Richtlijn “Trombocytentransfusies bij kinderen met kanker”

Versie 4
Juli 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
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 TROMBOCYTENTRANSFUSIES BIJ KINDEREN MET KANKER ©, 2022

Nederlandse Vereniging voor Kindergeneeskunde
Postbus 20059, 3502 LB Utrecht
Tel. 088 282 33 06
nvk@nvk.nl
www.nvk.nl

INHOUDSOPGAVE

LIJST MET AFKORTINGEN

ALL	Acute lymfatische leukemie
AML	Acute myeloïde leukemie
APL	Acute promyelocyten leukemie
ASCO	American Society of Clinical Oncology
EtD	Evidence-to-decision
FMS	Federatie Medisch Specialisten
GIN	Guidelines International Network
GRADE	Grading Recommendations Assessment, Development and Evaluation
IGHG	International Guideline Harmonization Group
IPOG	International Pediatric Oncology Group
LP	Lumbaalpunctie
NICE	National Institute for Health and Care Excellence
NVA	Nederlandse Vereniging voor Anesthesiologie
NVB	Nederlandse Vereniging voor Bloedtransfusie
NVvH	Nederlandse Vereniging voor Heelkunde
NVK	Nederlandse Vereniging voor Kindergeneeskunde
NVKC	Nederlandse Vereniging voor Klinische Chemie en Laboratoriumgeneeskunde
PEG sonde	Percutane endoscopische gastronomie sonde
PICC lijn	Perifeer ingebrachte centrale lijn
RCT	Randomized controlled trial
RevMan	Review Manager
RR	Risk ratio
SCT	Stamceltransplantatie
SKION	Stichting Kinderoncologie Nederland
VKN	Vereniging Kinderkanker Nederland
VP drain	Ventriculoperitoneale drain
V&VN	Verpleegkundigen & Verzorgenden Nederland

SAMENSTELLING VAN DE WERKGROEP

Samenstelling kernwerkgroep:

- Drs. D.C. (Debbie) Stavleu, arts-onderzoeker kinderoncologie Prinses Máxima Centrum, Utrecht en Beatrix Kinderziekenhuis (Universitair Medisch Centrum Groningen), 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
- Dr. R.L. (Renée) Mulder, postdoc onderzoeker, richtlijn ontwikkelaar, methodoloog, Prinses Máxima Centrum, Utrecht, op persoonlijke titel
- Drs. D.M. (Demi) Kruimer, ANIOS kindergeneeskunde, MSc Healthcare Management en arts-onderzoeker kinderoncologie 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 “Trombocytentransfusies bij kinderen met kanker”:

- 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
- Dr. J.P.J. (Sjef) van Gestel, kinderarts-intensivist, Wilhelmina Kinderziekenhuis (UMC Utrecht), Utrecht, NVK
- 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
- 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
- Drs. I.E. (Indra) Morsing, kinderarts-intensivist, Wilhelmina Kinderziekenhuis (UMC Utrecht), Utrecht, NVK
- Dr. J. (Joppe) Nijman, kinderarts-intensivist, Wilhelmina Kinderziekenhuis (UMC Utrecht), Utrecht, NVK
- 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. J. (Janneke) Ottens, verpleegkundig specialist kinderoncologie, Beatrix Kinderziekenhuis (Universitair Medisch Centrum Groningen), V&VN
- Mw. W. (Willemijn) Plieger, beleidsmedewerker VKN (Vereniging Kinderkanker Nederland), VKN
- 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 – OVERZICHT (NEDERLANDS)

1) Profylactische trombocytentransfusie <u>algemeen:</u>

Profylactische trombocytentransfusie bij een trombocytengrens van <50x10^9/L
Kinderen met een APL of een andere vorm van AML waarbij stollingsstoornissen kunnen voorkomen, tijdens inductie

Profylactische trombocytentransfusie bij een trombocytengrens van <20x10^9/L
Kinderen met AML tijdens inductie

Profylactische trombocytentransfusie bij een trombocytengrens van <10x10^9/L
Kinderen met ALL tijdens inductie
Kinderen met kanker en sepsis

2) Profylactische trombocytentransfusie <u>voorafgaand aan een procedure:</u>

Profylactische trombocytentransfusie bij een trombocytengrens van <100x10^9/L
Grote chirurgische ingreep (bijvoorbeeld tumor resectie)
Neurochirurgie (inclusief VP drain) en oogheelkundige ingrepen

Profylactische trombocytentransfusie bij een trombocytengrens van <50x10^9/L
Broncho-alveolaire lavage met behulp van een scoop
Chirurgisch botbiopt (ten behoeve van diagnostiek van een tumor)
Drain inbrengen
Lumbaalpunctie bij eerste work-up bij diagnose van een hematologische maligniteit
Lymfeklierbiopt (zowel naald biopt als excisie biopt)
PEG sonde inbrengen of verwijderen
Geplande, niet-spoedeisende nasale intubatie.
Getunnelde centraal veneuze lijn inbrengen of verwijderen
Tandextractie

Profylactische trombocytentransfusie bij een trombocytengrens van <20x10^9/L
Blaaskatheter inbrengen
Geplande, niet-spoedeisende endotracheale intubatie

Profylactische trombocytentransfusie bij een trombocytengrens van <10x10^9/L
Echogeleid inbrengen van een niet-getunnelde centraal veneuze lijn of een PICC lijn (perifeer ingebrachte centrale lijn).
Verwijderen niet-getunnelde centraal veneuze lijn of een PICC lijn
Lumbaalpunctie (met uitzondering van de LP bij eerste work-up bij diagnose van een hematologische maligniteit)

Profylactische trombocytentransfusie niet nodig
Beenmergaspiratie of biopt
Huidbiopt met huidstans
Intramusculaire injectie (bijvoorbeeld vaccinatie)
Klysma
Neusmaagsonde inbrengen of verwijderen
Rectale thermometer (sonde) of rectaal toedienen medicatie

SAMENVATTING – AANBEVELINGEN (NEDERLANDS)

Onderstaande is een samenvatting van de belangrijkste aanbevelingen uit de richtlijn “Trombocytentransfusies 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.

Samenvatting van de aanbevelingen:

1) Profylactische trombocytentransfusie algemeen/per ziektebeeld

Profylactische transfusie (algemeen)

-	De werkgroep is van mening dat het vanwege onvoldoende bewijs in de literatuur niet mogelijk is een aanbeveling te maken over profylactische trombocytentransfusie in het algemeen bij kinderen met kanker. Mocht u toch overwegen een profylactische trombocytentransfusie te geven, dan is een trombocytengrens van $10x10^9$/L voldoende. (1-3)

Kinderen met ALL

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytentransfusie grens van $10x10^9$/L voldoende is voor kinderen met ALL tijdens inductie.

Kinderen met AML (of APL)

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $20x10^9$/L voldoende is voor kinderen met AML tijdens inductie. De werkgroep is van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor kinderen met APL of een andere vorm van AML waarbij stollingsstoornissen kunnen voorkomen tijdens inductie.

Kinderen met sepsis

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $10x10^9$/L voldoende is voor kinderen met kanker en sepsis.

2) Profylactische trombocytentransfusie voorafgaand aan een procedure

Botbiopt (chirurgisch)

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het uitvoeren van een chirurgisch botbiopt ten behoeve van diagnostiek van een tumor bij kinderen met kanker.

Beenmerg aspiratie of biopt

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat er geen trombocytentransfusie nodig is voorafgaand aan een beenmergaspiratie of biopt bij kinderen met kanker.

Broncho-alveolaire lavage

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het uitvoeren van een broncho-alveolaire lavage met behulp van een scoop bij kinderen met kanker

Drain

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het inbrengen van een drain bij kinderen met kanker.

Tandextractie

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het uitvoeren van een tandextractie bij kinderen met kanker.

Klysma

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat er geen trombocytentransfusie nodig is voorafgaand aan een klysma bij kinderen met kanker.

Intramusculaire injecties

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat er geen trombocytentransfusie nodig is voorafgaand aan een intramusculaire injectie (bijvoorbeeld vaccinatie) bij kinderen met kanker, gegeven dat de injectieplaats gedurende 10 minuten afgedrukt wordt.

Intubatie

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $20x10^9$/L voldoende is voor een geplande, niet spoedeisende endotracheale intubatie ondergaan bij kinderen met kanker.

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor een geplande, niet spoedeisende nasale intubatie bij kinderen met kanker.

Lijnen

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het inbrengen of verwijderen van een getunnelde centraal veneuze lijn bij kinderen met kanker.

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $10x10^9$/L voldoende is voor het echogeleid inbrengen van een niet-getunnelde centraal veneuze lijn of een PICC lijn (perifeer ingebrachte centrale lijn) bij kinderen met kanker. De werkgroep is van mening dat een trombocytengrens van $10x10^9$/L voldoende is voor het verwijderen van een niet-getunnelde centraal veneuze lijn of een PICC lijn bij kinderen met kanker.

Lumbaal punctie

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence	Wij suggereren dat een trombocytengrens van $10x10^9$/L voldoende is voor het uitvoeren van een lumbaalpunctie bij kinderen met kanker *zonder* leukemische blasten in het bloed.

STERKE aanbeveling, EXPERT evidence	De werkgroep is sterk van mening dat een trombocytengrens van $50x10^9$/L aangehouden zou moeten worden voor het uitvoeren van een lumbaalpunctie bij kinderen (met kanker) *met* leukemische blasten in het bloed.

Lymfeklier biopt

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het uitvoeren een lymfeklierbiopt (zowel naald biopt als excisie biopt) bij kinderen met kanker.

Grote chirurgische ingrepen

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $100x10^9$/L voldoende is voor het uitvoeren een grote chirurgische ingreep, bijvoorbeeld tumor resectie, bij kinderen met kanker.

Neusmaagsonde

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat er geen trombocytentransfusie nodig is voorafgaand aan het inbrengen of verwijderen van een neusmaagsonde bij kinderen met kanker.

Neurochirurgie en oogheelkundige ingrepen

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $100x10^9$/L voldoende is voor het uitvoeren van neurochirurgie (inclusief VP drain) en oogheelkundige ingrepen bij kinderen met kanker.

PEG sonde inbrengen of verwijderen

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het inbrengen of verwijderen van een PEG sonde bij kinderen met kanker.

Rectale thermometer (sonde) of het rectaal toedienen medicatie

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat er geen trombocytentransfusie nodig is bij een rectale thermometer (sonde) of het rectaal toedienen van medicatie bij kinderen met kanker.

Huidbiopt

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat er geen trombocytentransfusie nodig is voorafgaand aan een huidbiopt (met gebruik van huidstans) bij kinderen met kanker.

Blaaskatheter

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $20x10^9$/L voldoende is voor het inbrengen van een blaaskatheter bij kinderen met kanker.

ALGEMENE INLEIDING (NEDERLANDS)

Aanleiding voor het maken van de richtlijn

Jaarlijks krijgen in Nederland ongeveer 600 kinderen kanker. Met het stijgen van de overleving van kinderen met kanker, is er meer plaats gekomen voor het verlagen van morbiditeit (door de behandeling) en het verhogen van kwaliteit van leven. Er is veel aandacht hiervoor en dit krijgt een steeds prominentere plek in de behandeling. Nog steeds is er veel variatie in de aanbevelingen die worden gebruikt in de klinische praktijk, wat een negatieve invloed heeft op de zorg. Hierom is het belangrijk om evidence-based richtlijnen te ontwikkelen. (4)

De behandeling van kanker is zwaar, intensief en langdurig, en gaat gepaard met veel bijwerkingen en toxiciteit. Zo is er bijvoorbeeld een kans op bloedingen door een laag aantal bloedplaatjes (trombocyten) in het bloed. Een belangrijke onderwerp in de dagelijkse praktijk en daarmee ook voor een dergelijke richtlijn is dus ook de bloedtransfusies. Deze transfusies hebben een belangrijke rol binnen de ondersteunende zorg (*supportive care*) bij kinderen met kanker. Kinderen met kanker kunnen bijvoorbeeld een trombocytentransfusie nodig hebben als gevolg van hun onderliggende ziekte of als bijwerking van de chemotherapie. Ook kan het voorkomen dat kinderen met kanker een te lage waarde hebben van hun trombocyten, en dat ze hierom een transfusie nodig hebben voordat ze een bepaalde behandeling ondergaan. Omdat dit soort situaties vaak voorkomen, en het een belangrijk evenwicht is tussen op het juiste moment een transfusie geven en kinderen niet teveel transfusies geven, is een duidelijke richtlijn op dit gebied zeer gewenst en zelfs noodzakelijk voor het bieden van goede zorg. Het is echter een lastige balans tussen zoveel mogelijk bijwerkingen of complicaties voorkomen en de kwaliteit van leven zo optimaal mogelijk te houden.
In deze evidence-based richtlijn bespreken wij in een multidisciplinaire groep alle relevante aspecten per onderwerp en bespreken we uitgebreid alle voor- en nadelen. We maken een afgewogen beslissing met daarin de mogelijke complicaties, toxiciteit of negatieve effecten en de kwaliteit van leven in acht nemend.

Er is behoefte aan een praktische leidraad voor zorgverleners, kinderen met kanker en hun ouders of verzorgers. In deze richtlijn is er door de werkgroep getracht duidelijke evidence-based aanbevelingen over trombocytentransfusies op te stellen. Voor de klinische vragen waar geen literatuur beschikbaar voor was, is een aanbeveling op basis van gedeelde *expert opinion* gemaakt. Dit om ervoor te zorgen dat er een praktische, bruikbare richtlijn beschikbaar voor zorgprofessionals met handvatten om patiënten en hun ouders te informeren.

Belangrijke onderwerpen in de ontwikkeling van deze richtlijn zijn dus de zaken uit het dagelijks leven van kinderen met kanker en hun ouders en de interventies waarmee zij tijdens hun behandeling te maken krijgen, o.a.:
1) Trombocytentransfusies algemeen of per ziektebeeld (denk aan kinderen met ALL of AML, kinderen met sepsis)
2) Trombocytentransfusies voorafgaand aan een procedure (denk aan voorafgaand aan een grote operatie, inbrengen van een lijn, een lumbaalpunctie).

Voor meer informatie over de erytrocyten transfusies verwijs ik u graag naar de richtlijn: “Erytrocytentransfusies bij kinderen en neonaten met kanker”.

Doel van de richtlijn

Het doel van deze richtlijn is dat er eenduidige, heldere indicaties komen voor trombocytentransfusies bij kinderen met kanker, met een goede balans tussen negatieve gevolgen (bijwerkingen, toxiciteit, etc.) en kwaliteit van leven.

Afbakening van de richtlijn
De richtlijn betreft kinderen met kanker van 0 tot 18 jaar.

In deze richtlijn worden alleen en specifiek indicaties voor profylactische trombocytentransfusies beschreven. Andere (medicamenteuze) interventies of factoren die van invloed zijn op (de verbetering van) de stolling van de patiënt vallen buiten de scoop van deze richtlijn. Trombocytentransfusies bij actief bloedverlies (therapeutische transfusies) vallen daarmee ook buiten de scoop van deze richtlijn.

Beoogde gebruikers van de 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 en begrippen
De definities en begrippen die worden gebruikt, zijn zo veel mogelijk toegelicht in de afzonderlijke aanbevelingen.

VERANTWOORDING ALGEMEEN (NEDERLANDS)

Geldigheid
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 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 Nederlandse Vereniging voor Kindergeneeskunde 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
Nederlandse Vereniging voor Kindergeneeskunde

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.

Doelgroep
Deze richtlijn is geschreven voor alle leden van de beroepsgroepen die betrokken zijn bij de zorg voor kinderen met kanker.

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 te maken hebben (zie hiervoor de samenstelling van de werkgroep op pagina 6).

Belangenverklaringen
Alle werkgroep ledenhebben 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 Nederlandse Vereniging voor Kindergeneeskunde.

Tabel 1: (Neven)functies en belangen werkgroep leden

Werkgroeplid	Functie	Nevenfuncties	Gemelde belangen	Ondernomen acties
D.C. Stavleu	Arts-onderzoeker kinderoncologie Prinses Máxima Centrum, Utrecht en Beatrix Kinderziekenhuis (Universitair Medisch Centrum Groningen)	-	Geen	Geen

E.A.H. Loeffen	AIOS kindergeneeskunde, epidemioloog en postdoc onderzoeker kinderoncologie Prinses Máxima Centrum, Utrecht en Beatrix Kinderziekenhuis (Universitair Medisch Centrum Groningen)	Voorzitter Stichting Kinderboek & Wetenschap (onbetaald).	Geen	Geen
R.L. Mulder	Postdoc onderzoeker, richtlijn ontwikkelaar, methodoloog, Prinses Máxima Centrum, Utrecht	-	Geen	Geen
D.M. Kruimer	Arts-onderzoeker kinderoncologie Prinses Máxima Centrum, Utrecht	ANIOS Kindergeneeskunde	Geen	Geen
L.C.M. 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
W.J.E. Tissing	Kinderoncoloog, hoogleraar Supportive Care, Prinses Máxima Centrum, Utrecht en Beatrix Kinderziekenhuis (Universitair Medisch Centrum Groningen)	Geen relevante nevenfuncties.	Geen	Geen
D. Bresters	Kinderoncoloog, Prinses Máxima Centrum, Utrecht	-	Geen	Geen
J.H.P. Evers	Verpleegkundig specialist, Prinses Máxima Centrum, Utrecht	-	Geen	Geen
J.P.J. van Gestel	Kinderarts-intensivist, Wilhelmina Kinderziekenhuis, Utrecht	-	Geen	Geen
M.M. Hagleitner	Kinderoncoloog, Prinses Máxima Centrum, Utrecht	-	Geen	Geen
K.J.M. Heitink-Pollé	Kinderhematoloog-oncoloog, Prinses Máxima Centrum, Utrecht	Voorzitter redactie werkboek kinderhematologie (onbetaald)	Geen	Geen
E.J. Huisman	Kinderarts-hematoloog, Sophia Kinderziekenhuis (Erasmus MC), Rotterdam	Transfusie specialist, Sanquin Bloedvoorziening, PhD student	Geen	Geen
P.H.M. Kuijper	Labaratorium specialist hematologie, Máxima Medisch Centrum, Veldhoven	Docent Fontys Hogeschool	Geen	Geen

M.O. Mensink	Kinderanesthesioloog, Prinses Máxima Centrum, Utrecht	Bestuurslid sectie pijn- en palliatieve geneeskunde NVA (onbetaald)	Geen	Geen
I.E. Morsing	Kinderarts-intensivist, Wilhelmina Kinderziekenhuis, Utrecht	-	Geen	Geen
J. Nijman	Kinderarts-intensivist, Wilhelmina Kinderziekenhuis, Utrecht	-	Geen	Geen
J.G. Noordzij	Kinderarts, Reinier de Graaf Gasthuis, Delft	-	Geen	Geen
I. Ophorst	Kinderoncologie verpleegkundige, expert verpleegkundig onderzoek, Prinses Máxima Centrum, Utrecht	-	Geen	Geen
J. Ottens	Verpleegkundig specialist kinderoncologie, Beatrix Kinderziekenhuis (Universitair Medisch Centrum Groningen)	-	Geen	Geen
W. Plieger	Beleidsmedewerker VKN (Vereniging Kinderkanker Nederland)	-	Geen	Geen
J. Spijkerman	Kinderarts, fellow kinderoncologie, Prinses Máxima Centrum, Utrecht	-	Geen	Geen
A.F.W. van der Steeg	Kinderchirurg, Prinses Máxima Centrum, Utrecht	-	Geen	Geen
M.D. van de Wetering	SKION taakgroep Supportive Care, Kinderoncoloog, Prinses Máxima Centrum, Utrecht	-	Geen	Geen

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

Knelpunteninventarisatie
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 werkgroep leden. Hier is een volledige sessie aan gewijd met alle werkgroep leden 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
Op basis van de uitkomsten van de knelpunteninventarisatie zijn door de kernwerkgroep concept-uitgangsvragen opgesteld. Deze zijn met de werkgroep gedeeld ter goedkeuring, waarna de werkgroep de definitieve uitgangsvragen heeft vastgesteld. Knelpunten gingen met name over profylactische trombocytentransfusies rondom procedures zoals inbrengen van een neusmaagsonde, het uitvoeren van een lumbaalpunctie, chirurgische ingrepen zoals een biopt etc. Zie alle uitgangsvragen in “Verantwoording Methodologie” vanaf pagina 20 voor een compleet overzicht. Alle besproken knelpunten zijn omgezet naar definitieve uitgangsvragen.

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 van elke aanbeveling.

Kennislacunes
Tijdens de ontwikkeling van deze richtlijn is bij elke uitgangsvraag is door de werkgroep nagegaan of er (aanvullend) wetenschappelijk onderzoek gewenst is om de uitgangsvraag te kunnen beantwoorden. Een overzicht van de onderwerpen waarvoor (aanvullend) wetenschappelijk van belang wordt geacht, is beschreven in bijlage 1 “Kennislacunes”.

Implementatie
In de verschillende fasen van de richtlijnontwikkeling is rekening gehouden met de implementatie van de richtlijn en de praktische uitvoerbaarheid van de aanbevelingen. De implementatie zal plaatsvinden in het Prinses Máxima Centrum en de Shared Care centra en de werkgroep ziet geen grote belemmeringen. Een implementatieplan is bijgevoegd in bijlage 2.

Commentaar- en autorisatiefase
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 26-04-2022. De definitieve richtlijn werd aan de deelnemende (wetenschappelijke) verenigingen en (patiënt) organisaties voorgelegd voor autorisatie en is op 29-06-2022 door het NVK bestuur geautoriseerd.

VERANTWOORDING METHODOLOGIE (ENGELS)

This guideline was developed using the GRADE methodology (Grades of Recommendation, Assessment, Development and Evaluation Working Group). All necessary steps towards creating recommendations for clinical practice are described below.

First, already existing guidelines were extracted from guideline-databases (GIN, NICE, IPOG, ASCO) and those were evaluated for applicability and direct implementation.
In the absence of an applicable, usable guideline for children with cancer, then,, together with a multidisciplinary guideline panel, clinical questions were defined.

1. Clinical questions:

*The purpose of this guideline is to provide recommendations for children with cancer, receiving anti-cancer treatment with **curative intent.** This accounts for all of the following patient groups. The guideline was not intended to provide recommendations for palliative care settings.*

1) Platelet transfusions (disease or clinical-status related)

PICO (1A)

P = Children with any type of cancer (aged 28 days-18 years), receiving anti-cancer treatment
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer?

