfusievolume leidt tot minder blootstelling en deze optie wordt waarschijnlijk acceptabel geacht voor alle belanghebbenden. Daarom raden we deze optie aan.

Referenties

Federation of Medical Specialists. (2019). Startpagina - Bloedtransfusiebeleid - Richtlijn - Richtlijnendatabase. Federation of Medical Specialists. https://richtlijnendatabase.nl/richtlijn/bloedtransfusiebeleid/startpagina_-_bloedtransfusiebeleid.html

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Module 7B: Supplemental materials

Supplemental materials 1: Additional guidelines

The full description of the additional guidelines and the AGREE II-scores are presented in Addendum 5.

Research question 7B - The effect of low-volume prophylactic RBC transfusion compared to high-volume RBC transfusion in neonates with cancer	
Recommendation for neonates	**Federation of Medical Specialists (2019): Blood transfusion policy.** *AGREE II assessment: Domain 1 = 94%, Domain 2 = 100%, Domain 3 = 71%, Domain 4 = 89%, Domain 5 = 13%, Domain 6 = 100%, Overall Guideline Assessment: Score 6.* Recommendations according to the Federation of Medical Specialists (2019): - In case of (extremely) premature neonates the blood transfusions must be given "top-up" considering the "anemia of the premature". The transfusion volume differs between 10 to 20 ml/kg. There is little literature regarding the optimal transfusion volume: - Supporting arguments: 2 studies have shown that a high-volume transfusion does not have negative effects on the patient. However in another studie it has been shown that a high-volume (20 ml/kg) transfusion does not have any beneficial effects for the patients as well, but a low-volume (15 ml/kg) reduces the total transfusion volume and thus donor exposition. Conclusion: **Transfuse with 15 ml/kg** (Wong, 2005; Paul, 2002; Khodabux, 2009).
	British Committee for Standards in Haematology (2016): Guidelines on transfusion for fetuses, neonates and older children. *AGREE II assessment: Domain 1 = 83%, Domain 2 = 55%, Domain 3 = 54%, Domain 4 = 83%, Domain 5 = 29%, Domain 6 = 50%, Overall Guideline Assessment: Score 4.* Recommendations according to New (2016): - **A volume of 15 ml/kg**. Supporting arguments: Based on consensus

Supplemental materials 2: Evidence to Decision Framework & Overall conclusions - <10 ml/kg versus >10 ml/kg

Prophylactic RBC transfusion volume 10 ml/kg versus >10 ml/kg				
	Criteria	**Judgements**	**Research evidence**	**Additional considerations**
PROBLEM	Is the problem a priority?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ■ **Yes**	RBC transfusions are one of the backbones in the supportive care management of children with oncologic diagnoses and those who are undergoing hematopoietic stem cell transplants (HSCT). Children with cancer may require RBC transfusions due to the underlying oncologic disease or bone marrow suppression as a result of the anti-cancer treatment. This guideline is the first guideline to be established specifically for RBC transfusion volumes in children with cancer.	
BENEFITS AND HARMS	What is the overall certainty of this evidence?	☐ No included studies ■ **Very low** ☐ Low ☐ Moderate ☐ High	Summary of findings: <u>Morbidity</u> - Pediatric oncology: no included studies. - Pediatric: Paul (2002) reported no significant differences regarding morbidity when comparing a volume of 10 ml/kg with 20 ml/kg. - Adults: no included studies.	
	Is there important uncertainty about how much people value the main outcomes?	☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ■ **No important uncertainty or variability** ☐ No known undesirable outcomes		The relative importance of all outcomes was unanimously determined.
	Are the desirable anticipated effects large?	☐ No ☐ Probably no ■ **Uncertain** ☐ Probably yes ☐ Yes ☐ Varies		The desirable effects are unknown e.g., quality of life, hospital admission, costs.

	Are the undesirable anticipated effects small?	☐ No ☐ Probably no ☐ Uncertain ■ **Probably yes** ☐ Yes ☐ Varies		There is no significant difference regarding morbidity. Thus, there are probably small undesirable anticipated effects.
	Are the desirable effects large relative to undesirable effects?	☐ No ☐ Probably no ■ **Uncertain** ☐ Probably yes ☐ Yes ☐ Varies		Considering that there are probably no large, anticipated effects and the undesirable effects are uncertain. Thus, the desirable effects are uncertain relative to the undesirable effects.
RESOURCE USE	Are the resources required small?	☐ No ☐ Probably no ☐ Uncertain ■ **Probably yes** ☐ Yes ☐ Varies		The guideline panel decided that the resources necessary are probably small.
	Is the incremental cost small relative to the net benefits?	☐ No ☐ Probably no ■ **Uncertain** ☐ Probably yes ☐ Yes ☐ Varies		There are costs involved (e.g., hospital admission costs). However, benefits are considered uncertain.
EQUITY	What would be the impact on health inequities?	☐ Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ■ **Varies**		The panel expected that implementing this option has no effect on health inequities, given the structure of the Dutch healthcare system. However, in other countries this may vary depending on their healthcare system.

ACCEPTABILITY	Is the option acceptable to key stakeholders?	☐ No ☐ Probably no ☐ Uncertain ■ **Probably yes** ☐ Yes ☐ Varies		The panel considered the option of a transfusion volume of 10 ml/kg probably acceptable for the key stakeholders, e.g., doctors and parents.
FEASIBILITY	Is the option feasible to implement?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ■ **Yes** ☐ Varies		The panel considered the option of a transfusion volume of 10 ml/kg feasible to implement.

Balance of consequences – Prophylactic RBC transfusion volume 10 ml/kg versus >10 ml/kg				
Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	**The balance between desirable and undesirable consequences *is uncertain*** ■	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐

Type of recommendation – Prophylactic RBC transfusion volume 10 ml/kg versus >10 ml/kg			
We recommend against offering this option ☐	We suggest not offering this option ☐	**We suggest offering this option** ■	We recommend offering this option ☐
Recommendation (text)	We suggest offering a transfusion volume of 10 ml/kg in neonates with cancer (Weak recommendation).		
Justification	Based on limited evidence there is a suggestion that a RBC transfusion volume of 10 ml/kg in comparison to a RBC transfusion volume of >10 ml/kg does not lead to more morbidity (Paul, 2002). However, other outcomes were not included. Moreover, there are no studies included that report any potential benefit from a RBC transfusion volume >10 ml/kg. In addition, the		

	expert panel decided that a lower transfusion volume leads to less exposure and this option is considered probably acceptable for all stakeholders. Therefore we suggest offering this option.
Subgroup considerations	No subgroup considerations were formulated.
Implementation considerations	No implementation considerations were formulated.
Monitoring and evaluation	Not applicable
Research priorities	See chapter "Gaps in research".