PICO (1B)

P = Neonates (aged 0-28 days)* with any type of cancer
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event-free survival

* *A 28-day boundary was unanimously determined by the guideline panel as age for neonates.*

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in neonates with cancer?

PICO (2A)

P = Children (aged 28 days-18 years) with acute myeloid leukemia (AML)
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with AML?

PICO (2B)

P = Neonates (aged 0-28 days) with AML
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in neonates with AML?

PICO (3A)

P = Children (aged 28 days-18 years) with acute promyelocytic leukemia (APL)
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with APL?

PICO (3B)

P = Neonates (aged 0-28 days) with APL
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes[1] in neonates with APL?

PICO (4A)

P = Children (aged 28 days-18 years) with acute lymphoblastic leukemia (ALL)
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with ALL?

PICO (4B)

P = Neonates (aged 0-28 days) with ALL
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in neonates with ALL?

PICO (5A)

P = Children (aged 28 days-18 years) with cancer who suffer from septicemia (author-defined)
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who suffer from septicemia?

PICO (5B)

P = Neonates (aged 0-28 days) with cancer who suffer from septicemia (author- defined)
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in neonates with cancer who suffer from septicemia?

2) Platelet transfusions (procedure-related)

PICO (6A)

P = Children (aged 28 days-18 years) with cancer who need to undergo a lumbar puncture **for the purpose of diagnosis**
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment related complications, procedure-related complications, morbidity, mortality, admission to hospital, delay of procedure, influence, on outcome material, success-rate procedure, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need to undergo a lumbar puncture for the purpose of diagnosis?

PICO (6B)

P = Neonates (aged 0-28 days) with cancer who need to undergo a lumbar puncture **for the purpose of diagnosis**
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment related complications, procedure-related complications, morbidity, mortality, admission to hospital, delay of procedure, influence, on outcome material, success-rate procedure, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in neonates with cancer who need to undergo a lumbar puncture for the purpose of diagnosis?

PICO (7A)

P = Children (aged 28 days-18 years) with cancer who need to undergo a lumbar puncture **for therapeutic/treatment related purposes**
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-

cancer treatment related complications, procedure-related complications, morbidity, mortality, admission to hospital, delay of procedure, influence, on outcome material, success-rate procedure, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need to undergo a lumbar puncture for therapeutic/treatment-related purposes?

PICO (7B)

P = Neonates (aged 0-28 days) with cancer who need to undergo a lumbar puncture **for therapeutic/treatment-related purposes**
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment related complications, procedure-related complications, morbidity, mortality, admission to hospital, delay of procedure, influence, on outcome material, success-rate procedure, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in neonates with cancer who need to undergo a lumbar puncture for therapeutic/treatment-related purposes?

PICO (8A)

P = Children (aged 28 days-18 years) with cancer who need to undergo a nasogastric tube insertion
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Hemorrhagic events (mild or severe), transfusion-related complications, procedure-related complications, anti-cancer treatment related complications, morbidity, mortality, success-rate procedure, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need to undergo a nasogastric tube insertion?

PICO (8B)

P = Neonates (aged 0-28 days) with cancer who need to undergo a nasogastric tube insertion
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Hemorrhagic events (mild or severe), transfusion-related complications, procedure-related complications, anti-cancer treatment related complications, morbidity, mortality, success-rate procedure, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in neonates with cancer who need to undergo a nasogastric tube insertion?

PICO (9A)

P = Children (aged 28 days-18 years) with cancer who need to undergo a bone marrow aspiration or biopsy
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment related complications, procedure-related complications, morbidity, mortality, admission to hospital, delay of procedure, influence, on outcome material, success-rate procedure, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes transfusion in children with cancer who need to undergo a bone marrow aspiration or biopsy ?

PICO (9B)

P = Neonates (aged 0-28 days) with cancer who need to undergo a bone marrow aspiration or biopsy
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment related complications, procedure-related complications, morbidity, mortality, admission to hospital, delay of procedure, influence, on outcome material, success-rate procedure, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes transfusion in neonates with cancer who need to undergo a bone marrow aspiration or biopsy ?

PICO (10A)

P = Children (aged 28 days-18 years) with cancer who need to undergo neurosurgery
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment related complications, procedure-related complications, morbidity, mortality, admission to hospital, delay of procedure, influence, on outcome material, success-rate procedure, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need to undergo neurosurgery?

PICO (10B)

P = Neonates (aged 0-28 days) with cancer who need to undergo neurosurgery
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment related complications, procedure-related complications, morbidity, mortality, admission to hospital, delay of procedure, influence, on outcome material, success-rate procedure, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in neonates with cancer who need to undergo neurosurgery?

PICO (11A)

P = Children (aged 28 days-18 years) with cancer who need to undergo ocular surgery/procedures
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment related complications, procedure-related complications, morbidity, mortality, admission to hospital, delay of procedure, influence, on outcome material, success-rate procedure, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need to undergo ocular surgery/procedures?

PICO (11B)

P = Neonates (aged 0-28 days) with cancer who need to undergo ocular surgery/procedures
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment related complications, procedure-related complications, morbidity, mortality, admission to hospital, delay of procedure, influence, on outcome material, success-rate

procedure, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in neonates with cancer who need to undergo ocular surgery/procedures?

PICO (12A)

P = Children (aged 28 days-18 years) with cancer who need to undergo minor surgery (bone biopsy, skin biopsy, lymph node biopsy, insertion of gastrostomy catheter, ultrasound-guided biopsy)
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment related complications, procedure-related complications, morbidity, mortality, admission to hospital, delay of procedure, influence, on outcome material, success-rate procedure, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need to undergo minor surgery?

PICO (12B)

P = Neonates (aged 0-28 days) with cancer who need to undergo minor surgery (bone biopsy, skin biopsy, lymph node biopsy, insertion of gastrostomy catheter, ultrasound-guided biopsy)

I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment related complications, procedure-related complications, morbidity, mortality, admission to hospital, delay of procedure, influence, on outcome material, success-rate procedure, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in neonates with cancer who need to undergo minor surgery?

PICO (13A)

P = Children (aged 28 days-18 years) with cancer who need to undergo major cancer-related surgery such as tumor resection or debulking
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment related complications, procedure-related complications, morbidity, mortality, admission to hospital, delay of procedure, influence, on outcome material, success-rate procedure, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need to undergo major surgery?

PICO (13B)

P = Neonates (aged 0-28 days) with cancer who need to undergo major cancer-related surgery such as tumor resection or debulking
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment related complications, procedure-related complications, morbidity, mortality, admission to hospital, delay of procedure, influence, on outcome material, success-rate procedure, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in neonates with cancer who need to undergo major surgery?

PICO (14A)

P = Children (aged 28 days-18 years) with cancer who need to undergo a bronchoalveolar lavage
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment related complications, procedure-related complications, morbidity, mortality, admission to hospital, delay of procedure, influence, on outcome material, success-rate procedure, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need to undergo a bronchoalveolar lavage?

PICO (14B)

P = Neonates (aged 0-28 days) with cancer who need to undergo a bronchoalveolar lavage
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment related complications, procedure-related complications, morbidity, mortality, admission to hospital, delay of procedure, influence, on outcome material, success-rate procedure, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in neonates with cancer who need to undergo a bronchoalveolar lavage?

PICO (15A)

P = Children (aged 28 days-18 years) with cancer who need to undergo line insertion or removal (central venous line, PICC line)
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment related complications, procedure-related complications, morbidity, mortality, admission to hospital, delay of procedure, influence, on outcome material, success-rate procedure, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need to undergo line insertion or removal?

PICO (15B)

P = Neonates (aged 0-28 days) with cancer with who need to undergo line insertion or removal (central venous line, PICC line)
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment related complications, procedure-related complications, morbidity, mortality, admission to hospital, delay of procedure, influence, on outcome material, success-rate procedure, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in neonates with cancer who need to undergo line insertion or removal?

PICO (16A)

P = Children (aged 28 days-18 years) with cancer who need to undergo other (minimally) invasive procedure such as enemas, urinary catheter insertions

I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment related complications, procedure-related complications, morbidity, mortality, admission to hospital, delay of procedure, influence, on outcome material, success-rate procedure, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need to undergo other (minimally) invasive procedures?

PICO (16B)
P = Neonates (aged 0-28 days) with cancer who need to undergo other (minimally) invasive procedure such as enemas, urinary catheter insertions
I = Prophylactic platelet transfusion (at any threshold)
C = (No prophylactic platelet transfusion or transfusion at any other threshold)
O = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment related complications, procedure-related complications, morbidity, mortality, admission to hospital, delay of procedure, influence, on outcome material, success-rate procedure, quality of life, event-free survival

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in neonates with cancer who need to undergo other (minimally) invasive procedures?

2. In- and exclusion criteria

Population:

- Children with cancer;
- Aged 0-18 years.

- When not enough studies are found in this group: guidelines in other pediatric patient groups (hematology) or adult guidelines will be searched (applicability depending per clinical question).

Outcomes:

- Mild hemorrhagic event (defined as: nose bleeds, small bleedings that can easily be controlled, petechiae of oral mucosa or skin, spontaneous hematoma)
- Severe hemorrhagic event (defined as hemorrhage leading to severe and permanent damage, severe morbidity, severe brain-bleeding, bleeding associated with severe hemodynamic instability, fatal bleeding)
- Delay of procedure
- Influence on outcome material
- Difficulty of procedure
- Quality of life
- Transfusion-related complications
- Anti-cancer treatment-related complications
- Morbidity
- Mortality
- Admission to hospital
- Costs
- Event-free survival (author-defined)
- Late complications

Type of studies:

- Firstly, RCTs are preferred. Then, if these studies provide not enough evidence, other controlled studies can be included
- Case series and case reports will be excluded
- No language resection
- No year restriction
- Databases: PubMed, Embase, Cochrane CENTRAL

3. Search strategy

Together with a medical librarian, an extensive literature search was created and performed (see Appendix 3). We searched for all terms regarding platelet transfusions in pediatric oncology patients, as defined in the clinical questions. PubMed, Embase and Cochrane CENTRAL were searched, with a total of 7486 results (most recently: December 2020). The entire in- and exclusion process is shown in Appendix 4).

Additionally, an extra search was performed by researcher DS. A search was made with entry terms ‘children with cancer’, ‘thrombocyte’ and ‘bleed’. Through this search, we aimed to find additional evidence from observational studies which reported bleeding in children with a specific platelet count. In total, 2167 unique entries were found. After title and abstract selection, 0 articles were eligible for inclusion for the development of this guideline.

Then, thirdly, in order to collect additional evidence from other guidelines, various established guideline databases were searched (i.e. GIN, NICE etc). Then after critically evaluating 11 additional guidelines, three of them (ASCO (3), NICE (2), FMS (1)) were eligible for inclusion and therefore were added as additional evidence. These three guidelines were chosen because of their methods and evidence-based approach. The applicable guidelines are mentioned per clinical question. For some, the single studies that were cited in those guidelines, were also individually assessed.

4. Quality of single studies

4.1 Evaluating methodological quality of included RCTs

Bias evaluation was performed according to the Cochrane handbook. (5)

- *Selection bias*: random sequence generation and the allocation concealment;
- *Performance bias*: blinding of participants and personnel;
- *Detection bias*: blinding of outcome assessors for all separate outcomes;
- *Attrition bias*: based on incomplete outcome data for all separate outcomes;
- *Reporting bias:* selective reporting;
- *Other potential sources of bias*.

4.2 Evaluating methodological quality of included non-RCTs

The methodology for Risk of Bias assessment had to be adjusted for the non-RCT studies. We combined the Risk of Bias tool for observational studies, as described in the IGHG Handbook (6), 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 our types of studies. The tool that we used is shown in Table 2.

Table 2: Adjusted Risk of Bias criteria

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 nog 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 or 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

4.3 Dual appraisal
All relevant steps (study identification, data extraction and management, assessment of risk of bias in included studies) were performed by two review authors (DS, DK), independently. Discrepancies will be resolved by consensus.

4.4 Summary of findings tables
For each clinical question a summary of findings table of the body of evidence will be completed. A summary of findings table provides key information of every single study about the main patient characteristics, the magnitude of effects for the defined outcomes and determinants, and the quality of that study.

5. Total body of evidence
5.1 Importance of outcomes
According to the GRADE methodology, the outcomes were defined as 'low important, important or critical'. The importance of outcomes and its hierarchy were discussed in the guideline panel meeting. Based on consensus, the following hierarchy of importance was determined by the guideline panel:

Table 3: Importance of outcomes social restrictions

Critical	9	Severe hemorrhagic events Mortality
	8	
	7	Transfusion-related complications Anti-cancer treatment-related complications Morbidity Event-free survival Quality of life
Important	6	Mild hemorrhagic events Admission to hospital Influence on outcome material Success rate procedure
	5	
	4	Costs Delay of procedure
Low importance	3	
	2	
	1	

5.2 Grading the quality of the body of evidence (GRADE)
Then, the quality of the body of evidence per outcome is assessed. According to the GRADE methodology, a randomized controlled trial starts at a high quality evidence level, whereas a cohort study or other type of study starts at a lower quality evidence level. Then, the following considerations can lower the quality of evidence: inconsistency (degree of consistency of effect between or within studies), imprecision (the precision of the results), indirectness (the generalizability of population and outcomes from each study to the population of interest), publication bias or other study limitations.
Some factors might increase the quality of the evidence: for example, a large magnitude of effect or a dose-response gradient.

A total GRADE score for the total body of evidence will be appointed per outcome:
⨁⨁⨁⨁ High quality evidence
⨁⨁⨁⊖ Moderate quality evidence
⨁⨁⊖⊖ Low quality evidence
⨁⊖⊖⊖ Very low quality evidence

6. Translate evidence into recommendations – Evidence-to-Decision Framework
Results of literature studies were used to formulate recommendations. If no studies were identified, we carefully considered expert consensus.

According to the GRADE methodology, an evidence-to-decision (EtD) framework was used to translate evidence into recommendations. Below examples of the questions in such a EtD framework are shown. These questions were answered by the guideline panel to help form a recommendation.

- PROBLEM:
  Is the problem a priority?
- BENEFITS AND HARMS:
  What is the overall certainty of this evidence?
  Is there important uncertainty about how much people value the main outcomes?
  Are the desirable anticipated effects large?
  Are the undesirable anticipated effects small?
  Are the desirable effects large relative to undesirable effects?
- RESOURCE USE:
  Are the resources required small?
  Is the incremental cost small relative to the net benefits?
  What would be the impact on health inequities?
- EQUITY:
  What would be the impact on health inequities?
- ACCEPTABILITY:
  Is the option acceptable to key stakeholders?
- FEASIBILITY:
  Is the option feasible to implement?

7. Terminology in recommendations
We used the GRADE terminology for evidence-based guidelines, such as ‘we suggest’ or ‘we recommend’. For our expert evidence recommendations, we used the terminology from the following article: “Lexicon for guidance terminology in pediatric hematology/oncology: A White Paper” (7). For example, we used ‘we believe’, to emphasize that these recommendations are based on expert opinion and group consensus, and not on a relevant body of identified studies. For further information about this terminology, we refer to this specific paper.

General remarks applicable to all recommendations:
1) The purpose of this guideline is to provide recommendations for children with cancer, receiving anti-cancer treatment with curative intent. The guideline was not intended to provide recommendations for palliative care settings.

2) No evidence was found for neonates.

Module 1: Children with cancer – in general (therapeutic versus prophylactic platelet transfusions) (ENGLISH)

A: Recommendations

Research question: What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer?

A1.1: Recommendation (English)

-	Due to lack of evidence, a recommendation about prophylactic platelet transfusions in general in children with cancer cannot be made. However, if you do consider giving a prophylactic platelet transfusion, a platelet threshold of $10x10^9$/L is sufficient. (1-3)

(3) ASCO (2018) (2) NICE (2015) (1) FMS (2019)

B: Clinical question, search and selection

B1: Clinical question:
What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer?

Patients = Children with any type of cancer (aged 28 days-18 years), receiving anti-cancer treatment
Intervention = Prophylactic platelet transfusion (at any threshold)
Control = No prophylactic platelet transfusion
Outcome(s) = Severe hemorrhagic events, mortality, mild hemorrhagic events, transfusion related complications, anti-cancer treatment-related complications, morbidity, admission to hospital, costs, quality of life, event-free survival

B2: Search and selection:
B.2.1 Study selection criteria
During the phase in which the guideline panel defined clinical questions and outcomes, we also established a four-step pathway towards collecting evidence.
Step 1. Evidence in pediatric oncology patients – studies found in the extensive literature search, including pediatric oncology patients only. We will search both single studies as guidelines for children with cancer.
Step 2. Guidelines in adult oncology patients – if not enough studies were retrieved from step 1, we will continue to search for extra evidence in guidelines for adult oncology patients. Firstly, we will extract the recommendation from this guideline. If necessary, we will discuss the overall in

conclusions and if of relevance, we will extract evidence from that single studies in adult oncology patients to help in our decision making.
Step 3. Evidence in pediatric patients – the guideline panel determined that we will not use these studies as primary evidence, but we might use them in our decision making. We do consider this evidence inferior to step 1 and 2 evidence.
Step 4. Expert evidence – if not enough evidence is found, the panel will make a recommendation based on expert evidence.

B.2.2 Literature search
Together with a medical librarian, an extensive literature search was created and performed. We searched for all terms regarding platelet transfusions in pediatric oncology patients, as defined in the clinical questions. PubMed, Embase and Cochrane CENTRAL were searched (most recently: December 2020). The included studies were separately assessed by two individual researchers (DS, DK). The evidence was extracted and risk of bias assessments were made.
Additionally, an extra search was performed by researcher DS. A search was made with entry terms 'children with cancer', 'thrombocyte' and 'bleed'. Through this search, we aimed to find additional evidence from observational studies which reported bleeding in children with a specific platelet count. Then, thirdly, in order to collect additional evidence from other guidelines, various established guideline databases were searched (i.e. GIN, NICE etc). Lastly, the single studies that were cited in those guidelines, were also individually assessed.

B3: Study selection
PubMed, Embase and Cochrane CENTRAL were searched, with a total of 7486 citations. Only one study with pediatric oncology patients (Murphy et al (8)) was included. Evidence was extracted and assessed using the GRADE methodology. In the second additional search, in total, 2167 unique entries were found. After title and abstract selection, 0 articles were eligible for inclusion for the development of this guideline.
Then after critically evaluating 11 additional guidelines, three of them (ASCO (3), NICE(2), FMS(1)) were eligible for inclusion and therefore were added as additional evidence.
Relevant single studies including adult cancer patients cited in the ASCO (3) and NICE(2) guideline were individually assessed to collect indirect evidence. In the FMS guideline (2019) (1), they refer to evidence of the NICE guideline, and is therefore not described separately here.

The ASCO guideline (2018) included two original studies 1) Stanworth et al (9) (2013) and 2) Wandt et al (10) (2012) and one Cochrane review (Crighton et al, 2015 (11)). The Cochrane review included six studies. Two of those are Stanworth et al (9) and Wandt et al (10) and one of those is the study of Murphy et al (8), described in "C1 Evidence in pediatric oncology patients". Three studies were excluded for further assessment in our guideline; two out of three studies were very small (12 and 31 patients) and most importantly, all three studies did not report their definitions of significant bleeding or life-threatening bleeding, and therefore those results cannot be used.

In the NICE guideline (2015) (2), seven articles were included, of which three studies report on the effect of therapeutic versus prophylactic transfusions. These three studies are Murphy et al (8), Stanworth et al (9) and Wandt et al (10). The other four studies were excluded because they focus on a lower versus a higher threshold of a prophylactic transfusion.

C: Results in pediatric and adult oncology patients

C1.1 Evidence in pediatric oncology patients

One RCT was found that reported therapeutic only (transfusion when bleeding occurred) versus prophylactic platelet transfusions in children with cancer. Murphy et al (1982)(8) reported on a cohort of 56 children with acute leukemia who were randomized to the therapeutic only strategy or to the prophylactic strategy (platelet transfusion when morning platelet count was $20x10^9$ or lower).

Hemorrhagic events in this study were defined as epistaxis not controlled by initial packing, gross gastrointestinal bleeding, gross genitourinary tract bleeding, any central nervous system bleeding, or any bleeding episode felt to be life-threatening. Severity of 'bleeds' or 'bleeding' was not further specified.

In the prophylactic group, 1.9 bleeds per 100 patient-months were reported versus 7.9 bleeds per 100 patients-months in the therapeutic group ($p<0.05$) (8). Within 4 years of the study period, in the prophylactic group, bleeds were reported in 10 out of 35 patients compared to 11 out of 21 in the therapeutic group with a relative risk (RR) of 1.83 (95% CI 0.94, 3.56) (calculated by researcher DS in Review Manager and calculated by Crighton et al (11)). In total, there were 21 patients (10 and 11 patients in both groups) with bleeds with a total of 47 bleeding episodes. Of this 47 bleeding episodes, 34 were nasal and oral and 10 were gastrointestinal with approximately the same distribution seen in the two groups (not further specified).

In conclusion, the original study (Murphy et al, 1982) reported significantly more bleeding regarding bleeds per patient-months in the therapeutic group. (8) However, the number of patients with any bleeding episode (severity not specified) during the study period did not differ between the groups.

Table 4: Study characteristics Murphy, 1982

Article **Author, year** **Study type**	**Population** **a. No. of patients** **b. Population**	**Case group*** **a. Group definition** **b. No. of patients, age, gender (% males)**	**Control Group** **a. Group definition** **b. No. of patients, age, gender (% males)**	**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**
Murphy, 1982 Randomized controlled trial	a. 56 patients b. Not provided c. Not provided d. ALL and acute nonlymphoblastic leukemia	a. Prophylactic group; patients were given transfusion if platelet count fell below 20 $\times10^9$/L, irrespective of clinical events b. 35 patients c. 4 units/m^2 of platelets	a. Therapeutic group, patients were not given a transfusion, unless bleeding event occurred b. 21 patients c. Not provided	- Mild/severe hemorrhagic event	a. Unclear b. Unclear c. Low d. Low e. High f. Unclear g. High

*or possible risk factor group, or intervention group

Table 5: Outcomes Murphy – Hemorrhagic events

Author, study design	No. of participants, total (cases vs controls) & Group definition	Results	Statistical methods	Effect size	Quality of evidence
1) Murphy, 1982 RCT	1) 56 patients with ALL and acute nonlymphoblastic leukemia. Prophylactic group (n=35) received thrombocyte transfusion when platelet count <20×10^9/L. Therapeutic group (n=21) received thrombocyte transfusion when they had symptoms of bleeding.	1A) In prophylactic group 1.9 bleeds per 100 patient-months vs 7.9 bleeds per 100 patients-months in therapeutic group *Of the 47 bleeding episodes, 34 were nasal and oral and 10 were gastrointestinal with approximately the same distribution seen in the two groups.	1A) Unclear	1A) **p<0.05**	⨁◯◯◯[A] VERY LOW

*Hemorrhagic event in this study is defined as epistaxis not controlled by initial packing, gross gastrointestinal bleeding, gross genitourinary tract bleeding, any central nervous system bleeding, or any bleeding episode felt to be life-threatening. No subanalyses can be performed.

A: GRADE: Grade quality assessment mild/severe hemorrhagic event in prophylactic versus therapeutic thrombocyte transfusion in children with cancer: design is randomized controlled trial, inconsistency not serious, indirectness not serious, imprecision serious (downgraded one level because of small study population), publication bias unlikely, downgraded 2 levels because of very serious risk of bias (random sequence generation unclear, allocation concealment unclear, performance bias low, detection bias low, attrition bias high, reporting bias unclear, other bias high)

C1.2 Evidence in adult oncology patients

The ASCO guideline (3), the NICE guideline (2) and the FMS guideline (1) recommend a platelet threshold of 10x10^9/L for prophylactic platelet transfusions. Their recommendations are based on expert opinions, but also on conclusions of studies in adult oncology patients by Stanworth et al (9) and Wandt et al (10), both studies performed in adult oncology patients.
Stanworth et al (9) included 600 patients with a mean age of 55 years, who were receiving chemotherapy or undergoing a stem cell transplantation. Wandt et al (10) included 391 patients, with a median age of 55 years undergoing intensive chemotherapy for AML or autologous HSCT for hematological cancers. To gain more information, the results of these single studies are discussed below.

C.1.2.1 Severe hemorrhagic events

For the outcome number of patients with severe or life-threatening bleeding, a meta-analysis of these 2 studies was performed by Crighton et al (11). Stanworth et al (9) reported 6 out of 301 severe or life-threatening bleeding events in the therapeutic group versus 1 out of 299 in the prophylactic group. Wandt et al (10) reported 1 out of 103 severe or life threatening bleeding events in the therapeutic group versus 0 out of 98 in the prophylactic group. The meta-analysis performed by Crighton et al (11) provided no difference between the 2 interventions with a relative risk (RR) of 4.91 (95% CI 0.86, 28.12) for the outcome severe hemorrhagic events in these two studies.

C.1.2.2 Mortality
Stanworth et al (9) reported mortality from all causes within 30 days from the start of the study. They report 5 out of 301 deaths in the therapeutic group versus 4 out of 299 in the prophylactic group with an RR 1.24 (95% CI 0.34, 4.58). Wandt et al (10) reported mortality due to bleeding within 90 days from the start of the study, and reported none in either the therapeutic or prophylactic group.

C.1.2.3 Additional interventions
Both Stanworth et al (9) and Wandt et al (10) (unpublished data, retrieved by Crighton et al (11)) reported the use of surgical, endoscopic, or other procedures to stop bleeding. There was no evidence of a difference in the use of surgical or other procedures. Crighton et al (11) showed these results in a meta-analysis with an RR 3.96 (95% CI 0.44 to 35.27). Stanworth et al (9) (unpublished data) also analyzed the use of medical interventions to stop bleeding, for example tranexamic acid or vitamin K. There was no evidence for a difference between the two groups, with a relative risk (RR) of 4.97 (95% CI 0.24, 103.02).

D: Conclusion(s) of evidence (pediatric oncology patients)

⊕◯◯◯ (1 study)[A*] **VERY LOW** QUALITY OF EVIDENCE	In one study, significantly less bleeding was observed in patients who received platelet transfusions prophylactically when platelet count fell <20 $\times 10^9$/L versus the group who received platelet transfusions therapeutically (i.e. when patients were bleeding).

***** The letter refers to the specific GRADE assessment described in section C1.

E: Considerations
Note, specific conditions such as AML, sepsis or platelet transfusion before a procedure are discussed elsewhere in this guideline.

E1.1 Therapeutic versus prophylactic platelet transfusions
In conclusion, the guideline panel believes that despite the results of three RCTs (Murphy et al (8), Stanworth et al (9), Wandt et al (10)) described above, there remains a gap in knowledge due to lack of evidence (of good enough quality) and that therefore, no recommendation can be formulated.

- One RCT in children was eligible for inclusion for this guideline (8). This study showed more bleeding per patient-months in the therapeutic group, but did not show a difference in number of bleeds per patients, nor did they define the severity of the bleeds. This study by Murphy et al (8) was of very low quality due to important imprecision, i.e. a small population (total 56 children) and very serious risk of bias i.e. unclear randomization and inclusion criteria, no patient characteristics and unclear outcome definitions. Most importantly, the severity of the bleeding episodes per study group is not specified and therefore conclusions cannot be drawn from this study.

- Two studies in adult oncology patients (9, 10) (total patients n=991) and recommendations from ASCO (3), NICE (2) and FMS (1) guidelines were used as additional evidence.
  These two studies in adult oncology patients (9, 10) had well defined outcome definitions, clear insight in inclusion criteria, patient characteristics and results per subgroup. However, as defined in the early stages of this guideline development, we

consider evidence from adult oncology patients as indirect evidence. We believe that adults with cancer are not comparable to children with cancer. It is reasonable to assume that adults have a higher a priori chance of severe bleeding than children due to the quality of the vascular system. The risk of bleeding in adults with cancer versus children with cancer is therefore, according to the guideline panel, not comparable. The guideline panel is aware that we thereby deviate from other guidelines such as ASCO (3) , NICE (2) and FMS (1). In our opinion, it makes sense that these guideline panels decide on higher thresholds for adults due to a higher risk of bleeding in adult oncology patients. However, we question the use and extrapolation of results from adult studies in recommendations for children.

We found no differences in severe hemorrhagic events and mortality between the therapeutic or prophylactic platelet transfusion groups (in adult oncology patients). These results might suggest a therapeutic-only strategy. However, the guideline panel strongly believes that these results also are insufficient evidence to recommend a therapeutic-only strategy for platelet transfusions. The panel identifies several additional potential advantages for a therapeutic-only strategy, for example lower costs, lower incidence of adverse transfusion reactions, shorter duration of hospitalization etc. However, one of the disadvantages of a therapeutic-only transfusion strategy is that there remains a possibility that this will increase the occurrence of severe hemorrhagic events. We believe that such an event could greatly affect morbidity, quality of life and possibly even survival.
However, a gap in knowledge of a clinically relevant issue remains and thus it is currently not possible to make a recommendation about therapeutic versus prophylactic platelet transfusions.

E1.2. (Potential) threshold prophylactic platelet transfusions
As described in D1.1, the guideline panel is not able to make a recommendation on therapeutic or prophylactic platelet transfusion. However, if you do consider administering your patient a prophylactic platelet transfusion, a threshold of $10x10^9$/L is sufficient and not inferior to a threshold of $20x10^9$/L or higher. We adapt these recommendations from the ASCO (3), NICE (2) and FMS (1) guidelines. This threshold of $10x10^9$/L was also discussed in the guideline panel and unanimously supported by all members.

The recommendations of ASCO (3) , NICE (2) and FMS (1) are based on multiple studies in adults that compared thresholds of $10x10^9$/L with 20, 30 or 50 $x10^9$/L. The NICE guideline reports: “Evidence from four studies comparing low platelet threshold with high platelet threshold in adult haematology patients showed that there was benefit with the use of a low threshold with respect to number of units of platelets transfused per patient and adverse events, but there was some uncertainty. There was no important difference between the groups for the outcomes mortality (all cause), number of patients with bleeding events (WHO grade 2 or 3), number of patients with major bleeding events (WHO grade 3 or 4) and infections (bacteraemia); but there was some uncertainty in the effect estimates. (2)”
The ASCO (3) guideline refers to a Cochrane review on “Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation” by Estcourt et al (12). “The review included three RCTs, with a total of 499 participants. The trials compared a standard transfusion threshold ($10x10^9$/L) with a higher threshold ($20x10^9$/L or $30x10^9$/L). Using the lower threshold of $10x10^9$/L did not increase the risk of bleeding and resulted in fewer transfusions. (3)”

Given these data and the expert opinions expressed in these guidelines, our guideline panel

feels that a platelet threshold of $10x10^9$/L is sufficient if you do consider giving a prophylactic platelet transfusion. We will not elaborate on this specific threshold further, and for more information we refer to the original ASCO (3), NICE (2) and FMS (1) guidelines.

E2. Research recommendations
There is definitely need for more research regarding prophylactic platelet transfusions in general in children with cancer. Deciding towards either the prophylactic or therapeutic strategy can have a lot of consequences, and should only be done if based on high quality research in our specific population.

We suggest a randomized controlled trial in children with cancer, who are randomized to either the prophylactic or therapeutic strategy group. In the Netherlands, standard of care in children in general is administering a platelet transfusion only when children are bleeding (the therapeutic strategy). In countries with the same policy, a study like this is more ethical and more feasible to start. Then, outcomes such as quality of life, severe hemorrhagic events, adverse events of platelet transfusion, hospitalization etc. should be measured. Once we have a high quality study with a large number of patients and a sufficient follow up, we might consider changing the strategy of administering platelet transfusions.

Module 1: Kinderen met kanker – in het algemeen (NEDERLANDS)

F: Aanbeveling (Nederlands)

-	De werkgroep is van mening dat het vanwege onvoldoende bewijs in de literatuur niet mogelijk is een aanbeveling te maken over profylactische trombocytentransfusie in het algemeen bij kinderen met kanker. Mocht u toch overwegen een profylactische trombocytentransfusie te geven, dan is een trombocytengrens van $10x10^9$/L voldoende. (1-3)

G: Overwegingen (Nederlands)

NB, specifieke aanbevelingen over AML, sepsis of een trombocytentransfusie voorafgaand aan een procedure, worden ergens anders in deze richtlijn besproken.

G1.1 Therapeutische versus profylactische trombocytentransfusies

Concluderend, de werkgroep is van mening dat ondanks de resultaten van 3 RCTs (Murphy et al (8), Stanworth et al (9), Wandt et al (10)) zoals hierboven beschreven, er nog steeds geen aanbeveling gemaakt kan worden door te weinig evidence (van goede kwaliteit).

- Een RCT in kinderen met kanker werd geïncludeerd in deze richtlijn (8). Deze studie liet meer bloedingen zien per patiënt-maanden in de therapeutische groep, maar lieten geen verschil zien in het aantal bloedingen per patiënt en zij rapporteerden de ernst van de bloedingen niet. De studie van Murphy et al (8) was van zeer lage kwaliteit door imprecisie, i.e. een kleine populatie (totaal 56 kinderen) en door zeer serieuze risk of bias door onduidelijke randomisatie en inclusie criteria, geen patiënten karakteristieken die werden beschreven en onduidelijke definities van de uitkomsten. Vanwege het feit dat de ernst van de bloedingen per studie groep niet gedefinieerd waren konden er dus geen conclusies werden getrokken uit deze studie.

- Twee studies in volwassen oncologie patiënten (9, 10) (totale patiënten n=991) en aanbevelingen van de ASCO (3), NICE (2) en FMS(1) richtlijnen werden gebruikt als additioneel evidence.
  Deze twee studies in volwassen oncologie patiënten (9, 10) hadden goed gedefinieerde uitkomsten, duidelijke inclusie criteria, patiënten karakteristieken en resultaten per subgroep. Echter, zoals al bepaald in een eerder stadium van deze richtlijnontwikkeling, beschouwen wij evidence in volwassen oncologie patiënten als indirect bewijs. Wij zijn van mening dat volwassenen niet vergelijkbaar zijn met kinderen met kanker. Het is aannemelijk om te denken dat volwassenen een hogere a priori kans hebben op bloedingen dan kinderen door de kwaliteit van hun vaatstelsel. De kans en het risico op bloedingen tussen volwassenen met kanker en kinderen met kanker is daarom niet vergelijkbaar naar mening van de werkgroep. De werkgroep is zich ervan bewust dat we hiermee afwijken van andere richtlijnen zoals ASCO (3), NICE (2) en FMS(1) richtlijnen. Naar onze mening is het logisch dat deze richtlijnen besluiten om een hogere grens aan te houden voor volwassenen vanwege en hoger risico op bloeding in deze patiënten.

Echter, wij zetten onze vraagtekens bij het gebruik en extrapolatie van de resultaten van studies in volwassenen ten behoeve van de aanbevelingen voor kinderen met kanker.

Wij vonden geen verschil in ernstige bloedingen en mortaliteit in de therapeutische of profylactische trombocytentransfusie groepen (in volwassen oncologie patiënten). Deze resultaten wijzen misschien op een therapeutische transfusie strategie. Echter, de werkgroep is sterk van mening dat deze resultaten alleen onvoldoende zijn om een dergelijke aanbeveling op te baseren. De werkgroep beschrijft een aantal voordelen van een therapeutische transfusie strategie, bijvoorbeeld lagere kosten, lagere incidentie van transfusiereacties, kortere opname in het ziekenhuis et cetera. Echter, één van de nadelen van een therapeutische transfusie strategie is dat er een mogelijkheid blijft dat ernstige bloedingen kunnen. Een dergelijke bloeding kan een zeer groot effect hebben op morbiditeit, kwaliteit van leven en eventueel zelfs overleving en mortaliteit.
Er blijft een tekort aan bewijs over klinisch relevante uitkomsten betreffende dit onderwerp en daarom is het op dit moment niet mogelijk een aanbeveling te maken over therapeutische danwel profylactische trombocytentransfusies.

G1.2. (Mogelijke) grens voor profylactische trombocytentransfusies
Zoals beschreven in G1.1 kan de werkgroep geen aanbeveling maken over het therapeutisch danwel profylactisch transfunderen van trombocyten. Echter, als u overweegt om uw patiënt toch een profylactische trombocytentransfusie te geven, dan is een grens van $10x10^9$/L voldoende en niet inferieur aan een grens van $20x10^9$/L of hoger. Wij nemen deze aanbevelingen over van de ASCO (3), NICE (2) en FMS (1) richtlijnen. Deze grens van $10x10^9$/L werd ook besproken binnen de werkgroep en werd door alle werkgroep leden gesteund.

De aanbevelingen van ASCO (3) , NICE (2) en FMS (1) zijn gebaseerd op meerdere studies die grenzen van $10x10^9$/L vergelijken met grenzen van 20, 30 or 50 $x10^9$/L. De NICE richtlijn rapporteert: “Bewijs van 4 studies die een lagere grens vergelijken met een hogere grens in volwassen hematologie patiënten laten zien dat er een voordeel was bij de lagere grens betreffende het aantal units nodig voor transfusie per patiënt en bijwerkingen, maar er was ook onduidelijkheid. Er was geen belangrijk verschil tussen de groepen voor uitkomsten zoals mortaliteit, aantal patiënten met een bloeding (WHO graad 2 of 3), aantal patiënten met een ernstige bloeding (WHO graad 3 of 4) en infecties (bacteriëmie), maar er was onduidelijkheid in de schattingen van het effect. (2)”

De ASCO richtlijn (3) refereert naar een Cochrane review over “*Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation*” door Estcourt et al (12). In deze review werden 3 RCTs geïncludeerd met totaal 499 deelnemers. Deze RCTs vergeleken een standard transfusie grens ($10x10^9$/L) met een hogere grens ($20x10^9$/L of $30x10^9$/L). Bij de grens van $10x10^9$/L werden niet meer bloedingen gerapporteerd en het resulteerde in minder transfusies (3).

Deze data en de meningen van de experts in acht nemend, is onze werkgroep van mening dat een grens van $10x10^9$/L voldoende is als u overweegt een profylactische trombocytentransfusie te geven. Wij zullen niet verder uitweiden over deze specifieke grens, voor verdere informatie hierover verwijzen wij naar de originele richtlijnen ASCO (3) , NICE (2) en FMS (1).

G2. Aanbevelingen verder onderzoek
Er is beslist meer onderzoek nodig over profylactische trombocytentransfusies in het algemeen in kinderen met kanker. De keuze maken voor één van deze strategieën kan veel consequenties hebben en moet alleen worden genomen als er onderzoek van hoge kwaliteit wordt gedaan in deze specifieke populatie.

Wij adviseren een RCT in kinderen met kanker die ofwel in de profylactische of in de therapeutische strategie worden gerandomiseerd. In Nederland is de standaard van zorg dat kinderen alleen een transfusie krijgen wanneer zij actief bloeden (i.e. de therapeutische strategie). In landen met hetzelfde beleid kan een dergelijke studie worden uitgevoerd, omdat dit ethisch verantwoord is en makkelijker op te starten. Uitkomsten zoals kwaliteit van leven, ernstige bloedingen, bijwerkingen van de transfusie, opname in het ziekenhuis et cetera zullen dan moeten worden gemeten. Zodra we een studie hebben van hoge kwaliteit met een groot aantal patiënten met een voldoende tijd van follow up, kunnen we wellicht overwegen de strategie te wijzigen.

Module 2: Children with ALL (ENGLISH)

A: Recommendations

Research question: What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with ALL?

A1.1: Recommendation (English)

WEAK recommendation, EXPERT evidence	We believe a platelet transfusion threshold of $10x10^9$/L is sufficient for children with ALL during induction therapy.

B: Clinical question, search and selection

B1: Clinical question:

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with ALL?

Patients = Children (aged 28 days-18 years) with acute lymphoblastic leukemia (ALL)
Intervention = Prophylactic platelet transfusion (at any threshold)
Control = (No prophylactic platelet transfusion or transfusion at any other threshold)
Outcomes = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event free survival

B2: Literature search and study selection

For the complete methodology of this guideline development and the search strategy, we refer to pages 20-31.
Of 7486 unique citations identified in the literature search, zero studies with pediatric oncology patients were included for this clinical question. Three additional guidelines (ASCO, NICE, FMS) were applicable to our clinical question. Additionally, the treatment protocol ALLtogether (2021) (13) was searched.

C: Results in pediatric and adult oncology patients

C1.1 Evidence in pediatric oncology patients

In our literature search, 0 studies were included for this clinical question.

C1.2 Evidence in adult oncology patients

In our literature search, 0 studies were included for this clinical question

C1.3 Additional evidence guidelines and treatment protocols

The ASCO guideline recommends: "*A threshold of <10x10^9 is recommended for prophylactic platelet transfusion in patients receiving therapy for hematologic malignancies. Transfusion at higher levels may be advisable in patients (…), or coagulation abnormalities (eg, acute promyelocytic leukemia) (…) (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).* (3)"
The NICE guideline recommends the following: "*Offer prophylactic platelet transfusions to patients with a platelet count below 10×10^9 per litre who are not bleeding or having invasive*

procedures or surgery". While this recommendation must be intended for patients with ALL, this patient group is not specifically mentioned (2).
The FMS guideline (translated from Dutch) recommends a threshold of $10x10^9$/L for patients with a thrombocytopenia due to a hematological cancer diagnosis (1).

In the treatment protocol ALLtogether (13) (2021), no threshold is mentioned, but only: ""All patients will ALL will have some degree of bone-marrow failure and may require transfusions of platelets and erythrocytes to treat or prevent bleeding and optimize oxygen uptake".

D: Conclusion(s) of evidence (pediatric oncology patients)

0 studies in pediatric oncology patients were found.	**-**

E: Considerations
No evidence in pediatric oncology patients was found. The ASCO (3), NICE (2) and FMS (1) guidelines recommend a threshold of $<10x10^9$/L. While these recommendations must be intended for patients with ALL, this patient group is not specifically mentioned. Therefore, the guideline panel additionally discussed expert opinions.
The guideline panel believes that a prophylactic platelet transfusion is appropriate in this specific patient group. Based on years of experience in the Netherlands with a threshold of $10x10^9$/L during induction therapy for children with ALL, the guideline panel believes that this threshold is sufficient. Thereby, the guideline panel also takes into an account the recommendations from ASCO (3), NICE (2) and FMS (1).
The guideline panel feels that during induction therapy for children with ALL, a prophylactic platelet threshold is appropriate because of a higher chance of bleeding. We believe that a threshold of $10x10^9$/L is sufficient and that it should not be higher, in accordance with the recommendation from "*D1.2. (Potential) threshold prophylactic platelet transfusions*". The guideline panel agrees that after induction therapy, a prophylactic platelet transfusion might no longer be necessary.

Module 2: Kinderen met ALL (NEDERLANDS)

F: Aanbeveling (Nederlands)

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytentransfusie grens van $10x10^9$/L voldoende is voor kinderen met ALL tijdens inductie.

G: Overwegingen (Nederlands)

Er werd geen literatuur gevonden over dit onderwerp bij kinderen met kanker. De ASCO (3), NICE (2) en FMS (1) richtlijnen raden aan grens van $10x10^9$/L aan voor profylactische trombocytentransfusie. Hoewel het lijkt dat deze aanbeveling ook bedoeld is voor patiënten met ALL, is dit niet geheel duidelijk. Daarom is deze aanbeveling mede gebaseerd op de meningen van de experts in de werkgroep.

De werkgroep is van mening dat een trombocytentransfusie grens van $10x10^9$/L voldoende is voor kinderen met ALL tijdens inductie. Gebaseerd op ervaringen in Nederland met een grens van $10x10^9$/L tijdens inductie, is de werkgroep van mening dat deze grens voldoende is voor deze patiënten groep. Dit is in lijn met de aanbevelingen van de ASCO (3), NICE (2) en FMS (1) richtlijnen.

De werkgroep is van mening dat voor kinderen met ALL tijdens inductie een profylactische trombocytentransfusie geoorloofd is vanwege een hogere kans op bloedingen tijdens deze fase. Wij denken dat een grens van $10x10^9$/L voldoende is en dat een nog hogere grens niet nodig is, in lijn met de eerdere aanbevelingen genoemd in G1.2 (Mogelijke) grens profylactische trombocytentransfusies. De werkgroep denkt dat na de inductie fase, deze profylactische trombocytentransfusie niet meer nodig zal zijn.

Module 3: Children with AML (or APL) (ENGLISH)

A: Recommendations

Research question: What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with AML (or APL)?

A1.1: Recommendation (English)

WEAK recommendation, EXPERT evidence	We believe a platelet threshold of $20x10^9$/L is sufficient for children with AML during induction therapy. We believe a platelet threshold of $50x10^9$/L is sufficient for children with APL or any other type of AML with coagulation abnormalities during induction therapy.