Supplemental materials 3: Evidence to Decision Framework & Overall conclusions - <15 ml/kg versus >15 ml/kg

Prophylactic RBC transfusion volume 15 ml/kg versus >15 ml/kg				
	Criteria	**Judgements**	**Research evidence**	**Additional considerations**
PROBLEM	Is the problem a priority?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ■ **Yes**	RBC transfusions are one of the backbones in the supportive care management of children with oncologic diagnoses and those who are undergoing hematopoietic stem cell transplants (HSCT). Children with cancer may require RBC transfusions due to the underlying oncologic disease or bone marrow suppression as a result of the anti-cancer treatment. This guideline is the first guideline to be established specifically for RBC transfusion volumes in children with cancer.	
BENEFITS AND HARMS	What is the overall certainty of this evidence?	☐ No included studies ■ **Very low** ☐ Low ☐ Moderate ☐ High	Summary of findings: <u>Mortality</u> - Pediatric oncology: no included studies. - Pediatric: Wong (2005) and Khodabux (2009) reported no significant differences regarding mortality when comparing a volume of 15 ml/kg with 20 ml/kg, RR 1.00 (95% CI 0.07 - 13.87) and RR 0.94 (95% CI 0.43 - 2.04) respectively. - Adult: no included studies. <u>Morbidity</u> Pediatric oncology: no included studies. - Pediatric: Wong (2005) and Khodabux (2009) reported no significant differences regarding morbidity when comparing a volume of 15 ml/kg with 20 ml/kg. - Adult: no included studies.	
	Is there important uncertainty about how much people value the main outcomes?	☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ■ **No important uncertainty or variability** ☐ No known undesirable outcomes		The relative importance of all outcomes was unanimously determined.
	Are the desirable anticipated effects large?	☐ No ☐ Probably no ■ **Uncertain** ☐ Probably yes ☐ Yes ☐ Varies		The desirable effects are unknown e.g., quality of life, hospital admission, costs.

	Are the undesirable anticipated effects small?	☐ No ☐ Probably no ☐ Uncertain ■ **Probably yes** ☐ Yes ☐ Varies		There is no significant difference regarding mortality and morbidity. Thus the undesirable effects are probably small.
	Are the desirable effects large relative to undesirable effects?	☐ No ☐ Probably no ■ **Uncertain** ☐ Probably yes ☐ Yes ☐ Varies		Considering that there are probably no large, anticipated effects and the undesirable effects are uncertain. Thus, the desirable effects are uncertain relative to the undesirable effects.
RESOURCE USE	Are the resources required small?	☐ No ☐ Probably no ☐ Uncertain ■ **Probably yes** ☐ Yes ☐ Varies		The guideline panel decided that the resources necessary are probably small.
	Is the incremental cost small relative to the net benefits?	☐ No ☐ Probably no ■ **Uncertain** ☐ Probably yes ☐ Yes ☐ Varies		There are costs involved (e.g., hospital admission costs). However, benefits are considered uncertain.
EQUITY	What would be the impact on health inequities?	☐ Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ■ **Varies**		The panel expected that implementing this option has no effect on health inequities, given the structure of the Dutch healthcare system. However, considering the different healthcare structures in the world the impact may vary per country.

ACCEPTABILITY	Is the option acceptable to key stakeholders?	☐ No ☐ Probably no ☐ Uncertain ■ **Probably yes** ☐ Yes ☐ Varies		The panel considered the option of a transfusion volume of 15 ml/kg probably acceptable for the key stakeholders, e.g., doctors and parents.
FEASIBILITY	Is the option feasible to implement?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ■ **Yes** ☐ Varies		The panel considered the option of a transfusion volume of 15 ml/kg feasible to implement.

Balance of consequences – Prophylactic RBC transfusion volume 15 ml/kg versus >15 ml/kg				
Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	**The balance between desirable and undesirable consequences *is closely balanced*** ■	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐

Type of recommendation – Prophylactic RBC transfusion volume 15 ml/kg versus >15 ml/kg			
We recommend against offering this option ☐	We suggest not offering this option ☐	**We suggest offering this option** ■	We recommend offering this option ☐
Recommendation (text)	We suggest offering a transfusion volume of 15 ml/kg in neonates with cancer (Weak recommendation).		
Justification	Based on limited evidence there is a suggestion that a RBC transfusion volume of 15 ml/kg in comparison to a RBC transfusion volume of >15 ml/kg does not lead to more mortality or morbidity (Khodabux, 2009; Wong 2005). Moreover, there are no studies included that report any potential benefit from a RBC transfusion volume >15 ml/kg. In addition, the expert panel		

	decided that a lower transfusion volume leads to less exposure and this option is considered probably acceptable for all stakeholders. Therefore we suggest offering this option.
Subgroup considerations	No subgroup considerations were formulated.
Implementation considerations	No implementation considerations were formulated.
Monitoring and evaluation	Not applicable
Research priorities	See chapter "Gaps in research".

Module 8A: Infusion rates of red blood cell transfusions in children with cancer - English

A. Recommendations

Research question: What is the effect of prophylactic RBC transfusion at any infusion rate compared to RBC transfusion at any other infusion rate on quality of life and other outcomes in children with cancer?

A1.1: Recommendations (English)

WEAK recommendation, EXPERT EVIDENCE[1]	We believe that the transfusion rate of a red blood cell (RBC) transfusion should be 5ml/kg/hour in children with cancer.

[1] No primary studies in childhood cancer patients, no evidence derived from studies from existing clinical practice guidelines.

B. Background, search and selection, relevant outcomes, and methods

B1: Background

The background of red blood cell (RBC) transfusions in pediatric oncology is discussed in the "Background section" of Research question 1A.

B2: Search and selection

In order to be able to answer the clinical question, a systematic literature analysis was carried out into the following search question:

What is the effect of prophylactic RBC transfusion at any infusion rate compared to RBC transfusion at any other infusion rate on quality of life and other outcomes in children with cancer?

P = Children with cancer (aged 28 days-18 years) with curative intent who need to undergo a RBC transfusion for any indication
I = Prophylactic RBC transfusion at any infusion rate (at any threshold)
C = Prophylactic RBC transfusion at any other infusion rate
O = Quality of life, transfusion-related complications, treatment-related complications, morbidity, mortality, admission to hospital, costs, late complications

B3: Relevant outcomes

The importance of outcomes and their hierarchy are discussed in the method section "Research questions and outcomes measures".

B4: Methods

Evidence was searched in three electronic databases, in which (randomized) controlled trials including children and adolescents with cancer were eligible for inclusion. There were no pediatric oncology studies included. Considering the scarcity of the primary evidence, the guideline panel decided that additional evidence ought to be sought in guidelines for general pediatric patients and for adults with cancer. One guideline was found. Details of the guideline are presented in supplemental material 1.

C. Discussion of the literature

C1: Discussion of the evidence

C1.1: Evidence in pediatric oncology

No pediatric oncology studies included children.

C1.2: Recommendations and evidence derived from guidelines

One guideline was identified. JPAC (2013) has recommended a RBC infusion rate of 5 ml/kg/hour and the transfusion must be completed within 4 hours, this was based on consensus.

C2: Description of the included studies

There were no primary pediatric oncology studies included from the systematic literature search and no additional studies from the additional literature review.

D. Results

As no studies were included, no results were presented.

E. Conclusions
As no studies were included, no conclusions were formulated.

F. Considerations
There are no studies regarding transfusion rates. However, the JPAC (2013) has recommended an infusion rate in children of 5 ml/kg/hour based on consensus and the guideline panel decided to adopt this recommendation. In addition, this option is found feasible to implement by the guideline panel.

Module 8A: Snelheden van erytrocytentransfusies bij kinderen met kanker - Nederlands

G. Aanbevelingen (Nederlands)

ZWAKKE aanbeveling, EXPERT EVIDENCE[1]	De werkgroep is van mening dat de transfusiesnelheid van een erytrocytentransfusie bij kinderen met kanker 5 ml/kg/uur moet zijn.

[1] Geen primaire studies bij kinderen met kankerpatiënten, geen bewijs afgeleid van onderzoeken uit bestaande klinische praktijkrichtlijnen.

H. Overwegingen (Nederlands)

Er zijn geen studies over transfusiesnelheden. De JPAC (2013) beveelt echter een transfusiesnelheid bij kinderen van 5 ml/kg/uur aan op basis van consensus. Daarom heeft de werkgroep besloten deze aanbeveling over te nemen. Daarnaast wordt deze optie haalbaar bevonden door de werkgroep.

Referenties

JPAC. United Kingdom Blood Services. (2013). Handbook Of Transfusion Medicine 5th Edi (5th ed., 2013 editie). TSO.

Module 8A: Supplemental materials

Supplemental materials 1: Additional guidelines

The full description of the additional guidelines and the AGREE II-scores are presented in Addendum 5.

Research question 8A - The effect of prophylactic RBC transfusion at any infusion rate in children with cancer	
Recommendations for children	**JPAC (2013): Transfusion Handbook** *AGREE II assessment: Domain 1 = 94%, Domain 2 = 56%, Domain 3 = 35%, Domain 4 = 56%, Domain 5 = 58%, Domain 6 = 25%, Overall Guideline Assessment: Score 4.* Recommendations according to the Transfusion Handbook from the JPAC (2013): - A Hb infusion rate of **5 ml/kg/hour** and the transfusion must be completed within 4 hours. - Supporting arguments: Based on the British Committee for Standards in Haematology Transfusion Guidelines on the Administration of Blood Components (Robinson, 2017)

Moldule 8B: Infusion rates of red blood cell transfusions in neonates with cancer - English

A. Recommendations

Research question: What is the effect of prophylactic RBC transfusion at any infusion rate compared to RBC transfusion at any other infusion rate on quality of life and other outcomes in neonates with cancer?

A1.1: Recommendations (English)

WEAK recommendation, EXPERT EVIDENCE[1]	We believe that the transfusion rate of a red blood cell (RBC) transfusion should be 5ml/kg/hour in neonates with cancer.

[1] No primary studies in childhood cancer patients, no evidence derived from studies from existing clinical practice guidelines.

B. Background, search and selection, relevant outcomes, and methods

B1: Background

The background of red blood cell (RBC) transfusions in pediatric oncology is discussed in the "Background section" of Research question 1A.

B2: Search and selection

In order to be able to answer the clinical question, a systematic literature analysis was carried out into the following search question:

What is the effect of prophylactic RBC transfusion at any infusion rate compared to RBC transfusion at any other infusion rate on quality of life and other outcomes in neonates with cancer?

P = Neonates with cancer (aged 0-28 days) with curative intent who need to undergo a RBC transfusion for any indication
I = Prophylactic RBC transfusion at any infusion rate (at any threshold)
C = Prophylactic RBC transfusion at any other infusion rate
O = Quality of life, transfusion-related complications, treatment-related complications, morbidity, mortality, admission to hospital, costs, late complication

B3: Relevant outcomes

The importance of outcomes and their hierarchy are discussed in the method section "Research questions and outcomes measures".

B4: Methods

Evidence was searched in three electronic databases, in which (randomized) controlled trials including children and adolescents with cancer were eligible for inclusion. There were no pediatric oncology studies included. Considering the scarcity of the primary evidence, the guideline panel decided that additional evidence ought to be sought in guidelines for general pediatric patients and for adults with cancer. One guideline was found. Details of the guideline are presented in supplemental material 1.

C. Discussion of the literature

C1: Discussion of the evidence

C1.1: Evidence in pediatric oncology

No pediatric oncology studies included neonates.

C1.2: Recommendations and evidence derived from guidelines

The Dutch Association of Medical Specialists (FMS, 2019) has recommended an infusion rate in neonates of 5 ml/kg/hour based on consensus.

C2: Description of the included studies

There were no primary pediatric oncology studies included from the systematic literature search and no additional studies from the additional literature review.

D. Results

As no studies were included, no results were presented.

E. Conclusions

As no studies were included, no conclusions were formulated.

F. Considerations

There are no studies regarding transfusion rates. However, the Dutch Association of Medical Specialists (FMS, 2019) has recommended an infusion rate in neonates of 5 ml/kg/hour based on consensus and the guideline panel decided to adopt this recommendation. In addition, this option is found feasible to implement by the guideline panel.

Module 8B: Snelheden van erytrocytentransfusies bij neonaten met kanker - Nederlands

G. Aanbevelingen (Nederlands)

ZWAKKE aanbeveling, EXPERT EVIDENCE[1]	De werkgroep is van mening dat de transfusiesnelheid van een erytrocytentransfusie bij neonaten met kanker 5 ml/kg/uur moet zijn.

[1] Geen primaire studies bij kinderen met kankerpatiënten, geen bewijs afgeleid van onderzoeken uit bestaande klinische praktijkrichtlijnen.

H. Overwegingen (Nederlands)

Er zijn geen studies over transfusiesnelheden. De FMS (2019) beveelt echter een transfusiesnelheid bij kinderen van 5 ml/kg/uur aan op basis van consensus. Daarom heeft de werkgroep besloten deze aanbeveling over te nemen. Daarnaast wordt deze optie haalbaar bevonden door de werkgroep.