B: Clinical question, search and selection

B1: Clinical question:

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with AML (or APL)?

Patients = Children (aged 28 days-18 years) with acute myeloid leukemia (AML)
Intervention = Prophylactic platelet transfusion (at any threshold)
Control = (No prophylactic platelet transfusion or transfusion at any other threshold)
Outcomes = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event free survival

B2: Literature search and study selection

For the complete methodology of this guideline development and the search strategy, we refer to pages 20-31.
Of 7486 unique citations identified in the literature search, zero studies with pediatric oncology patients were included for this clinical question.

One guideline, (ASCO) was applicable and therefore was added as additional evidence. Also, relevant studies cited in the ASCO guideline were individually assessed. The ASCO guideline included three studies among which Wandt et al (2012), which will be discussed. Additionally, the treatment protocol NOPHO-DBH-AML-2012 was searched and the recommendation from this protocols was used.

C: Results in pediatric and adult oncology patients

C1.1 Evidence in pediatric oncology patients

In our literature search, 0 studies were included for this clinical question.

C1.2 Evidence in adult oncology patients

Wandt et al (10) included 391 patients, aged 16-80 years undergoing intensive chemotherapy for AML or autologous HSCT for hematological cancers. In this study patients were randomized in 2 groups: 197 patients in the prophylactic platelet transfusion group versus 199 in the therapeutic strategy. The AML subgroup in this study (respectively 96 and 94 patients) had increased bleeding rates in the therapeutic-only platelet transfusion group. They reported more

WHO grade 4 bleeding in the therapeutic-only AML subgroup (13 bleeds total versus 4 bleeds in the prophylactic group), with note that half of those (7 bleeds) happened at a platelet count of 11-56 x10^9/L.

C1.3 Additional evidence guidelines and treatment protocols
The ASCO guideline recommends: "*A threshold of <10x10^9 is recommended for prophylactic platelet transfusion in patients receiving therapy for hematologic malignancies. Transfusion at higher levels may be advisable in patients with (…), or coagulation abnormalities (eg, acute promyelocytic leukemia) and (…) (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).* (3)" A specific threshold for this specific patient group is not mentioned, however they do suggest to maintain a higher threshold.

The NICE guideline recommends "*Consider a higher threshold (for example 50–75×10^9 per litre) for patients with a high risk of bleeding who are having invasive procedures or surgery, after taking into account: (…) any coexisting causes of abnormal haemostasis*. (2)"

The FMS guideline (translated from Dutch) recommends a threshold of 10x10^9/L for patients with a thrombocytopenia due to a hematological cancer diagnosis, but does not specifically mention AML patients (1).
In the treatment protocol NOPHO-DBH-AML (2012) (14), a recommendation is made for children with high risk of bleeding. "*Children with AML, especially those with promyelocytic (APL), myelomonocytic or monocytic AML (M4 and M5), have a high incidence of coagulation disturbances, which can cause disseminated intravasal coagulation. (…) Platelets should be given to maintain platelet counts over 50 x10^9/L*". Further, they recommend: "*It is recommended that the platelet count be prophylactically maintained above 10x10^9/L. Higher thresholds may be indicated, e.g. during lumbar punctures, surgical procedures and infections*. (14)"

D: Conclusion(s) of evidence (pediatric oncology patients)

0 studies in pediatric oncology patients were found.	**-**

E: Considerations
No evidence in pediatric oncology patients was found. However, two recommendations were used for the decision by the guideline panel. Both in the NOPHO-DBH-AML (2012) (14) protocol and the ASCO guideline (3), a threshold of <10x10^9/L is recommended, but they both report that higher thresholds can be indicated in specific situations. Also, the results from the subgroup analysis from Wandt et al (10) learns that (adult) patients are more likely to bleed at lower platelet counts. Therefore, all these results support the guideline panel to determine a prophylactic platelet threshold in this subgroup.

The guideline panel, together with an invited expert (Prof. dr. GJL Kaspers) on this subject, believes that a prophylactic platelet transfusion is definitely appropriate in this specific patient group. Based on years of experience in the Netherlands with a threshold of 20x10^9/L during induction therapy for children with AML, the guideline panel believes that this threshold is sufficient. Thereby, the guideline panel also takes into an account the recommendations from both ASCO (3) and the treatment protocol and then specifically their recommendations that higher thresholds can be appropriate in specific situations. The guideline panel feels that during

induction therapy for children with AML, a higher threshold is appropriate because of a higher chance of bleeding. The guideline panel feels that after induction therapy, a prophylactic platelet transfusion might no longer be necessary.

The guideline panel strongly believes that for APL or any other type of AML with coagulation abnormalities, a higher threshold should be maintained, in line with the recommendation that is made in the NOPHO-DBH-AML-2012 protocol (14), because of the high incidence of coagulation disturbances.

Module 3: Kinderen met AML (of APL) (NEDERLANDS)

F: Aanbeveling (Nederlands)

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van 20x10^9/L voldoende is voor kinderen met AML tijdens inductie. De werkgroep is van mening dat een trombocytengrens van 50x10^9/L voldoende is voor kinderen met APL of een andere vorm van AML waarbij stollingsstoornissen kunnen voorkomen tijdens inductie.

G: Overwegingen (Nederlands)

Er werd geen literatuur gevonden over dit onderwerp bij kinderen met kanker. Er zijn twee aanbevelingen meegenomen in de overwegingen, namelijk van het NOPHO-DBH-AML (2012) (14) protocol en van de ASCO richtlijn (3). In beide stukken wordt een grens van <10x10^9/L genoemd, maar wordt wel benoemd dat een hogere grens aangeraden wordt in specifieke situaties. Ook laten de resultaten van de subgroep analyse van Wandt et al (10) zien dat (volwassen) patiënten meer kans hebben op een bloeding bij een lager trombocyten getal. Al deze argumenten samen sterken de werkgroep in het maken van een aanbevelingen over een grens voor profylactische trombocytentransfusie.

De werkgroep, samen met een uitgenodigde expert op dit onderwerp (Prof. Dr. GJL Kaspers), is van mening dat een profylactische trombocytentransfusie in deze groep geoorloofd is. Gebaseerd op ervaring in Nederland met een grens van 20x10^9/ tijdens inductie therapie voor kinderen met AML, is de werkgroep van mening dat deze grens voldoende is. Hierbij worden ook de aanbevelingen van de ASCO en het behandelprotocol in acht genomen. De werkgroep vindt dat gedurende inductie therapie van AML een hogere grens nodig is vanwege een hogere kans op bloedingen. De werkgroep denkt dat na de inductie fase, deze profylactische trombocytentransfusie niet meer nodig zal zijn.

De werkgroep is van mening dat een trombocytengrens van 50x10^9/L voldoende is voor kinderen met APL of een andere vorm van AML waarbij stollingsstoornissen kunnen voorkomen tijdens inductie, in lijn met het behandelprotocol NOPHO-DBH-AML-2012 (14).

Module 4: Children with sepsis (ENGLISH)

A: Recommendations

Research question: What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer and sepsis?

A1.1: Recommendation (English)

WEAK recommendation, EXPERT evidence	We believe a platelet threshold of $10x10^9$/L is sufficient in children with cancer and sepsis.

B: Clinical question, search and selection

B1: Clinical question:

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer and sepsis?

Patients = Children (aged 28 days-18 years) with cancer with sepsis (author-defined)
Intervention = Prophylactic platelet transfusion (at any threshold)
Control = (No prophylactic platelet transfusion or transfusion at any other threshold)
Outcomes = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event free survival

B2: Literature search and study selection

For the complete methodology of this guideline development and the search strategy, we refer to pages 20-31.
Of 7486 unique citations identified in the literature search, zero studies with pediatric oncology patients were included for this clinical question.
One additional guideline (ASCO) was applicable and therefore was added as additional evidence. One other individual study was used for decision making by the guideline panel.

C: Results in pediatric and adult oncology patients

C1.1 Evidence in pediatric oncology patients

In our literature search, 0 studies were included for this clinical question.

C1.2 Evidence in adult oncology patients

From our additional searches, 0 studies were included for this clinical question.

C1.3 Additional evidence guidelines (adults) and other

The ASCO guideline recommends: "*A threshold of <10x10^9 is recommended for prophylactic platelet transfusion in patients receiving therapy for hematologic malignancies. Transfusion at higher levels may be advisable in patients with higher fever (…). (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).* (3)*"* This is the only recommendation that is made in the ASCO guideline that is usable for this clinical question. Other additional evidence that was used to support our decision making, was the "Surviving Sepsis campaign (15)". In this study, a panel of 49 experts aimed "to develop evidence-based recommendations for clinicians caring for children (including infants, school-aged children, and adolescents) with septic shock and other sepsis-associated organ dysfunction". This study does not focus on pediatric oncology patients, but it does focus on children and thus this evidence was taken into consideration.

The *Surviving sepsis campaign* panel (15) eventually: "***suggests against*** prophylactic platelet transfusion based solely on platelet levels in nonbleeding children with septic shock or sepsis-associated organ dysfunction and thrombocytopenia (weak recommendation, very low quality of evidence."
They report that one observational study (Du Pont-Thibodeau G, Tucci M, Robitaille N, et al. Platelet transfusions in pediatric intensive care) demonstrated an association between the administration of platelet transfusions to critically ill children and worse clinical outcomes including progressive organ dysfunction, and increased mortality. They further state: "Although existing evidence does not support a platelet threshold at which transfusion is absolutely indicated, the risk of spontaneous bleeding may be greater at lower platelet counts, for example, less than 10–20,000/mm^3. In addition, some populations of thrombocytopenic critically ill children may have a relatively high risk of bleeding, such as those with oncological diagnoses or those receiving ECMO. Because the threshold at which the benefits of platelet transfusion outweigh the risks is unknown, clinical judgment based on patient risk factors for bleeding in addition to the measured platelet level must be exercised carefully."
NICE (2) and FMS (1) made 0 recommendations regarding this clinical question.

D: Conclusion(s) of evidence (pediatric oncology patients)

0 studies in pediatric oncology patients were found.	**-**

E: Considerations
No evidence in pediatric oncology patients or adult oncology patients was found. Therefore, the guideline panel formed a recommendation based mainly on expert opinions.

The guideline panel used the "Surviving sepsis campaign (15)" as a base for their expert opinion. The panel recognizes the importance of the recommendation this study makes, but believes that a certain platelet threshold should be maintained in a pediatric oncology population, as also stated in the "Surviving sepsis campaign".

The guideline panel believes that a prophylactic platelet transfusion is appropriate in this specific patient group. The guideline panel believes that if platelet count falls below $10x10^9$/L in a child with cancer and sepsis, the risk of bleeding and other complications are higher. The panel does not see any evidence for a threshold higher than $10x10^9$/L, also supported by the "Surviving sepsis campaign. (15)" A higher threshold can be considered in specific clinical situations.

Module 4: Kinderen met sepsis (NEDERLANDS)

F: Aanbeveling (Nederlands)

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $10x10^9$/L voldoende is voor kinderen met kanker en sepsis.

G: Overwegingen (Nederlands)

Er werd geen literatuur gevonden over dit onderwerp bij kinderen met kanker. Daarom is deze aanbeveling gebaseerd op de meningen van de experts in de werkgroep.
De werkgroep is van mening dat een profylactische trombocytentransfusie in deze groep geoorloofd is. De werkgroep is van mening dat een trombocytengrens van $10x10^9$/L voldoende is voor kinderen met kanker en sepsis.

De werkgroep heeft de “Surviving Sepsis Campaign” (15) gebruikt als basis voor onze expert opinions. De werkgroep erkent het belang van de aanbeveling die deze studie maakt, maar wij vinden dat er wel een bepaalde grens moet zijn voor kinderen met kanker, iets wat ook benoemd wordt in deze studie.
De werkgroep is van mening dat een profylactische trombocytentransfusie in deze groep geoorloofd is. De werkgroep is van mening dat als het trombocyten getal lager dan $10x10^9$/L wordt in een kind met kanker en sepsis, de kans op bloedingen en andere complicaties groter worden. Daarom is de werkgroep van mening dat de minimale grens $10x10^9$/L moet zijn, en dat een hogere grens uiteraard in specifieke klinische situaties kan worden overwogen. De werkgroep ziet geen reden om een grens hoger dan $10x10^9$/L aan te bevelen, ook in lijn met de “Surviving sepsis campaign. (15)”.

Module 5: Bone biopsy (surgical) (ENGLISH)

A: Recommendations

Research question: What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need a bone

biopsy?

A1.1: Recommendation (English)

WEAK recommendation, EXPERT evidence	We believe a platelet threshold of 50x10^9/L is sufficient for children with cancer who need a surgical bone biopsy for diagnostic purpose of a tumor.

B: Clinical question, search and selection

B1: Clinical question:

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need a bone biopsy?

Patients = Children (aged 28 days-18 years) with cancer who need to undergo a bone biopsy
Intervention = Prophylactic platelet transfusion (at any threshold)
Control = (No prophylactic platelet transfusion or transfusion at any other threshold)
Outcomes = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event free survival, procedure-related complications, influence on outcome material

B2: Literature search and study selection

For the complete methodology of this guideline development and the search strategy, we refer to pages 20-31.
Of 7486 unique citations identified in the literature search, zero studies with pediatric oncology patients were included for this clinical question.
Three additional guidelines (ASCO, NICE, FMS) were applicable to our clinical question.

C: Results in pediatric and adult oncology patients

C1.1 Evidence in pediatric oncology patients

In our literature search, 0 studies were included for this clinical question.

C1.2 Evidence in adult oncology patients

From our additional searches, 0 studies were included for this clinical question.

C1.3 Additional evidence guidelines (adults) and other

Firstly, the ASCO guideline recommends: "*A threshold of 40 x10^9/L to 50 x10^9/L is recommended for performing major invasive procedures in the absence of associated coagulation abnormalities (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: weak).* (3)"
They cite no evidence and their recommendation is mainly based on expert opinions.
The NICE guideline recommends: "*Consider prophylactic platelet transfusions to raise the platelet count above 50×10^9 per litre in patients who are having invasive procedures or surgery.* (2)"
The FMS (1) recommends that regarding surgical procedures, they believe a threshold of

$50x10^9$/L prior to the procedure is sufficient.
No additional evidence was cited by all three guidelines and recommendations were mostly based on expert opinions.

D: Conclusion(s) of evidence (pediatric oncology patients)

0 studies in pediatric oncology patients were found.	**-**

E: Considerations
No evidence in pediatric oncology patients or adult oncology patients was found. Therefore, the guideline panel formed a recommendation based mainly on expert opinions and recommendations from other guidelines.
The guideline panel believes that a prophylactic platelet transfusion is appropriate in this specific patient group. The panel recommends a threshold of $50x10^9$/L when a surgical bone biopsy is performed. This procedure lasts long, is invasive and has a significant bleeding risk.

The ASCO (3), NICE (2) and FMS (1) guidelines formed their recommendations based on limited evidence and expert opinions. The guideline panel recognizes the importance of their expert opinions, and carefully considered their recommendations in every evidence-to-decision for our clinical questions. The recommendations seem to support our decision making. Therefore, we believe a platelet threshold of $50x10^9$/L is sufficient for children with cancer who need a surgical bone biopsy for diagnostic purpose of a tumor.

Module 5: Botbiopt (chirurgisch) (NEDERLANDS)

F: Aanbeveling (Nederlands)

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het uitvoeren van een chirurgisch botbiopt ten behoeve van diagnostiek van een tumor bij kinderen met kanker.

G: Overwegingen (Nederlands)

Er werd geen literatuur gevonden over dit onderwerp bij kinderen met kanker. Daarom is deze aanbeveling gebaseerd op de meningen van de experts in de werkgroep.
De werkgroep is van mening dat een profylactische trombocytentransfusie in deze groep geoorloofd is. De werkgroep is van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het uitvoeren van een chirurgisch botbiopt ten behoeve van diagnostiek van een tumor bij kinderen met kanker. De procedure is invasief en de kans op een bloeding is reëel.

De ASCO (3), NICE (2) en FMS (1) richtlijnen hebben hun aanbevelingen gebaseerd op zeer beperkt evidence en meningen van experts. De werkgroep erkent het belang van de door hun geformuleerde aanbevelingen op basis van expert opinions en wij nemen deze dan ook zorgvuldig mee in onze overwegingen in het evidence-to-decision proces. De aanbevelingen van deze richtlijnen zijn in lijn met onze expert opinions. Concluderend, is de werkgroep van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het uitvoeren van een chirurgisch botbiopt ten behoeve van diagnostiek van een tumor bij kinderen met kanker.

Module 6: Bone marrow aspirate or biopsy (ENGLISH)

A: Recommendations

Research question: What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need to undergo a bone marrow aspiration or biopsy?

A1.1: Recommendation (English)

WEAK recommendation, EXPERT evidence	We believe that a prophylactic platelet transfusion is not necessary in children with cancer who need a bone marrow aspiration or biopsy.

B: Clinical question, search and selection

B1: Clinical question:

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need to undergo a bone marrow aspiration or biopsy ?

Patients = Children (aged 28 days-18 years) with cancer who need to undergo a bone marrow puncture
Intervention = Prophylactic platelet transfusion (at any threshold)
Control = (No prophylactic platelet transfusion or transfusion at any other threshold)
Outcomes = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event free survival, procedure-related complications, influence on outcome material

B2: Literature search and study selection

For the complete methodology of this guideline development and the search strategy, we refer to pages 20-31.
Of 7486 unique citations identified in the literature search, zero studies with pediatric oncology patients were included for this clinical question.
Three additional guidelines (ASCO, NICE, FMS) were applicable to our clinical question.

C: Results in pediatric and adult oncology patients

C1.1 Evidence in pediatric oncology patients

In our literature search, 0 results were found for this clinical question.

C1.2 Evidence in adult oncology patients

From our additional searches, 0 results were found for this clinical question.

C1.3 Additional evidence guidelines (adults) and other

Firstly, the ASCO guideline recommends: "*Certain procedures, such as bone marrow aspirations (…) can be performed safely at counts <20x10^9 (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: weak).* (3)" They cite no evidence and their recommendation is mainly based on expert opinions.
The NICE (2) guideline recommends: "Do not offer prophylactic platelet transfusions to patients having procedures with a low risk of bleeding, such as (…) any patients having bone marrow aspiration (…). (2)"
The FMS recommends that regarding the bone marrow biopsy, they believe that a prophylactic

platelet transfusion is not necessary prior to the procedure (1). No additional evidence was cited by all three guidelines and recommendations were mostly based on expert opinions.

D: Conclusion(s) of evidence (pediatric oncology patients)

0 studies in pediatric oncology patients were found.	**-**

E: Considerations

No evidence in pediatric oncology patients or adult oncology patients was found. Therefore, the guideline panel formed a recommendation based mainly on expert opinions and recommendations from other guidelines.

The panel believes that a prophylactic platelet transfusion prior to a bone marrow aspiration or biopsy is not necessary. A sufficient amount of pressure can be exerted on the skin locally where potential bleeding from the bone marrow biopsy might occur. Therefore, the panel feels that a possible bleeding can be managed sufficiently and that a transfusion prior to the procedure is not necessary.

The ASCO (3), NICE (2) and FMS (1) guidelines formed their recommendations based on limited evidence and expert opinions. The guideline panel recognizes the importance of their expert opinions, and carefully considered their recommendations in every evidence-to-decision for our clinical questions.

The recommendation of NICE (2) and FMS (1) supports our decision making. The guideline panel is aware that the ASCO (3) guideline recommends a much higher threshold (namely $20x10^9$/L) than we do now, but we strongly feel that the potential bleeding is adequately manageable because of the pressure you can exert on the wound, and therefore the guideline panel is confident to recommend that a prophylactic platelet transfusion is not necessary prior to the procedure.

Module 6: Beenmergaspiratie of biopt (NEDERLANDS)

F: Aanbeveling (Nederlands)

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat er geen trombocytentransfusie nodig is voorafgaand aan een beenmergaspiratie of biopt bij kinderen met kanker.

G: Overwegingen (Nederlands)

Er werd geen literatuur gevonden over dit onderwerp bij kinderen met kanker. Daarom is deze aanbeveling gebaseerd op de meningen van de experts in de werkgroep.
De werkgroep is van mening dat er geen trombocytentransfusie nodig is voorafgaand aan een beenmergaspiratie of biopt bij kinderen met kanker. De wond die wordt gecreëerd door het biopt is oppervlakkig en klein, en kan goed worden afgedrukt. Daarom ziet de werkgroep geen noodzaak tot een profylactische transfusie voorafgaand aan deze procedure.

De ASCO (3), NICE (2) en FMS (1) richtlijnen hebben hun aanbevelingen gebaseerd op zeer beperkt evidence en meningen van experts. De werkgroep erkent het belang van de door hun geformuleerde aanbevelingen op basis van expert opinions en wij nemen deze dan ook zorgvuldig mee in onze overwegingen in het evidence-to-decision proces.

De aanbevelingen van NICE (2) en FMS (1) zijn in lijn met onze aanbeveling. De werkgroep is zich ervan bewust dat de aanbeveling van de ASCO (3) een hogere grens aanraadt dan wij (namelijk $20x10^9$/L), maar wij zijn sterk van mening dat de bloeding goed controleerbaar is als je goed afdrukt en dat er daarom geen trombocytentransfusie nodig is voorafgaand aan een beenmergaspiratie of biopt bij kinderen met kanker.

Module 7: Broncho-alveolar lavage (ENGLISH)

A: Recommendations

Research question: What is the effect of prophylactic platelet transfusion on

hemorrhagic events and other outcomes in children with cancer who need a broncho-alveolar lavage?

A1.1: Recommendation (English)

WEAK recommendation, EXPERT evidence	We believe a platelet threshold of $50x10^9$/L is sufficient in children with cancer who need a broncho-alveolar lavage with use of a scope.

B: Clinical question, search and selection

B1: Clinical question:

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need a broncho-alveolar lavage?

Patients = Children (aged 28 days-18 years) with cancer who need a broncho-alveolar lavage
Intervention = Prophylactic platelet transfusion (at any threshold)
Control = (No prophylactic platelet transfusion or transfusion at any other threshold)
Outcomes = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event free survival, procedure-related complications

B2: Literature search and study selection

For the complete methodology of this guideline development and the search strategy, we refer to pages 20-31.
Of 7486 unique citations identified in the literature search, zero studies with pediatric oncology patients were included for this clinical question.
One additional guideline (FMS) was applicable to our clinical question.