Referenties

Federation of Medical Specialists. (2019). Startpagina - Bloedtransfusiebeleid - Richtlijn - Richtlijnendatabase. Federation of Medical Specialists. https://richtlijnendatabase.nl/richtlijn/bloedtransfusiebeleid/startpagina_-_bloedtransfusiebeleid.html

Module 8B: Supplemental materials

Supplemental materials 1: Additional guidelines

The full description of the additional guidelines and the AGREE II-scores are presented in Addendum 5.

Research question 8B - The effect of prophylactic RBC transfusion at any transfusion rate in neonates with cancer	
Recommendations for neonates	**Federation of Medical Specialists (2019): Blood transfusion policy.** *AGREE II assessment: Domain 1 = 94%, Domain 2 = 100%, Domain 3 = 71%, Domain 4 = 89%, Domain 5 = 13%, Domain 6 = 100%, Overall Guideline Assessment: Score 6.* Recommendations according to the Federation of Medical Specialists (2019): - An infusion rate of **5 ml/kg/hour** - Supporting arguments: recommendation is based on consensus.

Addenda

Addendum 1. Gaps in research

During the development of the guideline for erythrocytetransfusions in children and neonates with cancer, a systematic search was created to answer the predetermined research questions. However, only part of these research questions could be answered with the results of this search and it has become clear that there are still many gaps in the available evidence for RBC transfusions in children and neonates with cancer. The guideline panel, therefore, believes that (follow up) research is not only desirable, but also necessary in order to be able to provide clearer answers to these research questions:

1. We recommend undertaking future (randomized controlled) trials aiming to identify the appropriate hemoglobin (Hb) concentration to guide administration of a RBC transfusion in:
    a. Children with cancer;
    b. Neonates with cancer;
    c. Children with cancer and sepsis;
    d. Neonates with cancer and sepsis;
    e. Children with cancer who undergo radiotherapy;
    f. Neonates with cancer who undergo radiotherapy
    g. Children with cancer with cardiac and pulmonary comorbidities;
    h. Neonates with cancer with cardiac and pulmonary comorbidities;

2. We recommend undertaking future (randomized controlled) trials aiming to guide the management of hyperleukocytosis in children and neonates with cancer.

3. We recommend further investigation in irradiated RBC transfusions aiming to guide the indications for irradiated RBC transfusions in children and neonates with cancer.

4. We recommend undertaking future (randomized controlled) trials aiming to identify the appropriate volume of RBC transfusions in children and neonates with cancer.

5. We recommend undertaking future (randomized controlled) trials aiming to identify the appropriate infusion rate of RBC transfusions in children and neonates with cancer.

6. We recommend undertaking future studies into the incidence of transfusion-related iron toxicity and its clinical consequences in children with an oncological disease considering the hypothesis that the risk for transfusion-related iron toxicity increases when >10 RBC transfusions are given.

Addendum 2. Zoekstrategie Richtlijnen "Erytrocytentransfusies en trombocyten transfusies bij kinderen met kanker"

Uitgevoerd door: Mw H.W.J. (Rikkie) Deurenberg, research specialist

Cochrane search

ID Search

#1 (Cancer OR cancers OR cancer* OR oncology OR oncolog* OR neoplasm OR neoplasms OR neoplasm* OR carcinoma OR carcinom* OR tumor OR tumour OR tumor* OR tumour* OR tumors OR tumours OR malignan* OR malignant OR hematooncological OR hemato oncological OR hemato-oncological OR hematologic neoplasms OR hematolo*):ti,ab,kw (Word variations have been searched)

#2 "P variant breed":ti

#3 MeSH descriptor: [Stem Cell Transplantation] explode all trees

#4 stem NEAR/2 cell NEAR/3 transplan*:ti,ab

#5 stem NEAR/2 cell NEAR/3 transplan*:kw

#6 [mh "bone marrow transplantation"]

#7 "bone marrow" NEAR/5 transplant*:ti,ab,kw

#8 "stem cell" NEAR/5 transplant*:ti,ab,kw

#9 #3 OR #4 OR #5 OR #6 OR #7 OR #8

#10 [**Error**]==>"P variant stam cel transplantatie".ti.

#11 MeSH descriptor: [Leukemia] explode all trees

#12 (leukemia or leukemi* or leukaemi*):ti,ab,kw

#13 (aml or anll or lymphoma or lymphom* or hodgkin* or T-cell or B-cell or non-hodgkin or sarcoma or sarcom* or Ewing* or osteosarcom* or wilms* or nephroblastom* or neuroblastom* or rhabdomyosarcom* or teratom* or hepatom* or hepatoblastom* or PNET or medulloblastom* or PNET* or (neuroectodermal adj2 tumors NEAR/2 primitive) or retinoblastoma or retinoblastom* or meningiom* or gliom*):ti,ab,kw

#14 [mh "lymphatic vessel tumors"]

#15 MeSH descriptor: [Lymphatic Vessel Tumors] explode all trees

#16 [mh lymphoma] OR [mh "neoplasms, complex and mixed"] OR [mh "neoplasms, connective and soft tissue"] OR [mh "neoplasms, germ cell and embryonal"] OR [mh "neoplasms, glandular and epithelial"] OR [mh "neoplasms, gonadal tissue"] OR [mh "neoplasms, nerve tissue"] OR [mh "neoplasms, plasma cell"] OR [mh "neoplasms, vascular tissue"] OR [mh "neoplasms by site"] OR [mh "neoplasms, hormone-dependent"] OR [mh "neoplasms, radiation-induced"] OR [mh "neoplastic syndromes, hereditary"]

#17 ((brain NEAR/1 tumor*) OR (brain NEAR/1 tumour) OR (brain NEAR/1 neoplasm*) or (central NEAR/1 nervous NEAR/1 system NEAR/1 neoplasm*) OR (central NEAR/1 nervous NEAR/1 system NEAR/1 tumo*) or (central NEAR/1 nervous NEAR/1 system NEAR/1 cancer*) or (brain NEAR/1 cancer*) or (brain NEAR/1 neoplasm*) or (intracranial NEAR/1 neoplasm*) or (leukemia NEAR/1 lymphocytic NEAR/1 acute*)):ti,ab,kw

#18 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

#19 #1 OR #9 OR #18

#20 ((pediatric NEAR/3 oncolog*) OR (paediatric NEAR/3 oncol*) OR (child* NEAR/3 (cancer* OR tumor* OR tumour* OR neoplasm*))):ti,ab,kw

#21 [mh "young adult"] OR [mh child] OR [mh infant]

#22 ((young NEAR/1 adult*) OR child* OR infant* OR pediatr* OR paediatr* OR perinat* OR neonat* OR newborn* OR infan* OR boy OR boys OR girl OR girls OR kid OR kids or schoolage* or juvenil* or teenage* or adolescen* or toddler*):ti,ab,kw

#23 #20 OR #21 OR #22

#24 #18 AND #23

#25 [mh "Platelet Transfusion"]

#26 [mh Plateletpheresis]

#27 [mh "Blood Platelets"]

#28 ((platelet* OR thrombocyte*) NEAR/5 (prophyla* OR transfus* OR infus* OR administ* OR requir* OR need* OR product* OR component* OR concentrate* OR apheres* OR pooled OR single NEAR/1 donor OR random NEAR/1donor)):ti,ab,kw

#29 (thrombocytopheres* or plateletpheres*):ti,ab,kw

#30 #25 OR #26 OR #27 OR #28 OR #29

#31 [mh "blood component transfusion"] OR [mh "erythrocyte transfusion"]

#32 ((blood NEAR/3 transfus*) or (erythrocyt* NEAR/2 transfus*)):ti,ab,kw

#33 ((erythrocy* OR hemoglobin* OR haemoglobin*) NEAR/5 (prophyla* OR transfus* OR infus* OR administ* OR requir* OR need* OR product* OR component* OR concentrate* OR apheres* OR pooled OR single NEAR/1 donor OR random NEAR/1donor)):ti,ab,kw

#34 #31 OR #32 OR #33

#35 [mh "blood component transfusion"] OR [mh "erythrocyte transfusion"] OR [mh "platelet transfusion"]

#36 [mh "Platelet Count"]

#37 #35 OR #36

#38 #30 OR #34 OR #37

#39 #24 AND #38

Medline search

Database: Ovid MEDLINE(R) ALL <1946 to December 11, 2020>
Search Strategy:
---
1 exp stem cell transplantation/ or exp hematopoietic stem cell transplantation/ (83929)
2 (stem adj2 cell adj3 transplan*).tw. (50727)
3 (stem adj2 cell adj3 transplan*).kf. (7551)
4 bone marrow transplantation/ (44746)
5 ("bone marrow" adj5 transplant$).tw. (38419)
6 ("bone marrow" adj5 transplant$).kf. (1865)
7 ("stem cell" adj5 transplant$).tw. (51747)
8 ("stem cell" adj5 transplant$).kf. (7713)
9 or/1-8 (151154)
10 exp Leukemia/ (234051)
11 (leukemia or leukemi* or leukaemi*).tw. (269738)
12 (leukemia or leukemi* or leukaemi*).kf. (32354)
13 (aml or anll or lymphoma or lymphom* or hodgkin* or T-cell or B-cell or non-hodgkin or sarcoma or sarcom* or Ewing* or osteosarcom* or wilms* or nephroblastom* or neuroblastom* or rhabdomyosarcom* or teratom* or hepatom* or hepatoblastom* or PNET or medulloblastom* or PNET* or (neuroectodermal adj2 tumors adj2 primitive) or retinoblastoma or retinoblastom* or meningiom* or gliom*).tw. (834591)
14 (aml or anll or lymphoma or lymphom* or hodgkin* or T-cell or B-cell or non-hodgkin or sarcoma or sarcom* or Ewing* or osteosarcom* or wilms* or nephroblastom* or neuroblastom* or rhabdomyosarcom* or teratom* or hepatom* or hepatoblastom* or PNET or medulloblastom* or PNET* or (neuroectodermal adj2 tumors adj2 primitive) or retinoblastoma or retinoblastom* or meningiom* or gliom*).kf. (90826)
15 exp lymphatic vessel tumors/ or exp lymphoma/ or exp "neoplasms, complex and mixed"/ or exp "neoplasms, connective and soft tissue"/ or exp "neoplasms, germ cell and embryonal"/ or exp "neoplasms, glandular and epithelial"/ or exp neoplasms, gonadal tissue/ or exp neoplasms, nerve tissue/ or exp neoplasms, plasma cell/ or exp neoplasms, vascular tissue/ or exp neoplasms by site/ or exp neoplasms, hormone-dependent/ or exp neoplasms, radiation-induced/ or exp neoplastic syndromes, hereditary/ (2727316)
16 ((brain adj tumo?r*) or (brain adj neoplasm?) or (central adj nervous adj system adj neoplasm?) or (central adj nervous adj system adj tumo?r?) or (central adj nervous adj system adj cancer?) or (brain adj cancer*) or (brain adj neoplasm*) or (intracranial adj neoplasm*) or (leukemia adj lymphocytic adj acute*)).tw. (49779)
17 ((brain adj tumo?r*) or (brain adj neoplasm?) or (central adj nervous adj system adj neoplasm?) or (central adj nervous adj system adj tumo?r?) or (central adj nervous adj system adj cancer?) or (brain adj cancer*) or (brain adj neoplasm*) or (intracranial adj neoplasm*) or (leukemia adj lymphocytic adj acute*)).kf. (10686)
18 or/10-17 (3380178)
19 "variant neurocognitive P".ti. (0)
20 "P variant breed".ti. (0)
21 ((p?ediatric adj3 oncolog*) or (child* adj3 (cancer? or tumo?r? or neoplasm?))).tw. (39721)
22 ((p?ediatric adj3 oncolog*) or (child* adj3 (cancer? or tumo?r? or neoplasm?))).kf. (2540)
23 young adult/ or exp child/ or exp infant/ (3206941)
24 ((young adj adult?) or child??? or childhood or infant* or p?ediatr* or perinat* or neonat* or newborn* or infan* or boy? or girl? or kid? or schoolage* or juvenil* or teenage* or adolescen* or toddler?).tw. (2465097)
25 ((young adj adult?) or child??? or childhood or infant* or p?ediatr* or perinat* or neonat* or newborn* or infan* or boy? or girl? or kid? or schoolage* or juvenil* or teenage* or adolescen* or toddler?).kf. (336883)
26 or/21-25 (4126178)
27 (cancer* or oncolog* or neoplasm* or carcinom* or tumor* or tumour* or malignan* or hematooncological or hemato?oncological or hemato-oncological or (hematologic adj neoplasm*)).tw. (3361279)
28 (cancer* or oncolog* or neoplasm* or carcinom* or tumor* or tumour* or malignan* or hematooncological or hemato?oncological or hemato-oncological or (hematologic adj neoplasm*)).kf. (611739)
29 9 or 18 or 27 or 28 (4682141)
30 "P in 3 varianten".ti. (0)
31 21 or 22 or 29 (4682141)
32 "P 3 variaties of kinderoncologie".ti. (0)
33 23 or 24 or 25 (4126038)
34 31 and 33 (506334)
35 29 and 31 (4682141)
36 9 or 18 (3468080)
37 33 and 36 (413142)
38 "onderdeel transfusies".ti. (0)
39 exp Platelet Transfusion/ (7273)
40 Plateletpheresis/ (1486)
41 Blood Platelets/ (77417)
42 ((platelet* or thrombocyte*) adj5 (prophyla* or transfus* or infus* or administ* or requir* or need* or product* or component* or concentrate* or apheres* or pooled or single donor or random donor)).tw,kf. (24757)
43 (thrombocytopheres* or plateletpheres*).tw,kf. (606)
44 ((platelet* or thrombocyte*) adj5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utili?ation)).tw,kf. (5706)