C: Results in pediatric and adult oncology patients

C1.1 Evidence in pediatric oncology patients

In our literature search, 0 results were found for this clinical question.

C1.2 Evidence in adult oncology patients

From our additional searches, 0 results were found for this clinical question.

C1.3 Additional evidence guidelines (adults) and other

ASCO (3) and NICE (2) made 0 recommendations regarding this clinical question.
The FMS (1) recommends a threshold of $<50x10^9$/L for a broncho-alveolar lavage. No additional evidence was cited and the recommendation was based on expert opinions.

D: Conclusion(s) of evidence (pediatric oncology patients)

0 studies in pediatric oncology patients	-

were found.	

E: Considerations

No evidence in pediatric oncology patients or adult oncology patients was found. Therefore, the guideline panel formed a recommendation based mainly on expert opinions.
The guideline panel believes that a prophylactic platelet transfusion is appropriate in this specific patient group. The panel believes that a platelet threshold of $50x10^9$/L is sufficient in children with cancer who need a broncho-alveolar lavage, in line with the recommendation of the FMS (1). This procedure is invasive and has potential bleeding sites. We believe that the potential consequences of a bleed during or after the procedure could be very harmful. In addition, the potential bleeding cannot be managed easily. The panel agrees to a threshold of $50x10^9$/L in children with cancer who need a broncho-alveolar lavage with use of a scope.

Module 7: Broncho-alveolaire lavage (NEDERLANDS)

F: Aanbeveling (Nederlands)

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het uitvoeren van een broncho-alveolaire lavage met behulp van een scoop bij kinderen met kanker

G: Overwegingen (Nederlands)

Er werd geen literatuur gevonden over dit onderwerp bij kinderen met kanker. Daarom is deze aanbeveling gebaseerd op de meningen van de experts in de werkgroep.

De werkgroep is van mening dat een profylactische trombocytentransfusie in deze groep geoorloofd is. De werkgroep is van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het uitvoeren van een broncho-alveolaire lavage met behulp van een scoop bij kinderen met kanker, in lijn met de aanbeveling van de FMS (1). De procedure is invasief en de kans op een bloeding is reëel. Ook zijn wij van mening dat de consequenties van een eventuele bloeding schadelijk kunnen zijn, zowel tijdens als na de procedure. Ook kan de bloeding niet makkelijk worden gecontroleerd.

Concluderend, is de werkgroep van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het uitvoeren van een broncho-alveolaire lavage met behulp van een scoop bij kinderen met kanker.

Module 8: Chest tube or drain elsewhere (ENGLISH)

A: Recommendations

Research question: What is the effect of prophylactic platelet transfusion on

hemorrhagic events and other outcomes in children with cancer who need a chest tube or drain elsewhere?

A1.1: Recommendation (English)

WEAK recommendation, EXPERT evidence	We believe a platelet threshold of 50x10^9/L is sufficient for children with cancer who need a chest tube or drain insertion elsewhere.

B: Clinical question, search and selection

B1: Clinical question:

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need a chest tube or drain elsewhere?

Patients = Children (aged 28 days-18 years) with cancer who need a chest tube or drain elsewhere
Intervention = Prophylactic platelet transfusion (at any threshold)
Control = (No prophylactic platelet transfusion or transfusion at any other threshold)
Outcomes = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event free survival, procedure-related complications

B2: Literature search and study selection

For the complete methodology of this guideline development and the search strategy, we refer to pages 20-31.
Of 7486 unique citations identified in the literature search, zero studies with pediatric oncology patients were included for this clinical question.
Three additional guidelines (ASCO, NICE, FMS) were applicable to our clinical question.

C: Results in pediatric and adult oncology patients

C1.1 Evidence in pediatric oncology patients

In our literature search, 0 results were found for this clinical question.

C1.2 Evidence in adult oncology patients

From our additional searches, 0 results were found for this clinical question.

C1.3 Additional evidence guidelines (adults) and other

Firstly, the ASCO guideline recommends: "*A threshold of 40 x10^9/L to 50 x10^9/L is recommended for performing major invasive procedures in the absence of associated coagulation abnormalities (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: weak).* (3)*"*
They cite no evidence and their recommendation is mainly based on expert opinions.
The NICE guideline recommends: "*Consider prophylactic platelet transfusions to raise the platelet count above 50×10^9 per litre in patients who are having invasive procedures or surgery.* (2)"
Note that both ASCO and NICE do not specifically mention chest tube or drain insertion as being an invasive procedure.
The FMS recommends that regarding surgical procedures (and also pleural or pericardial drain),

they believe a threshold of $50x10^9$/L prior to the procedure is sufficient (1).
No additional evidence was cited by all three guidelines and recommendations were mostly based on expert opinions.

D: Conclusion(s) of evidence (pediatric oncology patients):

0 studies in pediatric oncology patients were found.	**-**

E: Considerations
No evidence in pediatric oncology patients or adult oncology patients was found. Therefore, the guideline panel formed a recommendation based mainly on expert opinions.
The guideline panel believes that a prophylactic platelet transfusion is appropriate in this specific patient group. The panel believes that a platelet threshold of $50x10^9$/L is sufficient in children with cancer who need a chest tube or drain elsewhere. This procedure is invasive and has potential bleeding sites. We believe that the potential consequences of a bleed during or after the procedure could be harmful. In addition, the potential bleeding cannot be managed easily.

The ASCO (3), NICE (2) and FMS (1) guidelines formed their recommendations based on limited evidence and expert opinions. The guideline panel recognizes the importance of their expert opinions, and carefully considered their recommendations in every evidence-to-decision for our clinical questions.
The recommendations seem to support our decision making. Therefore, the panel recommends a platelet threshold of $50x10^9$/L prior to a chest tube or drain insertion.

Module 8: Drain inbrengen (NEDERLANDS)

F: Aanbeveling (Nederlands)

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het inbrengen van een drain bij kinderen met kanker.

G: Overwegingen (Nederlands)

Er werd geen literatuur gevonden over dit onderwerp bij kinderen met kanker. Daarom is deze aanbeveling gebaseerd op de meningen van de experts in de werkgroep.
De werkgroep is van mening dat een profylactische trombocytentransfusie in deze groep geoorloofd is. De werkgroep is van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het inbrengen van een drain bij kinderen met kanker. De procedure is invasief en de kans op een bloeding is reëel. Ook zijn wij van mening dat de consequenties van een eventuele bloeding schadelijk kunnen zijn, zowel tijdens als na de procedure. Ook kan de bloeding niet makkelijk worden gecontroleerd.

De ASCO (3), NICE (2) en FMS (1) richtlijnen hebben hun aanbevelingen gebaseerd op zeer beperkt evidence en meningen van experts. De werkgroep erkent het belang van de door hun geformuleerde aanbevelingen op basis van expert opinions en wij nemen deze dan ook zorgvuldig mee in onze overwegingen in het evidence-to-decision proces. De aanbevelingen van deze richtlijnen zijn in lijn met onze expert opinions. Concluderend, is de werkgroep van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het inbrengen van een drain bij kinderen met kanker.

Module 9: Dental extraction (ENGLISH)

A: Recommendations

Research question: What is the effect of prophylactic platelet transfusion on

hemorrhagic events and other outcomes in children with cancer who need a dental extraction?

A1.1: Recommendation (English)

WEAK recommendation, EXPERT evidence	We believe a platelet threshold of $50x10^9$/L is sufficient in children with cancer who need a dental extraction.

B: Clinical question, search and selection

B1: Clinical question:

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need a dental extraction?

Patients = Children (aged 28 days-18 years) with cancer who need a dental extraction
Intervention = Prophylactic platelet transfusion (at any threshold)
Control = (No prophylactic platelet transfusion or transfusion at any other threshold)
Outcomes = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event free survival, procedure-related complications

B2: Literature search and study selection

For the complete methodology of this guideline development and the search strategy, we refer to pages 20-31.
Of 7486 unique citations identified in the literature search, zero studies with pediatric oncology patients were included for this clinical question.
Three additional guidelines (ASCO, NICE, FMS) were applicable to our clinical question.

C: Results in pediatric and adult oncology patients

C1.1 Evidence in pediatric oncology patients

In our literature search, 0 results were found for this clinical question.

C1.2 Evidence in adult oncology patients

From our additional searches, 0 results were found for this clinical question.

C1.3 Additional evidence guidelines (adults) and other

Firstly, the ASCO guideline recommends: "*A threshold of 40 $x10^9$/L to 50 $x10^9$/L is recommended for performing major invasive procedures in the absence of associated coagulation abnormalities (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: weak).* (3)*"*
They cite no evidence and their recommendation is mainly based on expert opinions.
The NICE guideline recommends: "*Consider prophylactic platelet transfusions to raise the platelet count above 50×10^9 per litre in patients who are having invasive procedures or surgery.* (2)"
Note that both ASCO (3) and NICE (2) do not specifically mention dental extraction as being an invasive procedure.
The FMS recommends that regarding dental extractions, they believe a threshold of $50x10^9$/L prior to the procedure is sufficient (1). No additional evidence was cited by all three guidelines and recommendations were mostly based on expert opinions.

An additional guideline by the American Academy of Pediatric Dentistry (AAPD) (16) was found, in which they recommend a threshold between 40-75x10^9/L is sufficient for dental procedures. They recommend that dental care should be deferred when the platelet count falls below 40x10^9/L.

D: Conclusion(s) of evidence (pediatric oncology patients):

0 studies in pediatric oncology patients were found.	**-**

E: Considerations

No evidence in pediatric oncology patients or adult oncology patients was found. Therefore, the guideline panel formed a recommendation based mainly on expert opinions.
The guideline panel believes that a prophylactic platelet transfusion is appropriate in this specific patient group. The panel believes that a platelet threshold of 50x10^9/L is sufficient in children with cancer who need a dental extraction. This procedure is invasive and has potential bleeding sites. Also, the mouth is well vascularized and can bleed easily.
The ASCO (3), NICE (2) and FMS (1) guidelines formed their recommendations based on limited evidence and expert opinions. The guideline panel recognizes the importance of their expert opinions, and carefully considered their recommendations in every evidence-to-decision for our clinical questions. These recommendations supported our decision making. Therefore, the panel recommends a platelet threshold of 50x10^9/L prior to a dental extraction.

Module 9: Tandextractie (NEDERLANDS)

F: Aanbeveling (Nederlands)

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het uitvoeren van een tandextractie bij kinderen met kanker.

G: Overwegingen (Nederlands)

Er werd geen literatuur gevonden over dit onderwerp bij kinderen met kanker. Daarom is deze aanbeveling gebaseerd op de meningen van de experts in de werkgroep.
De werkgroep is van mening dat een profylactische trombocytentransfusie in deze groep geoorloofd is. De werkgroep is van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het uitvoeren van een tandextractie bij kinderen met kanker. De procedure is invasief en de kans op een bloeding is reëel. De mond is goed gevasculariseerd en bloedt daarom makkelijk.

De ASCO (3), NICE (2) en FMS (1) richtlijnen hebben hun aanbevelingen gebaseerd op zeer beperkt evidence en meningen van experts. De werkgroep erkent het belang van de door hun geformuleerde aanbevelingen op basis van expert opinions en wij nemen deze dan ook zorgvuldig mee in onze overwegingen in het evidence-to-decision proces. De aanbevelingen van deze richtlijnen zijn in lijn met onze expert opinions. Concluderend, is de werkgroep van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het uitvoeren van een tandextractie bij kinderen met kanker.

Module 10: Enema (ENGLISH)

A: Recommendations

Research question: What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need an enema?

A1.1: Recommendation (English)

WEAK recommendation, EXPERT evidence	We believe that a prophylactic platelet transfusion is not necessary in children with cancer who need an enema.

B: Clinical question, search and selection

B1: Clinical question:

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need an enema?

Patients = Children (aged 28 days-18 years) with cancer who need an enema
Intervention = Prophylactic platelet transfusion (at any threshold)
Control = (No prophylactic platelet transfusion or transfusion at any other threshold)
Outcomes = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event free survival, procedure-related complications

B2: Literature search and study selection

For the complete methodology of this guideline development and the search strategy, we refer to pages 20-31.
Of 7486 unique citations identified in the literature search, zero studies with pediatric oncology patients were included for this clinical question.

C: Results in pediatric and adult oncology patients

C1.1 Evidence in pediatric oncology patients

In our literature search, 0 results were found for this clinical question.

C1.2 Evidence in adult oncology patients

From our additional searches, 0 results were found for this clinical question.

C1.3 Additional evidence guidelines (adults) and other

ASCO (3), NICE (2) and FMS (1) made 0 recommendations regarding this clinical question.

D: Conclusion(s) of evidence (pediatric oncology patients):

0 studies in pediatric oncology patients	-

were found.	

E: Considerations

No evidence in pediatric oncology patients or adult oncology patients was found. Therefore, the guideline panel formed a recommendation based mainly on expert opinions.
The panel believes that a prophylactic platelet transfusion prior to an enema is not necessary. We believe that the initial chance of a bleeding due to this procedure is very small. In addition, the panel feels that the potential bleeding that occur from the procedure, would be very small and limited, can be easily recognized (as the bleeding is visible) and managed if necessary. Therefore, the panel feels that a possible bleeding can be managed sufficiently and that a transfusion prior to the procedure is not necessary.

Module 10: Klysma (NEDERLANDS)

F: Aanbeveling (Nederlands)

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat er geen trombocytentransfusie nodig is voorafgaand aan een klysma bij kinderen met kanker.

G: Overwegingen (Nederlands)

Er werd geen literatuur gevonden over dit onderwerp bij kinderen met kanker. Daarom is deze aanbeveling gebaseerd op de meningen van de experts in de werkgroep.
De werkgroep is van mening dat er geen trombocytentransfusie nodig is voorafgaand aan een klysma bij kinderen met kanker. Mocht er een bloeding optreden door deze procedure dan zou deze waarschijnlijk klein en beperkt zijn, het zal snel worden herkend (omdat de bloeding zichtbaar is) en het is dan goed te controleren. Daarom ziet de werkgroep geen noodzaak tot een profylactische transfusie voorafgaand aan deze procedure.

Module 11: Intramuscular injections (ENGLISH)

A: Recommendations

Research question: What is the effect of prophylactic platelet transfusion on

hemorrhagic events and other outcomes in children with cancer who need an intramuscular injection?

A1.1: Recommendation (English)

WEAK recommendation, EXPERT evidence	We believe that a prophylactic platelet transfusion is not necessary in children with cancer who need an intramuscular injection (including vaccination, provided that pressure is applied at the injection site for 10 minutes.

B: Clinical question, search and selection

B1: Clinical question:

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need an intramuscular injection?

Patients = Children (aged 28 days-18 years) with cancer who need an intramuscular injection
Intervention = Prophylactic platelet transfusion (at any threshold)
Control = (No prophylactic platelet transfusion or transfusion at any other threshold)
Outcomes = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event free survival, procedure-related complications

B2: Literature search and study selection

For the complete methodology of this guideline development and the search strategy, we refer to pages 20-31.
Of 7486 unique citations identified in the literature search, zero studies with pediatric oncology patients were included for this clinical question.

C: Results in pediatric and adult oncology patients

C1.1 Evidence in pediatric oncology patients

In our literature search, 0 results were found for this clinical question.

C1.2 Evidence in adult oncology patients

From our additional searches, 0 results were found for this clinical question.

C1.3 Additional evidence guidelines (adults) and other

ASCO (3), NICE (2) and FMS (1) made 0 recommendations regarding this clinical question.

D: Conclusion(s) of evidence (pediatric oncology patients):

0 studies in pediatric oncology patients	**-**

were found.	

E: Considerations

No evidence in pediatric oncology patients or adult oncology patients was found. Therefore, the guideline panel formed a recommendation based mainly on expert opinions.
The guideline panel has used various protocols and national advices in the considerations. The guideline panel feels that for a primary clotting disorder as thrombocytopenia, applying pressure at the injection site will be very efficient in preventing bleeding, due to the pathogenesis of the clotting disorder. The guideline feels that, in agreement with a Dutch advice "*Update COVID vaccinatie hematologische patiënten*" on 24.03.2021 by the *Nederlandse Vereniging voor Hematologie* (17) that a prophylactic platelet transfusion is not necessary provided that pressure is applied at the injection site for 10 minutes. When an intramuscular injection is given, it is advised that the smallest needle should be used.

The panel believes that a prophylactic platelet transfusion prior to an intramuscular injection is not necessary. The potential bleeding site that is created with the IM needle is superficial and small, and a sufficient amount of pressure can be exerted on the skin locally. Therefore, the panel feels that a possible bleeding can be managed sufficiently by exerting pressure after IM injection and that a transfusion prior to the procedure is not necessary provided that pressure is applied at the injection site for 10 minutes.

Module 11: Intramusculaire injecties (NEDERLANDS)

F: Aanbeveling (Nederlands)

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat er geen trombocytentransfusie nodig is voorafgaand aan een intramusculaire injectie (bijvoorbeeld vaccinatie) bij kinderen met kanker, gegeven dat de injectieplaats gedurende 10 minuten afgedrukt wordt.

G: Overwegingen (Nederlands)

Er werd geen literatuur gevonden over dit onderwerp bij kinderen met kanker. Daarom is deze aanbeveling gebaseerd op de meningen van de experts in de werkgroep.

De werkgroep heeft verschillende protocollen en adviezen meegenomen in de overwegingen. De werkgroep is van mening dat bij patiënten met een trombopenie, een primaire stollingsstoornis, afdrukken van de plek efficiënt is vanwege pathogenese van dit type stollingsstoornis. De werkgroep is van mening, in overeenstemming van het advies “Update COVID vaccinatie hematologische patiënten” op 24.03.2021 door de Nederlandse Vereniging voor Hematologie (17) dat er geen profylactische trombocyten transfusie nodig is, op voorwaarde dat de injectieplaats gedurende 10 minuten goed kan worden afgedrukt. Indien een intramusculaire injectie toegediend moet worden dan wordt geadviseerd, wanneer dit mogelijk is, om de kleinst mogelijke naald te gebruiken.

De werkgroep is van mening dat er geen trombocytentransfusie nodig is voorafgaand aan een intramusculaire injectie (bijvoorbeeld vaccinatie) bij kinderen met kanker. De wond die wordt gecreëerd door de injectie is oppervlakkig en klein, en kan goed worden afgedrukt. Daarom ziet de werkgroep geen noodzaak tot een profylactische transfusie voorafgaand aan deze procedure, op voorwaarde dat de injectieplaats gedurende 10 minuten goed kan worden afgedrukt.

Module 12: Intubation (ENGLISH)

A: Recommendations

Research question: What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need a (non-urgent) intubation?

A1.1: Recommendation (English)

WEAK recommendation, EXPERT evidence	We believe a platelet threshold of $20x10^9$/L is sufficient in children with cancer who need a planned, non-urgent oral endotracheal intubation.

WEAK recommendation, EXPERT EVIDENCE	We believe a platelet threshold of $50x10^9$/L is sufficient in children with cancer need a planned, non-urgent nasal intubation.

B: Clinical question, search and selection

B1: Clinical question:

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need a (non-urgent) intubation?

Patients = Children (aged 28 days-18 years) with cancer who need a (non-urgent) intubation
Intervention = Prophylactic platelet transfusion (at any threshold)
Control = (No prophylactic platelet transfusion or transfusion at any other threshold)
Outcomes = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event free survival, procedure-related complications

B2: Literature search and study selection

For the complete methodology of this guideline development and the search strategy, we refer to pages 20-31.

Of 7486 unique citations identified in the literature search, zero studies with pediatric oncology patients were included for this clinical question.

C: Results in pediatric and adult oncology patients

C1.1 Evidence in pediatric oncology patients

In our literature search, 0 results were found for this clinical question.

C1.2 Evidence in adult oncology patients

From our additional searches, 0 results were found for this clinical question.

C1.3 Additional evidence guidelines (adults) and other

ASCO (3), NICE (2) and FMS (1) made 0 recommendations regarding this clinical question.

D: Conclusion(s) of evidence (pediatric oncology patients):

0 studies in pediatric oncology patients were found.	**-**

E: Considerations

No evidence in pediatric oncology patients or adult oncology patients was found. Therefore, the guideline panel formed a recommendation based mainly on expert opinions.
Firstly, the guideline panel clearly states that these recommendations apply to planned, non-urgent intubation. When the intubation is (semi) urgent, the platelet transfusion is obviously inferior to a fast intubation. These recommendations do therefore not apply for (semi) urgent situations in which rapid intubation is required.

Based on experience and expert opinions, the panel felt like a difference should be made between oral endotracheal and nasal intubation.
The guideline panel believes that a prophylactic platelet transfusion is appropriate in this specific patient group. The panel believes that a platelet threshold of $50x10^9$/L is sufficient in children with cancer who need a planned, non-urgent nasal intubation. The nasal route of intubation is very narrow, well vascularized and can therefore bleed easily. When a bleeding does occur, vision can get impaired and that might severely affect the intubation. We believe that the potential consequences of a bleed during this procedure could be harmful. In addition, the potential bleeding cannot be managed easily.

The panel believes that a platelet threshold of $20x10^9$/L is sufficient in children with cancer who need a planned, non-urgent oral endotracheal intubation. This route is more accessible, is less vascularized and bleeds less easily. When a bleeding does occur, vision probably can be maintained and would be less likely to affect the intubation. We believe that the potential consequences of a bleed during this procedure in general are less harmful than a nasal intubation. In addition, the potential bleeding can be managed more easily than with nasal intubation.

Therefore, the guideline panel feels comfortable in lowering the threshold for non-urgent, planned oral endotracheal intubation to $20x10^9$/L. The threshold for non-urgent, planned nasal intubation is set on $50x10^9$/L because of higher risk of bleeding and complications

Module 12: Intubatie (NEDERLANDS)

F: Aanbeveling (Nederlands)

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van 20x10^9/L voldoende is voor een geplande, niet-spoedeisende orale endotracheale intubatie bij kinderen met kanker.

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van 50x10^9/L voldoende is voor een geplande, niet-spoedeisende nasale intubatie bij kinderen met kanker.

G: Overwegingen (Nederlands)

Er werd geen literatuur gevonden over dit onderwerp bij kinderen met kanker. Daarom is deze aanbeveling gebaseerd op de meningen van de experts in de werkgroep.
Ten eerste, de werkgroep benadrukt dat deze aanbeveling toepasbaar is op geplande, niet-spoedeisende intubaties. Wanneer de intubatie (semi) urgent is, is de grens van trombocyten uiteraard inferieur aan het snel intuberen van de patiënt. Deze aanbevelingen gelden dus niet voor (semi) urgente situaties waarin een snelle intubatie vereist is.