45 (platelet* or thrombocyte*).ti. (94077)
46 or/39-45 (133917)
47 blood component transfusion/ or erythrocyte transfusion/ (12677)
48 ((blood adj3 transfus*) or (erythrocyt* adj2 transfus*)).tw,kf. (65682)
49 ((erythrocy* or h?emoglobin*) adj5 (prophyla* or transfus* or infus* or administ* or requir* or need* or product* or component* or concentrate* or apheres* or pooled or single donor or random donor)).tw,kf. (13816)
50 47 or 48 or 49 (82926)
51 46 or 50 (211321)
52 "onderdeel transfusies".ti. (0)
53 37 and 51 (3603)
54 35 and 51 (29143)
55 exp Case Reports/ (2140140)
56 (case adj2 serie?).ti,ab,kf. (81166)
57 55 or 56 (2206004)
58 53 not 57 (2895)
59 blood component transfusion/ or erythrocyte transfusion/ or platelet transfusion/ (18929)
60 Platelet Count/ (21987)
61 transfus*.ti,kf. (46897)
62 46 or 50 or 59 or 60 or 61 (236803)
63 37 and 62 (4385)
64 63 not 57 (3528)
65 64 (3528)

Embase search

Database: Embase <1974 to 2020 December 10>
Search Strategy:
---
1 exp stem cell transplantation/ or exp allogeneic stem cell transplantation/ (156010)
2 exp hematopoietic stem cell transplantation/ (67381)
3 (stem adj2 cell adj3 transplan*).tw,kw. (98779)
4 bone marrow transplantation/ (51280)
5 ("bone marrow" adj5 transplant$).tw,kw. (55498)
6 ("stem cell" adj5 transplant$).tw,kw. (100630)
7 or/1-6 (236441)
8 exp leukemia/ (308369)
9 (leukemia or leukemi* or leukaemi*).tw,kw. (360281)
10 (aml or anll or lymphoma or lymphom* or hodgkin* or T-cell or B-cell or non-hodgkin or sarcoma or sarcom* or Ewing* or osteosarcom* or wilms* or nephroblastom* or neuroblastom* or rhabdomyosarcom* or teratom* or hepatom* or hepatoblastom* or PNET or medulloblastom* or PNET* or (neuroectodermal adj2 tumors adj2 primitive) or retinoblastoma or retinoblastom* or meningiom* or gliom*).tw,kw. (1143260)
11 exp lymphangioma/ (8661)
12 exp lymphoma/ (301746)
13 (neoplasms, complex and mixed).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (40)
14 (neoplasms, connective and soft tissue).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (15)
15 (neoplasms, germ cell and embryonal).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (176)
16 (neoplasms, glandular and epithelial).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (170)
17 exp gonad tumor/ (178138)
18 exp nerve tumor/ (53565)
19 plasmacytoma/ (11334)
20 exp vascular tumor/ (80957)
21 exp neoplasms subdivided by anatomical site/ (4055653)
22 neoplasms, hormone-dependent.mp. (47)
23 radiation induced neoplasm/ (2365)
24 exp hereditary tumor syndrome/ (47443)
25 or/8-24 (4628664)
26 ((brain adj tumo?r*) or (brain adj neoplasm?) or (central adj nervous adj system adj neoplasm?) or (central adj nervous adj system adj tumo?r?) or (central adj nervous adj system adj cancer?) or (brain adj cancer*) or (brain adj neoplasm*) or (intracranial adj neoplasm*) or (leukemia adj lymphocytic adj acute*)).tw,kw. (77614)

27 25 or 26 (4633475)
28 (cancer* or oncolog* or neoplasm* or carcinom* or tumor* or tumour* or malignan* or hematooncological or hemato?oncological or hemato-oncological or (hematologic adj neoplasm*)).tw,tw. (4490931)
29 7 or 27 or 28 (6033104)
30 "P in 3 varianten".ti. (0)
31 ((p?ediatric adj3 oncolog*) or (child* adj3 (cancer? or tumo?r? or neoplasm?))).tw,kw. (60814)
32 29 or 31 (6033185)
33 young adult/ (381995)
34 child/ or boy/ or girl/ or exp infant/ or preschool child/ or school child/ or toddler/ (2680621)
35 exp infant/ (1007136)
36 ((young adj adult?) or child??? or childhood or infant* or p?ediatr* or perinat* or neonat* or newborn* or infan* or boy? or girl? or kid? or schoolage* or juvenil* or teenage* or adolescen* or toddler?).tw,kw. (3075029)
37 or/33-36 (4109692)
38 32 and 37 (544704)
39 (7 or 27) and 37 (447217)
40 "onderdeel transfusies".ti. (0)
41 blood component therapy/ or erythrocyte transfusion/ or granulocyte transfusion/ or leukocyte transfusion/ or lymphocyte transfusion/ or thrombocyte transfusion/ (48068)
42 thrombocytopheresis/ (1878)
43 ((platelet* or thrombocyte*) adj5 (prophyla* or transfus* or infus* or administ* or requir* or need* or product* or component* or concentrate* or apheres* or pooled or single donor or random donor)).tw,kw. (39914)
44 (thrombocytopheres* or plateletpheres*).tw,kw. (924)
45 ((platelet* or thrombocyte*) adj5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utili?ation)).tw,kw. (9210)
46 (platelet* or thrombocyte*).ti. (116472)
47 ((blood adj3 transfus*) or (erythrocyt* adj2 transfus*)).tw,kw. (94695)
48 ((erythrocy* or h?emoglobin*) adj5 (prophyla* or transfus* or infus* or administ* or requir* or need* or product* or component* or concentrate* or apheres* or pooled or single donor or random donor)).tw,kw. (19578)
49 platelet count/ (23320)
50 blood transfusion/ (123544)
51 transfus*.ti,kw. (53810)
52 or/41-51 (351651)
53 or/41-49,51 (300466)
54 53 and 39 (7377)
55 case report/ (2565963)
56 case study/ (74534)
57 (case adj2 serie?).ti,ab,kw. (114100)
58 or/55-57 (2683514)
59 54 not 58 (4879)
60 59 (4879)
61 limit 60 to embase status (2920)
62 52 and 39 (9143)
63 62 not 58 (5988)
64 limit 63 to embase status (3704)
65 64 not 61 (784)
66 60 (4879)

Addendum 3. Risk of Bias-Tool for Non-RCTs

As only three of the studies were RCTs, the methodology for Risk of Bias assessment had to be adjusted for the non-RCTs. We combined the Risk of Bias tool for observational studies, as described in the IGHG Handbook (2), with a couple of aspects of the RCT tool as described earlier. By combining these tools, we aimed to have the best possible tool to assess the Risk of Bias in these types of studies.