De werkgroep is van mening dat een profylactische trombocytentransfusie in deze groep geoorloofd is. Op basis van expert opinions hebben we een onderscheid gemaakt tussen orale endotracheale intubatie en nasale intubatie. De werkgroep is van mening dat een trombocytengrens van 50x10^9/L voldoende is voor een geplande, niet-spoedeisende nasale intubatie bij kinderen met kanker. De nasale route van intubatie is zeer smal, goed gevasculariseerd en bloedt daarom makkelijk. Wanneer een bloeding optreedt, kan het zicht tijdens intubatie beperkt raken en dit kan de procedure zeer belemmeren. Bovendien kunnen dit soort bloedingen niet makkelijk gecontroleerd worden. Wij vinden dat de potentiële consequenties van dit soort bloedingen schadelijk kan zijn.

De werkgroep is van mening dat een trombocytengrens van 20x10^9/L voldoende is voor een geplande, niet-spoedeisende orale endotracheale intubatie bij kinderen met kanker. Deze route is toegankelijker, minder goed gevasculariseerd in vergelijking met de nasale route en daarom is de kans op een bloeding aldaar kleiner. Als hier een bloeding ontstaat, kan het zicht beter worden behouden en is er dus minder effect op de intubatie. Bovendien kan een bloeding alhier makkelijker gecontroleerd worden. Wij zijn van mening dat de potentiële consequenties van dit soort bloedingen minder schadelijk zijn dan die van de nasale intubatie.

Daarom is de werkgroep van mening de grens voor geplande, niet-spoedeisende orale endotracheale intubatie te verlagen naar 20 x10^9/L, en de grens voor geplande, niet-spoedeisende nasale intubatie te zetten op 50x10^9/L

Module 13: Line insertion or removal (ENGLISH)

A: Recommendations

Research question: What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need a line insertion or removal?

A1.1: Recommendation (English)

WEAK recommendation, EXPERT evidence	We believe a platelet threshold of $50x10^9$/L is sufficient for children with cancer who need a tunneled central venous line insertion or removal.

WEAK recommendation, EXPERT EVIDENCE	We believe a platelet threshold of $10x10^9$/L is sufficient for children with cancer who receive an ultrasound-guided line insertion of a non-tunneled central line or peripherally inserted central catheter (PICC). We believe a platelet threshold of $10x10^9$/L is sufficient for children with cancer for removal of a non-tunneled central line or PICC.

B: Clinical question, search and selection

B1: Clinical question:

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need a line insertion or removal?

Patients = Children (aged 28 days-18 years) with cancer who need a line insertion or removal
Intervention = Prophylactic platelet transfusion (at any threshold)
Control = (No prophylactic platelet transfusion or transfusion at any other threshold)
Outcomes = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event free survival, procedure-related complications

B2: Literature search and study selection

For the complete methodology of this guideline development and the search strategy, we refer to pages 20-31.
Of 7486 unique citations identified in the literature search, zero studies with pediatric oncology patients were included for this clinical question.
Three additional guidelines (ASCO, NICE, FMS) were applicable to our clinical question.

C: Results in pediatric and adult oncology patients

C1.1 Evidence in pediatric oncology patients

In our literature search, 0 results were found for this clinical question.

C1.2 Evidence in adult oncology patients

From our additional searches, 0 results were found for this clinical question.

C1.3 Additional evidence guidelines (adults) and other
Firstly, the ASCO guideline recommends: "*A threshold of 40 x10^9/L to 50 x10^9/L is recommended for performing major invasive procedures in the absence of associated coagulation abnormalities. Certain procedures, such as (…) removal of central venous catheters, can be performed safely at counts < 20x10^9. (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: weak).* (3)" They cite no evidence and their recommendation is mainly based on expert opinions.
The NICE guideline recommends: "*Consider prophylactic platelet transfusions to raise the platelet count above 50×10^9 per litre in patients who are having invasive procedures or surgery.* (2)". Note that NICE does not specifically mention central venous catheter insertion as being an invasive procedure.
The FMS recommends that regarding central venous catheter insertion, they believe a threshold of 50x10^9/L prior to the procedure is sufficient (1).
No additional evidence was cited by all three guidelines and recommendations were mostly based on expert opinions.

D: Conclusion(s) of evidence (pediatric oncology patients):

0 studies in pediatric oncology patients were found.	**-**

E: Considerations
No evidence in pediatric oncology patients or adult oncology patients was found. Therefore, the guideline panel formed a recommendation based mainly on expert opinions.
The guideline panel believes that a prophylactic platelet transfusion is appropriate in this specific patient group. The panel believes that a platelet threshold of 50x10^9/L is sufficient in children with cancer who need a tunneled line insertion. This procedure is invasive and has potential bleeding sites. We believe that the potential consequences of a bleed during or after the procedure could be harmful. In addition, the potential bleeding cannot be managed easily. Therefore, for all tunneled lines, a threshold of 50x10^9/L is recommended.

However, based on experience and expert opinions, the panel felt like a difference should be made between tunneled and non-tunneled lines. The guideline panel felt that lines with a lower risk of bleeding should have a different threshold. The panel discussed the 'lower bleeding risk' line insertions and decided on the ultrasound-guided line insertion of non-tunneled lines and also the removal of these type of lines. For these procedures, as the caregiver inserting the line has direct view on the insertion site through the ultrasound probe, potential bleeding will be visible and can then be managed.
The guideline panel feels that this procedure cannot be performed *without* any prophylactic platelet transfusion because of the potential harms (see above), but that a threshold of <20x10^9/L would be too high. By choosing a threshold of <10x10^9/L we prevent unnecessary platelet transfusions, still considering the benefits and harms of a possible bleeding episode because of the procedure. This is a deviation from the recommendation of the FMS (1) guideline, but the arguments for deviation are both *experience* as *practice based*.
The ASCO (3), NICE (2) and FMS (1) guidelines formed their recommendations based on limited evidence and expert opinions. The guideline panel recognizes the importance of their

expert opinions, and carefully considered their recommendations in every evidence-to-decision for our clinical questions. The recommendations partially support our decision making. The guideline panel feels comfortable in lowering the threshold for ultrasound-guided non-tunneled line insertions. The threshold for tunneled line insertion remains $50x10^9$/L in line with the other recommendations.

Module 13: Lijnen (NEDERLANDS)

F: Aanbeveling (Nederlands)

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het inbrengen of verwijderen van een getunnelde centraal veneuze lijn bij kinderen met kanker.

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $10x10^9$/L voldoende is voor het echogeleid inbrengen van een niet-getunnelde centraal veneuze lijn of een PICC lijn (perifeer ingebrachte centrale lijn) bij kinderen met kanker. De werkgroep is van mening dat een trombocytengrens van $10x10^9$/L voldoende is voor het verwijderen van een niet-getunnelde centraal veneuze lijn of een PICC lijn bij kinderen met kanker.

G: Overwegingen (Nederlands)

Er werd geen literatuur gevonden over dit onderwerp bij kinderen met kanker. Daarom is deze aanbeveling gebaseerd op de meningen van de experts in de werkgroep.
De werkgroep is van mening dat een profylactische trombocytentransfusie in deze groep geoorloofd is. De werkgroep is van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het inbrengen of verwijderen van een getunnelde centraal veneuze lijn bij kinderen met kanker. De procedure is invasief en de kans op een bloeding is reëel. Ook zijn wij van mening dat de consequenties van een eventuele bloeding schadelijk kunnen zijn, zowel tijdens als na de procedure. Ook kan de bloeding niet makkelijk worden gecontroleerd.

Echter, gebaseerd op meningen uit de werkgroep, is een andere grens nodig voor getunnelde lijnen en niet-getunnelde lijnen. De werkgroep is van mening dat het inbrengen van lijnen met een lager risico op bloeding, ook een andere grens moeten hebben. De werkgroep vindt dat niet-getunnelde lijnen die echo-geleid worden ingebracht, hieronder vallen. Ook het verwijderen van deze niet-getunnelde lijnen heeft een lager risico op bloeding. Bij deze procedures heeft de zorgverlener die de lijn inbrengt of verwijdert direct zicht op eventuele bloedingen en kan er ook direct gehandeld worden, indien nodig.
De werkgroep is dus van mening dat deze procedure niet uitgevoerd moet worden *zonder* profylactische trombocyten transfusie vanwege de mogelijke nadelen (zie bovenstaande argumenten), maar dat een grens van bijvoorbeeld $<20x10^9$/L te hoog zou zijn. Door een grens van $<10x10^9$/L aan te houden voorkomen we onnodige trombocytentransfusies, in acht nemend de voor- en nadelen van een transfusie en de mogelijke consequenties van een bloeding na de procedure. Er wordt hiermee afgeweken van de aanbeveling van de FMS (1), maar de voornaamste argumenten om hiervan af te wijken zijn *experience* en *practice based*.

De ASCO (3), NICE (2) en FMS (1) richtlijnen hebben hun aanbevelingen gebaseerd op zeer beperkt evidence en meningen van experts. De werkgroep erkent het belang van de door hun geformuleerde aanbevelingen op basis van expert opinions en wij nemen deze dan ook zorgvuldig mee in onze overwegingen in het evidence-to-decision proces. De aanbevelingen van deze richtlijnen zijn in deels lijn met onze expert opinions. De werkgroep staat achter het

verlagen van de grens voor niet-getunnelde lijnen. De grens voor getunnelde lijnen blijft $50x10^9$/L in lijn met de andere richtlijnen.

Module 14: Lumbar puncture (ENGLISH)

A: Recommendations

Research question: What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need a lumbar puncture?

A1.1: Recommendation (English)

WEAK recommendation, VERY LOW QUALITY evidence	We suggest that a platelet threshold of $10x10^9$/L is sufficient in children with cancer *without* leukemic blasts in their peripheral blood who need a lumbar puncture.

STRONG recommendation, EXPERT EVIDENCE	We strongly believe a platelet threshold of $50x10^9$/L should be maintained in children (with cancer) *with* leukemic blasts in their peripheral blood who need a lumbar puncture.

B: Clinical question, search and selection

B1: Clinical question:

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need a lumbar puncture?

Patients = Children (aged 28 days-18 years) with cancer who need a lumbar puncture
Intervention = Prophylactic platelet transfusion (at any threshold)
Control = (No prophylactic platelet transfusion or transfusion at any other threshold)
Outcomes = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event free survival, procedure-related complications, influence on outcome material

B2: Literature search and study selection

For the complete methodology of this guideline development and the search strategy, we refer to pages 20-31.
Of 7486 unique citations identified in the literature search, two studies with pediatric oncology patients (Howard et al (2000) (18), Foerster et al (2014) (19)) were included for this clinical question.
One additional guideline (FMS) was applicable to our clinical question.

C: Results in pediatric and adult oncology patients

C1.1 Evidence in pediatric oncology patients

In our literature search, 2 results were found for this clinical question.
One study by Howard et al (2000) (18) was a retrospective cohort study which included 958 patients. Their median age was 5.5 years (range 1 month-18 years) and they were all diagnosed with acute lymphoblastic leukemia (ALL). They reported on patients who underwent a lumbar puncture. Groups were defined by platelet level, first group platelet level of $1\text{-}5\times10^9$/L, second group $5\text{-}10\times10^9$/L, third group $11\text{-}20\times10^9$/L etc.
The second study by Foerster et al (2014) (19) was a cross-sectional observation study with 440 patients. The average age was 7.8 years (range 1 month-20.9 years) and the children were mostly diagnosed with leukemia, but also with other oncology diagnoses. They reported on patients who underwent a lumbar puncture. Groups were defined by platelet level, first group platelet level of $<10\times10^9$/L, second group $10\text{-}20\times10^9$/L, third group $30\text{-}40\times10^9$/L etc.

C.1.1.1 Severe hemorrhagic event

A severe hemorrhagic event in the study by Howard et al was defined as any neurologic, infectious or hemorrhagic problems that resulted from the LP. They reported a severe hemorrhagic event in 0 out of 5223 lumbar punctures (18).
Foerster et al defined their main outcome severe hemorrhagic event as a spinal hematoma. A spinal hematoma was reported in 0 out of 9088 lumbar punctures (19).

C.1.1.2 Influence on outcome material

Both studies reported the total incidence of traumatic lumbar puncture, i.e. the presence of red blood cells in the liquor after lumbar puncture. Howard et al report 10.5% of procedures were traumatic lumbar punctures (total of 5223 = 548 traumatic LPs) (18). Foerster et al report a traumatic LP in 16.9% of lumbar punctures (1112 LPs) (19). Unfortunately, in both studies, it was not reported which platelet level these patients had at the time of the lumbar puncture.

Table 6: Study characteristics Howard, 2000 and Foerster, 2014

Article Author, year Study type	**Population a. No. of patients b. Population**	**Case group* a. Group definition b. No. of patients, age, gender (% males)**	**Control Group a. Group definition b. No. of patients, age, gender (% males)**	**Included outcomes**	**Risk of bias assessment a. Selection bias b. Attrition bias c. Detection bias d. Reporting bias e. Confounding bias f. Other bias**
Howard, 2000 Retrospective cohort study	a. 958 patients b. Median age 5.5 years (range 1 month-18 years) c. 524 males (55%) d. Acute lymphoblastic leukemia (ALL)	a. Patients who undergo a lumbar puncture. Groups were defined by platelet level, first group platelet level of 1-5 $\times 10^9$/L, second group 5-10$\times 10^9$/L, third group 11-20 $\times 10^9$/L etc. b. Not reported c. Not reported	- Severe hemorrhagic event - Influence on outcome material	a. Low b. High c. Low d. Unclear e. High f. High	Howard, 2000 Retrospective cohort study
Foerster, 2014 Cross-sectional observation study	a. 440 patients b. Average age 7.8 years (range 1 month-20.9 years) c. 269 males (60.6%) d. Leukemia and other cancer diagnoses	a. Patients who undergo a lumbar puncture. Groups were defined by platelet level, first group platelet level of <10 $\times 10^9$/L, second group 10-20 $\times 10^9$/L, third group 30-40 $\times 10^9$/L etc. b. Not reported c. Not reported	- Severe hemorrhagic event (spinal hematoma) - Influence on outcome material	a. Low b. High c. Low d. Unclear e. High f. High	Foerster, 2014 Cross-sectional observation study

*or possible risk factor group, or intervention group

Table 7: Outcomes Howard, 2000 and Foerster, 2014 – Severe hemorrhagic event

Author, study design	**No. of participants, total (cases vs controls) & Group definition**	**Results**	**Statistical methods**	**Effect size**	**Quality of evidence**

1) Howard, 2000 Retrospective cohort study	1) Pediatric patients with ALL or AML undergoing a lumbar puncture at different platelet levels. Severe hemorrhagic event was defined as any neurologic, infectious or hemorrhagic problems that resulted from the LP.	1) Severe hemorrhagic event: 0/5223 LPs Exact numbers stated in Table 8.	1) 95% Confidence Interval for complications	1) Stated before per platelet count level	⊕◯◯◯[B] VERY LOW
2) Foerster, 2014 Cross sectional observational study	2) Pediatric oncology patients who undergo a lumbar puncture at different levels of platelet count.	2) Spinal hematoma in 0/9088 LPs. Spinal hematoma in: 0/379 LPs performed with platelet count <50 $\times 10^9$/L. 0/25 LPs performed with platelet count <10 $\times 10^9$/L 0/67 LPs performed with platelet count 10-20 $\times 10^9$/L 0/88 LPs performed with platelet count 20-30 $\times 10^9$/L 0/92 LPs performed with platelet count 30-40 $\times 10^9$/L 0/107 LPs performed with platelet count 40-50 $\times 10^9$/L 0/729 LPs performed with platelet count 50-100 $\times 10^9$/L 0/7980 LPs performed with platelet count >100 $\times 10^9$/L	2) Not reported	2) Not reported	⊕◯◯◯[C] VERY LOW

B: GRADE: Grade quality assessment severe hemorrhagic event in children with cancer undergoing a lumbar puncture: design is observational study, inconsistency not serious, indirectness not serious, imprecision not serious, publication bias unlikely, downgraded 1 level because of serious risk of bias (selection bias low, attrition bias high, detection bias low, reporting bias unclear, confounding bias high, other bias high)

C: GRADE: Grade quality assessment severe hemorrhagic event in children with cancer undergoing a lumbar puncture: design is observational study, inconsistency not serious, indirectness not serious, imprecision not serious, publication bias unlikely, downgraded 1 level because of serious risk of bias (selection bias low, attrition bias high, detection bias low, reporting bias unclear, confounding bias high, other bias high)

Table 8: Outcomes Howards, 2000 – Severe hemorrhagic events, specified

Platelet count $\times 10^9$/L	Number of LPs	Number of complications	95% CI for complications
1-5	6	0	0-40.19
6-10	23	0	0-13.21
11-20	170	0	0-2.05

21-30	234	0	0-1.49
31-40	235	0	0-1.48
41-50	273	0	0-1.27
51-100	858	0	0-0.40
>100	3424	0	0- 0.10
Total	**5223**	0	**0-0.07**

Table 9: Outcomes Howard, 2000 and Foerster, 2014 – Influence on outcome material

Author, study design	**No. of participants, total (cases vs controls) & Group definition**	**Results**	**Statistical methods**	**Effect size**	**Quality of evidence**
1) Howard, 2000 Retrospective cohort study	1) Pediatric patients with ALL or AML undergoing a lumbar puncture at different platelet levels.	1) 1A) In group with platelet count <20 x10^9/L, 111/258 (43%) traumatic lumbar punctures versus 1498/5248 (29%) traumatic LPs in group with platelet count >20 x10^9/L. 1B) In group with platelet count <50 x10^9/L, 427/1007 (42%) traumatic lumbar punctures versus 1182/4499 (26%) traumatic LPs in group with platelet count >50 x10^9/L. 1C) In group with platelet count <100 x10^9/L, 753/1900 (40%) traumatic lumbar punctures versus 856/3606 (24%) traumatic LPs in group with platelet count >100 x10^9/L. **Traumatic lumbar puncture defined as >10 RBC or more	1A) % traumatic LP in 2 groups *Calculated with RevMan (Risk Ratio) 1B)% traumatic LP in 2 groups * RevMan (Risk Ratio) 1C)% traumatic LP in 2 groups * RevMan (Risk Ratio)	1A) 43% vs 29% *RR 1.15 [1.30-1.75] 1B) 42% vs 26% *RR 1.61 [1.48-1.76] 1C) 40% vs 24% *RR 1.54 [1.54-1.81]	1) ⊕◯◯◯[D] VERY LOW
2) Foerster, 2014 Observational study	2) Pediatric oncology patients who undergo a lumbar puncture at different levels of platelet count.	2) 16.9% of LPs (1112 LPs) were traumatic LPs. Not reported which platelet level these patients had.	2) Not reported	2) Not reported	Not applicable

D: GRADE: Grade quality assessment influence on outcome material in children with cancer undergoing a lumbar puncture: design is observational study, inconsistency not serious, indirectness not serious, imprecision not serious, publication bias unlikely, downgraded 1 level because of serious risk of bias (selection bias low, attrition bias high, detection bias low, reporting bias unclear, confounding bias high, other bias high)

C1.2 Evidence in adult oncology patients
From our additional searches, 0 results were found for this clinical question.

C1.3 Additional evidence guidelines (adults) and other
ASCO (3) and NICE (2) made 0 recommendations regarding this clinical question.

The FMS (1) recommends a threshold of 20x10^9/L for a lumbar puncture, and recommends a threshold of 50x10^9/L when blasts are present in the peripheral blood. No additional evidence was cited and the recommendation was based on expert opinions.

D: Conclusion(s) of evidence (pediatric oncology patients):

Severe hemorrhagic events:

⊕◯◯◯ (1 study)[B*] **VERY LOW** QUALITY OF EVIDENCE	In one study, no severe hemorrhagic events occurred in patients with different levels of platelet count.

⊕◯◯◯ (1 study)[C*] **VERY LOW** QUALITY OF EVIDENCE	In one study, no severe hemorrhagic events (spinal hematoma) occurred in patients with different levels of platelet count.

Influence on outcome material:

⊕◯◯◯ (1 study)[D*] **VERY LOW** QUALITY OF EVIDENCE	In one study, significantly more traumatic lumbar punctures were observed in the group with platelet count <20 ×10^9/L compared to the group with platelet count >20 ×10^9/L, <50 ×10^9/L versus >50 ×10^9/L and <100 ×10^9/L versus >100 ×10^9/L.

***** The letter refers to the specific GRADE assessment described in section C1.

E: Considerations

For this clinical question, two observational studies in pediatric oncology patients were assessed.

In the development of this guideline, the guideline panel defined critical, important and low important outcomes. One of those predefined critical outcomes, was severe hemorrhage defined as WHO grade 3 or 4 bleeding or defined as hemorrhage leading to severe and permanent damage, severe morbidity, severe brain-bleeding, bleeding associated with severe hemodynamic instability, fatal bleeding. These two studies with a total of n=14 311 lumbar punctures, showed 0 results of severe hemorrhagic events.

One of our other outcomes was influence on outcome material. If a patient has leukemic blasts in the peripheral blood, and they end up in the liquor sample because of a traumatic lumbar puncture, it can be of great consequence for their treatment. For example, for children with ALL, they would need extra rounds of intrathecal chemotherapy. This is, because you are unable to determine if the leukemic blasts you find in the liquor sample are from the peripheral blood, or if the blasts have migrated to the liquor. Therefore, your central nervous system status is labeled positive and that has consequences for further therapy. These two studies unfortunately do not show the percentages of traumatic LPs per group, but they do provide a total percentage. They report a traumatic LP in 10-16% of all punctures. It is not known how many of these lumbar punctures were performed at important diagnostic moments during therapy.

The guideline panel believes that a prophylactic platelet transfusion is appropriate in this specific patient group. Firstly, the guideline panel strongly believes that a platelet threshold of 50x10^9/L is sufficient in children with cancer *with* leukemic blasts in their peripheral blood who need to undergo a lumbar puncture. Because the incidence of a traumatic LP is rather high, and

because of the possible consequences this traumatic LP has on further therapy, the guideline panel is comfortable in setting a higher threshold for this situation.