Table 1. Adjusted Risk of Bias criteria for non-RCTs

Selection bias	Is the study group representative? Cases and controls were selected based on comparable patient characteristics (i.e. age, gender and tumor type) *Low risk if:* no significant differences between cases and controls with respect to age, gender and tumor type *High risk if:* cases and controls differ with respect to age, gender and tumor type (baseline imbalances caused by selection)
Attrition bias	Is complete outcome data for all the participants available in this study? Is the follow up adequate? *Low risk if:* no missing data, reasons for missing data not related to outcome, missing data balanced across groups, proportion missing or plausible effect size not enough to have a clinically relevant effect *High risk if:* imbalance in numbers or reasons, proportion missing or plausible effect size enough to have a clinically relevant effect, inappropriate use of imputation, 'as treated' analysis with substantial departure from allocation
Detection bias	Are the outcome assessors blinded for important determinants related to the outcome? *Low risk if:* the outcome assessors were blinded for important determinants related to the outcome *High risk if:* no blinding or broken blinding, ***and*** measurement likely to be influenced
Reporting bias	Is the report complete? Are the outcomes that were planned to be measured also reported? *High risk if:* Outcomes not reported as pre-specified or expected Outcomes reported incompletely so they cannot be entered in meta-analysis
Confounding bias	Are the analyses adjusted for important confounding factors? *Low risk if*: important prognostic factors (i.e. age, gender, diagnosis and risk stratification) were taken adequately into account *High risk if:* important prognostic factors (i.e. age, gender, diagnosis and risk stratification) were inadequately or not taken into account
Other bias	The following list of other potential sources of bias in a clinical study may aid detection of further problems. *High if:* - The conduct of the study is affected by interim results (e.g. recruiting additional participants from a subgroup showing more benefit). - There is deviation from the study protocol in a way that does not reflect clinical practice (e.g. *post hoc* stepping-up of doses to exaggerated levels). - There is pre-randomization administration of an intervention that could enhance or diminish the effect of a subsequent, randomized, intervention. - Inappropriate administration of an intervention (or co-intervention). - Contamination (e.g. participants pooling drugs). - Occurrence of 'null bias' due to interventions being insufficiently well delivered or overly wide inclusion criteria for participants (Woods 1995). - An insensitive instrument is used to measure outcomes (which can lead to under-estimation of both beneficial and harmful effects). - Selective reporting of subgroups. - Fraud. - Baseline imbalances for other reasons than through selection - Other

Referenties

Mulder RL, Brown MC, Skinner R, Hudson MM, Kremer LCM. Handbook for guideline development; collaboration between International Guideline Harmonization Group, PanCare Guideline Group and Cochrane Childhood Cancer Group. 2019.

Addendum 4. Risk of Bias-Results

Figure 1. Risk of bias - RCTs

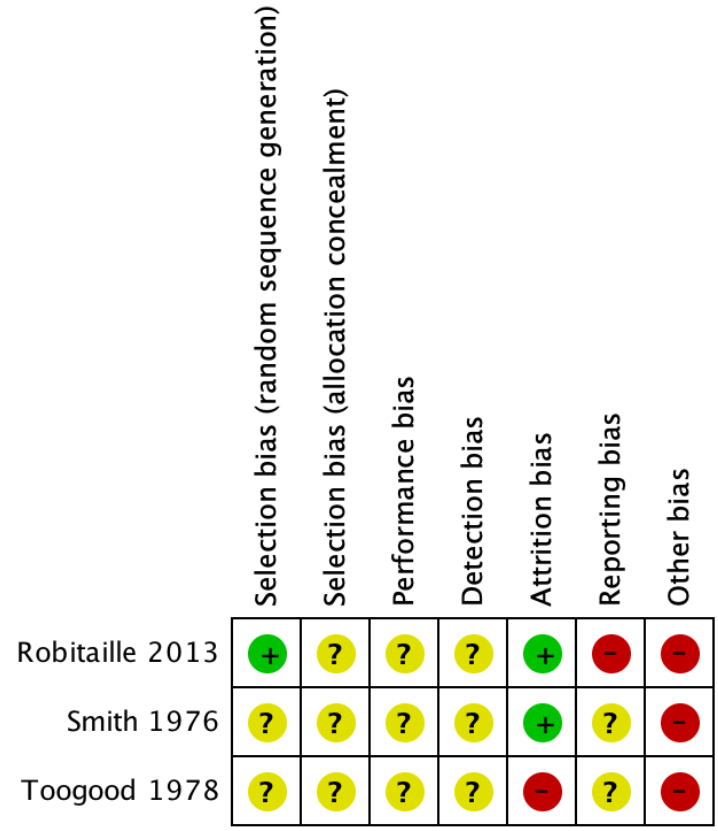

Figure 2. Risk of bias - non-RCTs

Addendum 5. Description of the additional guidelines (including AGREE II-scores)

Description of the guidelines

Valentine (2018)

Valentine (2018) created recommendations for RBC transfusions in critically ill children by bringing together international, multidisciplinary experts in a guideline panel. This to develop evidence-based and when evidence is lacking, expert-based consensus statements to guide transfusion and blood management practices. Thirty-eight content experts and 4 non-voting methodology and implementation experts, representing 8 countries, 29 academic institutions and 8 medical specialties, agreed and participated in all aspects. The following 9 clinical subtopics: indications for RBC transfusion based on Hb and physiologic thresholds in critically ill children 1) in the general PICU population, with 2) respiratory failure, 3) non-hemorrhagic shock, 4) non-life threatening bleeding and hemorrhagic shock, 5) acute brain injury, 6) acquired and congenital heart disease, 7) sickle cell and oncologic disease, 8) support from extracorporeal membrane oxygenation, ventricular assist devices, renal replacement therapy, and 9) the use of alternative processing of blood products are discussed. They conducted a systematic review for the 9 subtopics and analyzed the evidence using the GRADE methodology (Valentine, 2018).

AGREE II assessment

- Domain 1. Scope and Purpose: The scaled domain score = 89%
- Domain 2. Stakeholder Involvement: The scaled domain score = 44%
- Domain 3. Rigour of Development: The scaled domain score = 79%
- Domain 4. Clarity of Presentation: The scaled domain score = 78%
- Domain 5. Applicability: The scaled domain score = 63%
- Domain 6. Editorial Independence: The scaled domain score = 92%
- Overall Guideline Assessment: Score 5 (I would recommend this guideline for use)

JPAC (2013)

The Joint United Kingdom Blood Transfusion Services Professional Advisory Committee (JPAC) has the purpose to deliver detailed service guidelines for blood transfusions and is an advisory organ to the United Kingdom Blood Services. And they created a transfusion handbook (2013) and based their advice on other guidelines (JPAC, 2013).

AGREE II assessment

- Domain 1. Scope and Purpose: The scaled domain score = 94%
- Domain 2. Stakeholder Involvement: The scaled domain score = 56%
- Domain 3. Rigour of Development: The scaled domain score = 35%
- Domain 4. Clarity of Presentation: The scaled domain score = 56%
- Domain 5. Applicability: The scaled domain score = 58%
- Domain 6. Editorial Independence: The scaled domain score = 25%
- Overall Guideline Assessment: Score 4 (I would recommend this guideline for use, with modifications)

CBO (2011)

CBO (2011) created a guideline that consists of recommendations for the blood transfusion practice and the underlying arguments for these recommendations. These recommendations were established through extensive literature research and subsequent opinions within the multidisciplinary guideline panel that consisted of delegate representatives of the various professional associations involved. The literature research was performed according to the Evidence-Based Guideline method Development (EBRO). Initially, the search was focused on evidence-based guidelines and review in the period from early 2003 to February 2008. These guidelines and reviews were judged for quality using the AGREE instruments and the evidence was used from these guidelines to answer the research question. Then, there were searches for additional studies per chapter from the moment the search in the guideline and/or review ended (CBO, 2011).

AGREE II assessment

- Domain 1. Scope and Purpose: The scaled domain score = 89%
- Domain 2. Stakeholder Involvement: The scaled domain score = 94%
- Domain 3. Rigour of Development: The scaled domain score = 85%
- Domain 4. Clarity of Presentation: The scaled domain score = 61%
- Domain 5. Applicability: The scaled domain score = 50%
- Domain 6. Editorial Independence: The scaled domain score = 0%
- Overall Guideline Assessment: Score 5 (I would recommend this guideline for use)

NICE (2015)

The National Institute for Health and Care Excellence (NICE) (2015) provides national guidance and advice to improve health and social care. NICE produces evidence-based guidance and advice for health, public health and social care practitioners and develops quality standards and performance metrics (NICE, 2015).

AGREE II assessment

- Domain 1. Scope and Purpose: The scaled domain score = 100%
- Domain 2. Stakeholder Involvement: The scaled domain score = 89%
- Domain 3. Rigour of Development: The scaled domain score = 69%
- Domain 4. Clarity of Presentation: The scaled domain score = 94%
- Domain 5. Applicability: The scaled domain score = 54%
- Domain 6. Editorial Independence: The scaled domain score = 92%
- Overall Guideline Assessment: Score 5 (I would recommend this guideline for use)

New (2016)

New (2016) created a revision of the 2004 British Committee for Standards in Haematology (BCSH) guideline on transfusion in neonates and older children. The guideline writing group was a selection of medical representatives including specialists from fetal medicine, neonatology, pediatric intensive care, cardiac anesthesia, pediatric hematology, clinical and laboratory transfusion medicine. The guideline is based on a systematic literature search after the 2004 guideline up to November 2014. This together with other relevant papers identified. The guideline was externally reviewed by the members of the Transfusion Task Force of the BCSH and by a sounding board including UK hematologists, pediatricians, and neonatologists. The evidence was graded according to the GRADE method (New, 2016).

AGREE II assessment

- Domain 1. Scope and Purpose: The scaled domain score = 83%
- Domain 2. Stakeholder Involvement: The scaled domain score = 55%
- Domain 3. Rigour of Development: The scaled domain score = 54%
- Domain 4. Clarity of Presentation: The scaled domain score = 83%
- Domain 5. Applicability: The scaled domain score = 29%
- Domain 6. Editorial Independence: The scaled domain score = 50%

FMS (2019)

The Federation of Medical Specialists (2019) created an evidence-based blood transfusion guideline with a guideline panel. First, an exploratory search was conducted for existing foreign guidelines and systematic reviews (Medline). Subsequently, for the individual research questions, specific terms were used to search for literature in various electronic databases. Additional literature was sought based on the literature lists of the selected studies. The quality of the studies was assessed using the Risk of Bias tables and meta-analyses were performed with Review Manager 5. To assess the power of scientific evidence the GRADE method was used (Federation of Medical Specialists, 2019).

AGREE II assessment

- Domain 1. Scope and Purpose: The scaled domain score = 94%
- Domain 2. Stakeholder Involvement: The scaled domain score = 100%
- Domain 3. Rigour of Development: The scaled domain score = 71%
- Domain 4. Clarity of Presentation: The scaled domain score = 89%
- Domain 5. Applicability: The scaled domain score = 13%
- Domain 6. Editorial Independence: The scaled domain score = 100%
- Overall Guideline Assessment: Score 6 (I would recommend this guideline for use)

Patient Blood Management Guidelines National Blood Authority (2012)

The Patient Blood Management Guidelines National Blood Authority (2012) created an evidence-based blood management guideline by conducting a search to answer their research questions in relevant electronic databases, bibliographies of studies that were identified as relevant and by assessing the recommended literature from experts. This was done by the Expert Working Group and the Clinical/Consumer Reference Groups. For every research question the body of evidence was consolidated into evidence statements and rated based on five domains: evidence based, consistency, clinical impact, generalizability, and applicability. Initially, studies of higher levels of evidence were included in preference over lower levels of evidence and thus minimized the bias (Patient Blood Management Guidelines National Blood Authority, 2012).

AGREE II assessment

- Domain 1. Scope and Purpose: The scaled domain score = 89%
- Domain 2. Stakeholder Involvement: The scaled domain score = 44%
- Domain 3. Rigour of Development: The scaled domain score = 67%
- Domain 4. Clarity of Presentation: The scaled domain score = 89%
- Domain 5. Applicability: The scaled domain score = 29%
- Domain 6. Editorial Independence: The scaled domain score = 58%
- Overall Guideline Assessment: Score 4 (I would recommend this guideline for use, with modifications)