Then, the panel believes that a platelet threshold of $10x10^9$/L is sufficient in children with cancer without blasts in their peripheral blood who need to undergo a lumbar puncture. We feel that a prophylactic transfusion threshold is necessary, because of the chance of severe hemorrhagic events, which you definitely want to prevent in the central nervous system. However, the panel feels that a threshold higher than $10x10^9$/L is not necessary. The panel considers the threshold of $10x10^9$/L safe, based on experience in the center of our experts.

The FMS guideline (1) forms its recommendation based on very limited evidence and expert opinions. The guideline panel recognizes the importance of their expert opinions, and carefully considered their recommendations in every evidence-to-decision for our clinical questions.
The guideline panel is aware that the FMS guideline recommends a higher threshold than we do now. However, we feel that a threshold of $10x10^9$/L is also safe and prevents, given the frequency of the amount of lumber punctures the children have to undergo, a lot of unnecessary transfusions with all its risks.

Module 14: Lumbaal punctie (NEDERLANDS)

F: Aanbeveling (Nederlands)

ZWAKKE aanbeveling, ZEER LAGE KWALITEIT evidence	Wij suggereren dat een trombocytengrens van $10x10^9$/L voldoende is voor het uitvoeren van een lumbaalpunctie bij kinderen met kanker *zonder* leukemische blasten in het bloed.

STERKE aanbeveling, EXPERT evidence	De werkgroep is sterk van mening dat een trombocytengrens van 50x10^9/L aangehouden zou moeten worden voor het uitvoeren van een lumbaalpunctie bij kinderen (met kanker) *met* leukemische blasten in het bloed.

G: Overwegingen (Nederlands)

Voor dit specifieke onderwerp, werden twee observationele studies gevonden in kinderen met kanker. Tijdens de ontwikkeling van deze richtlijn heeft de werkgroep '*critical, important en low important'* uitkomsten gedefinieerd. Eén van deze uitkomsten was ernstige bloedingen, gedefinieerd als WHO graad 3 of 4 bloedingen of bloedingen die leiden tot ernstige en permanente schade, ernstige morbiditeit, ernstige hersenbloedingen, bloeding geassocieerd met ernstige hemodynamische instabiliteit of fatale bloeding.
Deze twee studies beschreven in totaal n= 14 311 lumbaal puncties, waarvan er bij geen enkel hiervan een ernstige bloeding werd beschreven.

Een andere uitkomst was invloed op het materiaal. Als een patiënt leukemische blasten in het perifere bloed heeft, en deze terecht komen in de liquor door een traumatische lumbaalpunctie, kan dit grote gevolgen hebben voor de behandeling van deze patiënten. Bijvoorbeeld, kinderen met ALL zullen dan meer behandelingen met intrathecale chemotherapie nodig hebben. Dit komt doordat je niet met zekerheid kan zeggen of de blasten komen van bloed dat bij de traumatische punctie aanwezig was, of daadwerkelijk in de liquor zaten. Hierdoor wordt de "CNS" status van een patiënt positief en dit kan dus consequenties hebben voor hun verdere therapie.
Deze twee studies laten helaas niet het percentage van traumatische LPs per groep zien, maar ze laten wel een totaal percentage zien. Ze rapporteren een traumatische LP in 10-16% van alle procedures. Het is niet bekend hoeveel van deze LPs uitgevoerd werd bij diagnose – een belangrijk meetmoment.

De werkgroep is van mening dat een profylactische trombocytentransfusie in deze groep geoorloofd is. Allereerst is de werkgroep van mening dat een trombocytengrens van 50x10^9/L aangehouden zou moeten worden voor het uitvoeren van een lumbaalpunctie bij kinderen (met kanker) *met* leukemische blasten in het bloed. Dit omdat de incidentie van een traumatische LP vrij hoog is en vanwege de potentiële consequenties dit heeft, zoals hierboven benoemd.

Ten tweede is de werkgroep van mening dat een trombocytengrens van 10x10^9/L voldoende is voor het uitvoeren van een lumbaalpunctie bij kinderen met kanker *zonder* leukemische blasten in het bloed. Wij vinden dat een profylactische transfusie nodig is, omdat je een ernstige bloeding te allen tijde dient te voorkomen. Een grens hoger dan 10x10^9/L vinden wij niet noodzakelijk, mede gezien de ervaringen van onze experts.

De FMS (1) richtlijn heeft zijn aanbevelingen gebaseerd op zeer beperkt evidence en meningen van experts. De werkgroep erkent het belang van de door hun geformuleerde aanbevelingen op basis van expert opinions en wij nemen deze dan ook zorgvuldig mee in onze overwegingen in het evidence-to-decision proces. De werkgroep is zich bewust van het feit dat de FMS een hogere grens aanbeveelt. Echter zijn wij van mening dat een grens van 10x10^9/L veilig is, mede

in acht nemend dat kinderen met kanker frequent LPs ondergaan en dat elke keer een (onnodige) transfusie tot een *nog* hogere grens niet gewenst is.

Module 15: Lymph node biopsy (ENGLISH)

A: Recommendations

Research question: What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need a lymph node biopsy?

A1.1: Recommendation (English)

WEAK recommendation, EXPERT evidence	We believe a platelet threshold of $50x10^9$/L is sufficient in children with cancer who need a lymph node biopsy (both needle

	and excision biopsy).

B: Clinical question, search and selection

B1: Clinical question:

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need a lymph node biopsy?

Patients = Children (aged 28 days-18 years) with cancer who need a lymph node biopsy
Intervention = Prophylactic platelet transfusion (at any threshold)
Control = (No prophylactic platelet transfusion or transfusion at any other threshold)
Outcomes = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event free survival, procedure-related complications, influence on outcome material

B2: Literature search and study selection

For the complete methodology of this guideline development and the search strategy, we refer to pages 20-31.
Of 7486 unique citations identified in the literature search, zero studies with pediatric oncology patients were included for this clinical question.
Three additional guidelines (ASCO, NICE, FMS) were applicable to our clinical question.

C: Results in pediatric and adult oncology patients

C1.1 Evidence in pediatric oncology patients

In our literature search, 0 results were found for this clinical question.

C1.2 Evidence in adult oncology patients

From our additional searches, 0 results were found for this clinical question.

C1.3 Additional evidence guidelines (adults) and other

Firstly, the ASCO guideline recommends: "*A threshold of 40 x10^9/L to 50 x10^9/L is recommended for performing major invasive procedures in the absence of associated coagulation abnormalities (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: weak).* (3)"They cite no evidence and their recommendation is mainly based on expert opinions.

The NICE guideline recommends: "*Consider prophylactic platelet transfusions to raise the platelet count above 50×10^9 per litre in patients who are having invasive procedures or surgery.* (2)"
The FMS recommends that regarding surgical procedures, they believe a threshold of 50x10^9/L prior to the procedure is sufficient (1).
No additional evidence was cited by all three guidelines and recommendations were mostly based on expert opinions.

D: Conclusion(s) of evidence (pediatric oncology patients):

0 studies in pediatric oncology patients were found.	**-**

E: Considerations

No evidence in pediatric oncology patients or adult oncology patients was found. Therefore, the guideline panel formed a recommendation based mainly on expert opinions.
The guideline panel believes that a prophylactic platelet transfusion is appropriate in this specific patient group. The panel believes that a platelet threshold of $50x10^9$/L is sufficient in children with cancer who need a lymph node biopsy. This procedure is invasive and has potential bleeding sites. We believe that the potential consequences of a bleed during or after the procedure could be harmful. In addition, the potential bleeding cannot be managed easily. The ASCO (3), NICE (2) and FMS (1) guidelines formed their recommendations based on limited evidence and expert opinions. The guideline panel recognizes the importance of their expert opinions, and carefully considered their recommendations in every evidence-to-decision for our clinical questions. The recommendations support our decision making. Therefore, the panel recommends a platelet threshold of $50x10^9$/L prior to a lymph node biopsy.

Module 15: Lymfeklierbiopt (NEDERLANDS)

F: Aanbeveling (Nederlands)

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het uitvoeren een lymfeklierbiopt (zowel naald biopt als excisie biopt) bij kinderen met kanker.

G: Overwegingen (Nederlands)

Er werd geen literatuur gevonden over dit onderwerp bij kinderen met kanker. Daarom is deze aanbeveling gebaseerd op de meningen van de experts in de werkgroep.
De werkgroep is van mening dat een profylactische trombocytentransfusie in deze groep geoorloofd is. De werkgroep is van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het uitvoeren een lymfeklierbiopt (zowel naald biopt als excisie biopt) bij kinderen met kanker. De procedure is invasief en de kans op een bloeding is reëel. Ook zijn wij van mening dat de consequenties van een eventuele bloeding schadelijk kunnen zijn, zowel tijdens als na de procedure. Ook kan de bloeding niet makkelijk worden gecontroleerd.

De ASCO (3), NICE (2) en FMS (1) richtlijnen hebben hun aanbevelingen gebaseerd op zeer beperkt evidence en meningen van experts. De werkgroep erkent het belang van de door hun geformuleerde aanbevelingen op basis van expert opinions en wij nemen deze dan ook zorgvuldig mee in onze overwegingen in het evidence-to-decision proces. De aanbevelingen van deze richtlijnen zijn in lijn met onze expert opinions. Concluderend, is de werkgroep van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het uitvoeren een lymfeklierbiopt (zowel naald biopt als excisie biopt) bij kinderen met kanker.

Module 16: Major surgery (e.g. tumor resection) (ENGLISH)

A: Recommendations

Research question: What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need major surgery (e.g. tumor resection)?

A1.1: Recommendation (English)

WEAK recommendation, EXPERT evidence	We believe a platelet threshold of 100x10^9/L is sufficient for children with cancer who need major surgery (e.g. tumor resection).

B: Clinical question, search and selection

B1: Clinical question:

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need major surgery (e.g. tumor resection)?

Patients = Children (aged 28 days-18 years) with cancer who need major surgery (e.g. tumor resection)?
Intervention = Prophylactic platelet transfusion (at any threshold)
Control = (No prophylactic platelet transfusion or transfusion at any other threshold)
Outcomes = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event free survival, procedure-related complications

B2: Literature search and study selection

For the complete methodology of this guideline development and the search strategy, we refer to pages 20-31.
Of 7486 unique citations identified in the literature search, zero studies with pediatric oncology patients were included for this clinical question.
Three additional guidelines (ASCO, NICE, FMS) were applicable to our clinical question.

C: Results in pediatric and adult oncology patients

C1.1 Evidence in pediatric oncology patients

In our literature search, 0 results were found for this clinical question.

C1.2 Evidence in adult oncology patients

From our additional searches, 0 results were found for this clinical question.

C1.3 Additional evidence guidelines (adults) and other

Firstly, the ASCO guideline recommends: "*A threshold of 40 x10^9/L to 50 x10^9/L is recommended for performing major invasive procedures in the absence of associated coagulation abnormalities (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: weak).* (3)*"* They cite no evidence and their recommendation is mainly based on expert opinions.
The NICE guideline recommends: "*Consider a higher threshold (for example 50–75×10^9 per litre) for patients with a high risk of bleeding who are having invasive procedures or surgery, after taking into account the specific procedure the patient is having*" and "*Consider prophylactic platelet transfusions to raise the platelet count above 100×10^9 per litre in patients having surgery in critical sites, such as the central nervous system (including the posterior segment of the eyes*) (2)."
The FMS recommends that regarding surgical procedures, including major surgery, they believe a threshold of 50x10^9/L prior to the procedure is sufficient (1).
No additional evidence was cited by all three guidelines and recommendations were mostly

based on expert opinions.

D: Conclusion(s) of evidence (pediatric oncology patients):

0 studies in pediatric oncology patients were found.	**-**

E: Considerations

No evidence in pediatric oncology patients or adult oncology patients was found. Therefore, the guideline panel formed a recommendation based mainly on expert opinions.
The guideline panel believes that a prophylactic platelet transfusion is appropriate in this specific patient group. The panel believes that a platelet threshold of $100x10^9$/L is sufficient in children with cancer who need major surgery such as tumor resection. This type of surgery is very invasive, has a long duration and a lot of potential bleeding sites. We believe that the potential consequences of a bleed during or after the procedure could be very harmful. In addition, the potential bleeding cannot be managed easily.

The ASCO (3), NICE (2) and FMS (1) guidelines formed their recommendations based on limited evidence and expert opinions. The guideline panel recognizes the importance of their expert opinions, and carefully considered their recommendations in every evidence-to-decision for our clinical questions.
The recommendations do not completely support our decision making, however, all the guidelines recognize that higher thresholds are applicable prior to major surgery.

The panel, including a surgeon with a lot of experience in major surgery or tumor resections like these in children with cancer, strongly feels that the potential bleeding can be very harmful both during the procedure and after. Therefore, the panel recommends a platelet threshold of $100x10^9$/L prior to major surgery.

Module 16: Grote chirurgische ingrepen (bijvoorbeeld tumor resectie) (NEDERLANDS)

F: Aanbeveling (Nederlands)

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van 100x10^9/L voldoende is voor het uitvoeren een grote chirurgische ingreep, bijvoorbeeld tumor resectie, bij kinderen met kanker.

G: Overwegingen (Nederlands)

Er werd geen literatuur gevonden over dit onderwerp bij kinderen met kanker. Daarom is deze aanbeveling gebaseerd op de meningen van de experts in de werkgroep.
De werkgroep is van mening dat een profylactische trombocytentransfusie in deze groep geoorloofd is. De werkgroep is van mening dat een trombocytengrens van 100x10^9/L voldoende is voor het uitvoeren een grote chirurgische ingreep, bijvoorbeeld tumor resectie, bij kinderen met kanker. De procedure is zeer invasief, langdurig en de kans op een bloeding is zeer reëel. Ook zijn wij van mening dat de consequenties van een eventuele bloeding zeer schadelijk kunnen zijn, zowel tijdens als na de procedure. Ook kan de bloeding niet makkelijk worden gecontroleerd.

De ASCO (3), NICE (2) en FMS (1) richtlijnen hebben hun aanbevelingen gebaseerd op zeer beperkt evidence en meningen van experts. De werkgroep erkent het belang van de door hun geformuleerde aanbevelingen op basis van expert opinions en wij nemen deze dan ook zorgvuldig mee in onze overwegingen in het evidence-to-decision proces. De aanbevelingen van deze richtlijnen komen niet volledig overeen met onze expert opinions, hoewel alle richtlijnen wel benoemen dat een hogere grens dan normaal van toepassing is voorafgaand aan een grote operatie.

De werkgroep, inclusief een kinderchirurg met veel ervaring op dit gebied, blijft sterk van mening dat een potentiële bloeding schadelijk kan zijn zowel tijdens de procedure als daarna. Concluderend, is de werkgroep van mening dat een trombocytengrens van 100x10^9/L voldoende is voor het uitvoeren een grote chirurgische ingreep, bijvoorbeeld tumor resectie, bij kinderen met kanker.

Module 17: Nasogastric tube insertion or removal (ENGLISH)

A: Recommendations

Research question: What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need a nasogastric

tube insertion or removal?

A1.1: Recommendation (English)

WEAK recommendation, EXPERT evidence	We believe that a prophylactic platelet transfusion is not necessary in children with cancer who need a nasogastric tube insertion or removal.

B: Clinical question, search and selection

B1: Clinical question:

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need a nasogastric tube insertion or removal?

Patients = Children (aged 28 days-18 years) with cancer who need a nasogastric tube insertion or removal
Intervention = Prophylactic platelet transfusion (at any threshold)
Control = (No prophylactic platelet transfusion or transfusion at any other threshold)
Outcomes = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event free survival, procedure-related complications

B2: Literature search and study selection

For the complete methodology of this guideline development and the search strategy, we refer to pages 20-31.
Of 7486 unique citations identified in the literature search, zero studies with pediatric oncology patients were included for this clinical question.
One additional guideline (FMS) was applicable to our clinical question.

C: Results in pediatric and adult oncology patients

C1.1 Evidence in pediatric oncology patients

In our literature search, 0 results were found for this clinical question.

C1.2 Evidence in adult oncology patients

From our additional searches, 0 results were found for this clinical question.

C1.3 Additional evidence guidelines (adults) and other

ASCO (3) and NICE (2) made 0 recommendations regarding this clinical question.
The FMS (1) recommends a threshold of $<20x10^9$/L for a nasogastric tube (no specifications are made for insertion or removal). No additional evidence was cited and the recommendation was based on expert opinions.

D: Conclusion(s) of evidence (pediatric oncology patients):

0 studies in pediatric oncology patients were found.	**-**

E: Considerations

No evidence in pediatric oncology patients or adult oncology patients was found. Therefore, the guideline panel formed a recommendation based mainly on expert opinions.

The panel believes that a prophylactic platelet transfusion prior to the insertion or removal of a nasogastric tube is not necessary. We believe that the initial chance of a bleeding due to this procedure is very small. In addition, the panel feels that the potential bleeding that occur from the procedure, would be very small and limited, can be easily recognized (as the bleeding is probably visible or noticeable by the patient) and managed if necessary. Therefore, the panel feels that a possible bleeding can be managed sufficiently and that a transfusion prior to the procedure is not necessary.

The FMS (1) guideline formed its recommendation on very limited evidence (not regarding this clinical question) and expert opinions. The guideline panel recognizes the importance of their expert opinions, and carefully considered their recommendations in every evidence-to-decision for our clinical questions.

The guideline panel is aware that the FMS guideline recommends a higher threshold (namely $<20x10^9$/L) than we do now (1), but we strongly feel that the potential bleeding is adequately manageable because of the reasons mentioned earlier, and therefore the guideline panel is confident to recommend that prophylactic platelet transfusion is not necessary prior to the procedure.

Module 17: Neusmaagsonde (NEDERLANDS)

F: Aanbeveling (Nederlands)

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat er geen trombocytentransfusie nodig is voorafgaand aan het inbrengen of verwijderen van een neusmaagsonde bij kinderen met kanker.

G: Overwegingen (Nederlands)

Er werd geen literatuur gevonden over dit onderwerp bij kinderen met kanker. Daarom is deze aanbeveling gebaseerd op de meningen van de experts in de werkgroep.

De werkgroep is van mening dat er geen trombocytentransfusie nodig is voorafgaand aan het inbrengen of verwijderen van een neusmaagsonde bij kinderen met kanker. Wij denken dat de a priori kans op een bloeding door deze procedure erg klein is, een eventuele bloeding klein en beperkt zal zijn, snel herkend kan worden (omdat dit waarneembaar is voor zorgverleners en patiënt) en goed gecontroleerd kan worden. Daarom ziet de werkgroep geen noodzaak tot een profylactische transfusie voorafgaand aan deze procedure.
De FMS (1) richtlijn heeft zijn aanbevelingen gebaseerd op zeer beperkt evidence en meningen van experts. De werkgroep erkent het belang van de door hun geformuleerde aanbevelingen op basis van expert opinions en wij nemen deze dan ook zorgvuldig mee in onze overwegingen in het evidence-to-decision proces. De werkgroep is op de hoogte dat de FMS een hogere grens aanbeveelt (namelijk $<20x10^9$/L) (1), maar wij zijn sterk van mening dat een potentiële bloeding, mocht deze al optreden, goed controleerbaar is door bovengenoemde redenen. Daarom blijven wij van mening dat er geen trombocytentransfusie nodig is voorafgaand aan het inbrengen of verwijderen van een neusmaagsonde bij kinderen met kanker.

Module 18: Neurosurgery/ocular surgery (ENGLISH)

A: Recommendations

Research question: What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need neurosurgery or ocular surgery?

A1.1: Recommendation (English)

WEAK recommendation, EXPERT evidence	We believe a platelet threshold of $100x10^9$/L is sufficient in children with cancer who need neurosurgery (including VP drain) or ocular surgery.

B: Clinical question, search and selection

B1: Clinical question:

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need neurosurgery or ocular surgery?

Patients = Children (aged 28 days-18 years) with cancer who need neurosurgery or ocular surgery
Intervention = Prophylactic platelet transfusion (at any threshold)
Control = (No prophylactic platelet transfusion or transfusion at any other threshold)
Outcomes = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event free survival, procedure-related complications

B2: Literature search and study selection

For the complete methodology of this guideline development and the search strategy, we refer to pages 20-31.
Of 7486 unique citations identified in the literature search, zero studies with pediatric oncology patients were included for this clinical question.
Two additional guidelines (NICE, FMS) were applicable to our clinical question.

C: Results in pediatric and adult oncology patients

C1.1 Evidence in pediatric oncology patients

In our literature search, 0 results were found for this clinical question.

C1.2 Evidence in adult oncology patients

From our additional searches, 0 results were found for this clinical question.

C1.3 Additional evidence guidelines (adults) and other

The ASCO does not make a specific recommendation about neurosurgery (3).
The NICE guideline recommends: "*Consider prophylactic platelet transfusions to raise the platelet count above 100×10^9 per litre in patients having surgery in critical sites, such as the central nervous system (including the posterior segment of the eyes*). (2)"
The FMS recommends that regarding neurosurgery or ocular surgery, they believe that a threshold of $100x10^9$/L prior to the procedure is sufficient (1).

No additional evidence was cited by all these guidelines and recommendations were mostly

based on expert opinions.

D: Conclusion(s) of evidence (pediatric oncology patients):

0 studies in pediatric oncology patients were found.	**-**

E: Considerations

No evidence in pediatric oncology patients or adult oncology patients was found. Therefore, the guideline panel formed a recommendation based mainly on expert opinions.
The guideline panel believes that a prophylactic platelet transfusion is appropriate in this specific patient group. The panel believes that a platelet threshold of $100x10^9$/L is sufficient in children with cancer who need neurosurgery or ocular surgery. This type of surgery is very invasive, has a long duration and a lot of potential bleeding sites. We believe that the potential consequences of a bleed during or after the procedure could be very harmful. In addition, the potential bleeding cannot be managed easily.

The ASCO (3), NICE (2) and FMS (1) guidelines formed their recommendations based on limited evidence and expert opinions. The guideline panel recognizes the importance of their expert opinions, and carefully considered their recommendations in every evidence-to-decision for our clinical questions.
The recommendations support our decision making. Therefore, the panel recommends a platelet threshold of $100x10^9$/L prior to neurosurgery or ocular surgery.

Module 18: Neurochirurgie en oogheelkundige ingrepen (NEDERLANDS)

F: Aanbeveling (Nederlands)

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $100x10^9$/L voldoende is voor het uitvoeren van neurochirurgie (inclusief VP drain) en oogheelkundige ingrepen bij kinderen met kanker.

G: Overwegingen (Nederlands)

Er werd geen literatuur gevonden over dit onderwerp bij kinderen met kanker. Daarom is deze aanbeveling gebaseerd op de meningen van de experts in de werkgroep.
De werkgroep is van mening dat een profylactische trombocytentransfusie in deze groep geoorloofd is. De werkgroep is van mening dat een trombocytengrens van $100x10^9$/L voldoende is voor het uitvoeren van neurochirurgie (inclusief VP drain) en oogheelkundige ingrepen bij kinderen met kanker. De procedure is zeer invasief, langdurig en de kans op een bloeding is zeer reëel. Ook zijn wij van mening dat de consequenties van een eventuele bloeding zeer schadelijk kunnen zijn, zowel tijdens als na de procedure. Ook kan de bloeding niet makkelijk worden gecontroleerd.

De ASCO (3), NICE (2) en FMS (1) richtlijnen hebben hun aanbevelingen gebaseerd op zeer beperkt evidence en meningen van experts. De werkgroep erkent het belang van de door hun geformuleerde aanbevelingen op basis van expert opinions en wij nemen deze dan ook zorgvuldig mee in onze overwegingen in het evidence-to-decision proces. De aanbevelingen van deze richtlijnen zijn in lijn met onze expert opinions. Concluderend, is de werkgroep van mening dat een trombocytengrens van $100x10^9$/L voldoende is voor het uitvoeren van neurochirurgie (inclusief VP drain) en oogheelkundige ingrepen bij kinderen met kanker.

Module 19: PEG tube insertion and removal (ENGLISH)

A: Recommendations

Research question: What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need PEG tube insertion or removal?

A1.1: Recommendation (English)

WEAK recommendation, EXPERT evidence	We believe a platelet threshold of 50x10^9/L is sufficient in children with cancer who need a PEG tube insertion or removal.

B: Clinical question, search and selection

B1: Clinical question:

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need PEG tube insertion or removal?

Patients = Children (aged 28 days-18 years) with cancer who need PEG tube insertion or removal
Intervention = Prophylactic platelet transfusion (at any threshold)
Control = (No prophylactic platelet transfusion or transfusion at any other threshold)
Outcomes = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event free survival, procedure-related complications

B2: Literature search and study selection

For the complete methodology of this guideline development and the search strategy, we refer to pages 20-31.
Of 7486 unique citations identified in the literature search, zero studies with pediatric oncology patients were included for this clinical question.
Three additional guidelines (ASCO, NICE, FMS) were applicable to our clinical question.

C: Results in pediatric and adult oncology patients

C1.1 Evidence in pediatric oncology patients

In our literature search, 0 results were found for this clinical question.

C1.2 Evidence in adult oncology patients

From our additional searches, 0 results were found for this clinical question.

C1.3 Additional evidence guidelines (adults) and other

Firstly, the ASCO guideline recommends: "*A threshold of 40 x10^9/L to 50 x10^9/L is recommended for performing major invasive procedures in the absence of associated coagulation abnormalities (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: weak).* (3)*"* They cite no evidence and their recommendation is mainly based on expert opinions. The NICE guideline recommends: "*Consider prophylactic platelet transfusions to raise the platelet count above 50×10^9 per litre in patients who are having invasive procedures or surgery.* (2)" The FMS recommends that regarding surgical procedures, they believe a threshold of 50x10^9/L prior to the procedure is sufficient (1).
No additional evidence was cited by all three guidelines and recommendations were mostly based on expert opinions.

D: Conclusion(s) of evidence (pediatric oncology patients)

0 studies in pediatric oncology patients were found.	**-**

E: Considerations

No evidence in pediatric oncology patients or adult oncology patients was found. Therefore, the guideline panel formed a recommendation based mainly on expert opinions.
The guideline panel believes that a prophylactic platelet transfusion is appropriate in this specific patient group. The panel believes that a platelet threshold of $50x10^9$/L is sufficient in children with cancer who need a PEG tube insertion or removal. This procedure is invasive and has potential bleeding sites. We believe that the potential consequences of a bleed during or after the procedure could be harmful. In addition, the potential bleeding cannot be managed easily.

The ASCO (3), NICE (2) and FMS (1) guidelines formed their recommendations based on limited evidence and expert opinions. The guideline panel recognizes the importance of their expert opinions, and carefully considered their recommendations in every evidence-to-decision for our clinical questions.
The recommendations support our decision making. Therefore, the panel recommends a platelet threshold of $50x10^9$/L prior to PEG insertion or removal.

Module 19: PEG sonde inbrengen of verwijderen (NEDERLANDS)

F: Aanbeveling (Nederlands)

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het inbrengen of verwijderen van een PEG sonde bij kinderen met kanker.

G: Overwegingen (Nederlands)

Er werd geen literatuur gevonden over dit onderwerp bij kinderen met kanker. Daarom is deze aanbeveling gebaseerd op de meningen van de experts in de werkgroep.
De werkgroep is van mening dat een profylactische trombocytentransfusie in deze groep geoorloofd is. De werkgroep is van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het inbrengen of verwijderen van een PEG sonde bij kinderen met kanker. De procedure is invasief en de kans op een bloeding is reëel. Ook zijn wij van mening dat de consequenties van een eventuele bloeding schadelijk kunnen zijn, zowel tijdens als na de procedure. Ook kan de bloeding niet makkelijk worden gecontroleerd.

De ASCO (3), NICE (2) en FMS (1) richtlijnen hebben hun aanbevelingen gebaseerd op zeer beperkt evidence en meningen van experts. De werkgroep erkent het belang van de door hun geformuleerde aanbevelingen op basis van expert opinions en wij nemen deze dan ook zorgvuldig mee in onze overwegingen in het evidence-to-decision proces. De aanbevelingen van deze richtlijnen zijn in lijn met onze expert opinions. Concluderend, is de werkgroep van mening dat een trombocytengrens van $50x10^9$/L voldoende is voor het inbrengen of verwijderen van een PEG sonde bij kinderen met kanker.

Module 20: Rectal thermometer (probe) and administering rectal medication (ENGLISH)

A: Recommendations

Research question: What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need a rectal thermometer probe?

A1.1: Recommendation (English)

WEAK recommendation, EXPERT evidence	We believe that a prophylactic platelet transfusion is not necessary in children with cancer with a rectal thermometer (probe) or for administering rectal medication.

B: Clinical question, search and selection

B1: Clinical question:

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need a rectal thermometer probe?

Patients = Children (aged 28 days-18 years) with cancer who need a rectal thermometer probe
Intervention = Prophylactic platelet transfusion (at any threshold)
Control = (No prophylactic platelet transfusion or transfusion at any other threshold)
Outcomes = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event free survival, procedure-related complications

B2: Literature search and study selection

For the complete methodology of this guideline development and the search strategy, we refer to pages 20-31.
Of 7486 unique citations identified in the literature search, zero studies with pediatric oncology patients were included for this clinical question.

C: Results in pediatric and adult oncology patients

C1.1 Evidence in pediatric oncology patients

In our literature search, 0 results were found for this clinical question.

C1.2 Evidence in adult oncology patients

From our additional searches, 0 results were found for this clinical question.

C1.3 Additional evidence guidelines (adults) and other

ASCO (3), NICE (2) and FMS (1) made 0 recommendations regarding this clinical question.

D: Conclusion(s) of evidence (pediatric oncology patients)

0 studies in pediatric	**-**

oncology patients were found.	

E: Considerations

No evidence in pediatric oncology patients or adult oncology patients was found. Therefore, the guideline panel formed a recommendation based mainly on expert opinions.

The panel believes that a prophylactic platelet transfusion is not necessary in children with cancer with a rectal thermometer, rectal thermometer probe (during the total duration of the monitoring instrument) or for administering rectal medication, is not necessary.
We believe that the initial chance of a bleeding due to this procedure is very small. In addition, the panel feels that the potential bleeding that occur from the procedure, would be very small and limited, can be easily recognized (as the bleeding is visible) and managed if necessary. Therefore, the panel feels that a possible bleeding can be managed sufficiently and that a transfusion prior to the procedure is not necessary.

Module 20: Rectale thermometer (sonde) en rectaal toedienen van medicatie (NEDERLANDS)

F: Aanbeveling (Nederlands)

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat er geen trombocytentransfusie nodig is bij een rectale thermometer (sonde) of het rectaal toedienen van medicatie bij kinderen met kanker.

G: Overwegingen (Nederlands)
Er werd geen literatuur gevonden over dit onderwerp bij kinderen met kanker. Daarom is deze aanbeveling gebaseerd op de meningen van de experts in de werkgroep.

De werkgroep is van mening dat er geen trombocytentransfusie nodig is bij een rectale thermometer, een rectale thermometer sonde (gedurende de hele meetperiode) of het rectaal toedienen van medicatie bij kinderen met kanker. Wij denken dat de a priori kans op een bloeding door deze procedure klein is, deze snel kan worden herkend (de bloeding is direct zichtbaar) en kan goed worden gecontroleerd indien nodig. Daarom ziet de werkgroep geen noodzaak tot een profylactische transfusie voorafgaand aan deze procedure.

Module 21: Skin biopsy (ENGLISH)

A: Recommendations
Research question: What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need to undergo a

skin biopsy?

A1.1: Recommendation (English)

WEAK recommendation, EXPERT evidence	We believe that a prophylactic platelet transfusion is not necessary in children with cancer who need to undergo a skin biopsy (with biopsy punch).

B: Clinical question, search and selection

B1: Clinical question:

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need to undergo a skin biopsy?

Patients = Children (aged 28 days-18 years) with cancer who need to undergo a skin biopsy
Intervention = Prophylactic platelet transfusion (at any threshold)
Control = (No prophylactic platelet transfusion or transfusion at any other threshold)
Outcomes = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event free survival, procedure-related complications

B2: Literature search and study selection

For the complete methodology of this guideline development and the search strategy, we refer to pages 20-31.
Of 7486 unique citations identified in the literature search, zero studies with pediatric oncology patients were included for this clinical question.

C: Results in pediatric and adult oncology patients

C1.1 Evidence in pediatric oncology patients

In our literature search, 0 results were found for this clinical question.

C1.2 Evidence in adult oncology patients

From our additional searches, 0 results were found for this clinical question.

C1.3 Additional evidence guidelines (adults) and other

ASCO (3), NICE (2) and FMS (1) made 0 recommendations regarding this clinical question.

D: Conclusion(s) of evidence (pediatric oncology patients)

0 studies in pediatric oncology patients	**-**

were found.	

E: Considerations

No evidence in pediatric oncology patients or adult oncology patients was found. Therefore, the guideline panel formed a recommendation based mainly on expert opinions.

The panel believes that a prophylactic platelet transfusion prior to a skin biopsy (with biopsy punch) is not necessary. The wound that is created with the biopsy punch is superficial and small, and a sufficient amount of pressure can be exerted on the skin locally. Therefore, the panel feels that a possible bleeding can be managed sufficiently and that a transfusion prior to the procedure is not necessary.

Module 21: Huidbiopt (NEDERLANDS)

F: Aanbeveling (Nederlands)

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat er geen trombocytentransfusie nodig is voorafgaand aan een huidbiopt (met gebruik van huidstans) bij kinderen met kanker.

G: Overwegingen (Nederlands)

Er werd geen literatuur gevonden over dit onderwerp bij kinderen met kanker. Daarom is deze aanbeveling gebaseerd op de meningen van de experts in de werkgroep.

De werkgroep is van mening dat er geen trombocytentransfusie nodig is voorafgaand aan een huidbiopt (met gebruik van huidstans) bij kinderen met kanker. De wond die wordt gecreëerd door het biopt is oppervlakkig en klein, en kan goed worden afgedrukt. Daarom ziet de werkgroep geen noodzaak tot een profylactische transfusie voorafgaand aan deze procedure.

Module 22: Urinary catheter insertion (ENGLISH)

A: Recommendations

Research question: What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need a urinary catheter insertion?

A1.1: Recommendation (English)

WEAK recommendation, EXPERT evidence	We believe a platelet threshold of $20x10^9$/L is sufficient in children with cancer who need a urinary catheter insertion.

B: Clinical question, search and selection

B1: Clinical question:

What is the effect of prophylactic platelet transfusion on hemorrhagic events and other outcomes in children with cancer who need a urinary catheter insertion?

Patients = Children (aged 28 days-18 years) with cancer who need a urinary catheter insertion
Intervention = Prophylactic platelet transfusion (at any threshold)
Control = (No prophylactic platelet transfusion or transfusion at any other threshold)
Outcomes = Mild hemorrhagic events, severe hemorrhagic events, transfusion-related complications, anti-cancer treatment-related complications, morbidity, mortality, admission to hospital, costs, quality of life, event free survival, procedure-related complications

B2: Literature search and study selection

For the complete methodology of this guideline development and the search strategy, we refer to pages 20-31.
Of 7486 unique citations identified in the literature search, zero studies with pediatric oncology patients were included for this clinical question.
One additional guideline (FMS) was applicable to our clinical question.

C: Results in pediatric and adult oncology patients

C1.1 Evidence in pediatric oncology patients

In our literature search, 0 results were found for this clinical question.

C1.2 Evidence in adult oncology patients

From our additional searches, 0 results were found for this clinical question.

C1.3 Additional evidence guidelines (adults) and other

ASCO (3), NICE (2) made 0 recommendations regarding this clinical question.
The FMS (1) recommends a threshold of $<20x10^9$/L for a urinary catheter insertion. No additional evidence was cited and the recommendation was based on expert opinions.

D: Conclusion(s) of evidence (pediatric oncology patients)

0 studies in pediatric oncology patients were found.	**-**

E: Considerations

No evidence in pediatric oncology patients or adult oncology patients was found. Therefore, the guideline panel formed a recommendation based mainly on expert opinions.
The guideline panel believes that a prophylactic platelet transfusion is appropriate in this specific patient group. The guideline panel, together with an invited expert on this subject (A.J. Klijn), believes that a platelet threshold of $20x10^9$/L is sufficient in children with cancer who need a urinary catheter insertion, in line with the recommendation of the FMS (1). We believe that the initial chance of a bleeding due to this procedure will probably be small, but there are potential consequences of a bleed. The bleeding cannot be recognized directly and most importantly not easily managed. The panel chooses to adapt the threshold of $20x10^9$/L recommended by the FMS (1). In addition to the expert in the guideline panel, a subspecialist (children's urologist) was asked for his opinion and also agreed with the threshold of $20x10^9$/L. One of the arguments was the inability of a child to relax during the insertion of the catheter, which can give a higher chance of bleeding. Therefore, the panel chooses the threshold of $20x10^9$/L prior to urinary catheter insertion.

Module 22: Blaaskatheter (NEDERLANDS)

F: Aanbeveling (Nederlands)

ZWAKKE aanbeveling, EXPERT evidence	De werkgroep is van mening dat een trombocytengrens van $20x10^9$/L voldoende is voor het inbrengen van een blaaskatheter bij kinderen met kanker.

G: Overwegingen (Nederlands)

Er werd geen literatuur gevonden over dit onderwerp bij kinderen met kanker. Daarom is deze aanbeveling gebaseerd op de meningen van de experts in de werkgroep.

De werkgroep is van mening dat een profylactische trombocytentransfusie in deze groep geoorloofd is. De werkgroep is van mening, net als een uitgenodigde expert op dit onderwerp (A.J. Klijn), dat een trombocytengrens van $20x10^9$/L voldoende is voor het inbrengen van een blaaskatheter bij kinderen met kanker. Dit is lijn met de aanbeveling van de FMS (1). Wij denken dat de a priori kans op een bloeding door deze procedure klein is, maar dat er wel consequenties van een bloeding kunnen zijn. Een bloeding door deze procedure zal niet tijdig worden herkend en is bovendien moeilijk te controleren. De werkgroep kiest ervoor om zich aan te sluiten bij de grens die de FMS (1) ook aanhoudt.
Ook de expert (kinderuroloog) voegde toe in te stemmen met een grens van $20x10^9$/L. Een van zijn argumenten was ook dat het voor kinderen moeilijk is om te ontspannen tijdens het inbrengen van de katheter, wat ook een hogere kans op bloeding geeft. Concluderend, is de werkgroep van mening dat een trombocytengrens van $20x10^9$/L voldoende is voor het inbrengen van een blaaskatheter bij kinderen met kanker.

Bijlage 1: Kennislacunes

Tijdens de ontwikkeling van de richtlijn Trombocytentransfusies bij kinderen met kanker is systematisch gezocht naar onderzoeksbevindingen die nuttig konden zijn voor het beantwoorden van de uitgangsvragen. Een deel (of een onderdeel) van de uitgangsvragen is

met het resultaat van deze zoekacties te beantwoorden, een zeer groot deel echter niet. Het is duidelijk geworden dat op het terrein van bloedtransfusies bij kinderen met kanker nog veel lacunes in de beschikbare kennis bestaan. De werkgroep is van mening dat (vervolg)onderzoek niet alleen wenselijk, maar ook noodzakelijk is, om in de toekomst een duidelijker antwoord te kunnen geven op vragen uit de praktijk.

Een aantal voorbeelden van deze kennislacunes werden benoemd:

Algemene kennislacunes

- Wat is het effect van een therapeutisch trombocytentransfusie versus een profylactische trombocytentransfusie?
- Wat zijn de lange termijn effecten van profylactische trombocytentransfusies?
- Kosteneffectiviteitsanalyse
- Wat is het optimale volume voor trombocytentransfusie bij kinderen met kanker?

Specifieke kennislacunes:

- Wat is het effect van een profylactische grens bij alle benoemde interventies binnen de in deze richtlijn geïncludeerde populaties?

  Deze specifieke kennislacunes gelden dus bijvoorbeeld voor de profylactische grens bij het inbrengen van een neusmaagsonde of een lijn, het uitvoeren van een beenmergaspiratie of biopt, het uitvoeren van een LP of een intubatie etc.

Bijlage 2: Implementatieplan

Inleiding

Deze bijlage is opgesteld ter bevordering van de implementatie van de richtlijn “Trombocytentransfusies bij kinderen met kanker”.

Werkwijze
De werkgroep heeft per aanbeveling geïnventariseerd:

- de verwachtte impact van implementatie van de aanbeveling op de zorgkosten;
- mogelijk barrières om de aanbeveling te kunnen implementeren;
- mogelijke acties om de implementatie van de aanbeveling te bevorderen;

Voor iedere aanbeveling is nagedacht over onder andere de hierboven genoemde punten. Deze richtlijn zal voornamelijk worden gebruikt in het Prinses Máxima Centrum en de Shared Care ziekenhuizen. Hierdoor is het verspreiden en het onder de aandacht van brengen van de richtlijn makkelijk. Hier zal met name de kernwerkgroep zich voor inzetten. Het streven is ook om samen met de VKN een implementatie plan te maken hoe we deze informatie op de juiste manier bij ouders en kinderen kunnen krijgen. Dit zal de kernwerkgroep in een later stadium met de VKN oppakken.

Er is door een multidisciplinaire werkgroep samen te stellen, geprobeerd zo veel mogelijk draagvlak te creëren voor de aanbevelingen. Hiermee hopen wij, samen met het geven van juiste informatie en voorlichten, barrières herkennen en te voorkomen.

Bijlage 3: Zoekstrategie

Search uitgevoerd door Mw. H.W.J. Deurenberg

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 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

P= kinderen met kanker **=** set 24
(er zijn 3 varianten voor termen voor kanker of stamcel transplantatie gebruikt zie = set 19)
2. leeftijd = set 23
3. bloedtransfusie =set 38
4. resultaat = P + bloedtransfusie= set 24 and set 38=set 39

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)=P kinderen met kanker
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)=resultaat
64 63 not 57 (3528)
65 64 (3528)

Medline P= kinderen met kanker = set 37
3 varianten voor termen voor kanker of stamcel transplantatie= set 33
2. leeftijd = set 29
3. bloedtransfusie =set 51
4. resultaat = P + bloedtransfusie= set 63 hierna case reports eruit = set 65

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)

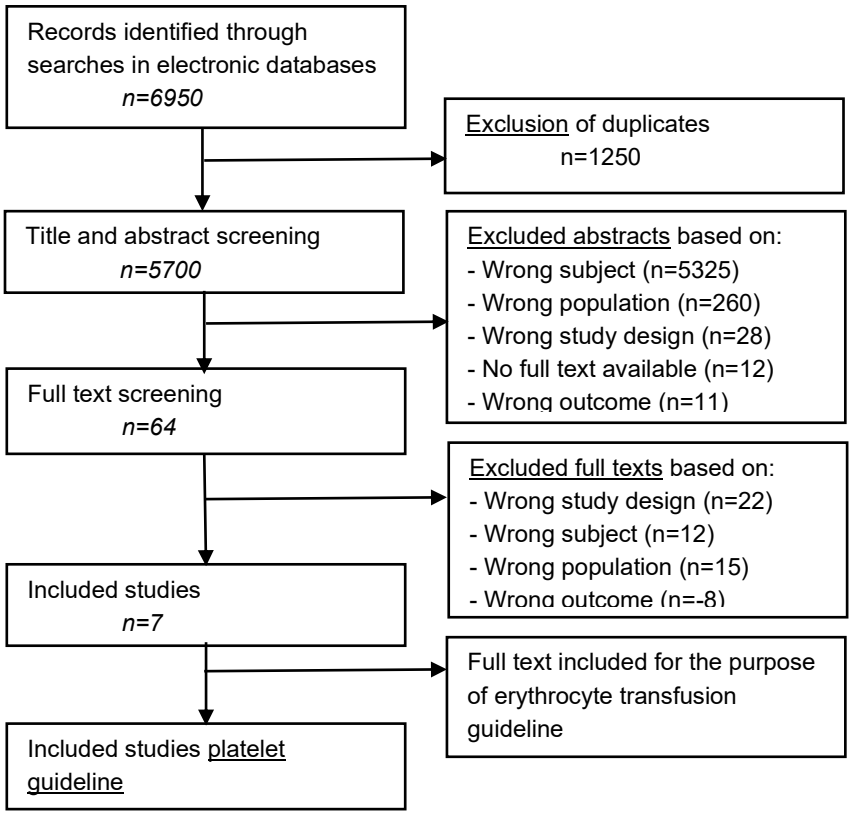
28 (cancer* or oncolog* or neoplasm* or carcinom* or tumor* or tumour* or malignan* or hematooncological or hemato?oncological or hemato-oncological or (hematologic adj neoplasm*)).tw,tw. (4490931)
29 7 or 27 or 28 (6033104)
30 "P in 3 varianten".ti. (0)
31 ((p?ediatric adj3 oncolog*) or (child* adj3 (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)= kinderen met kanker
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)=resultaat
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)

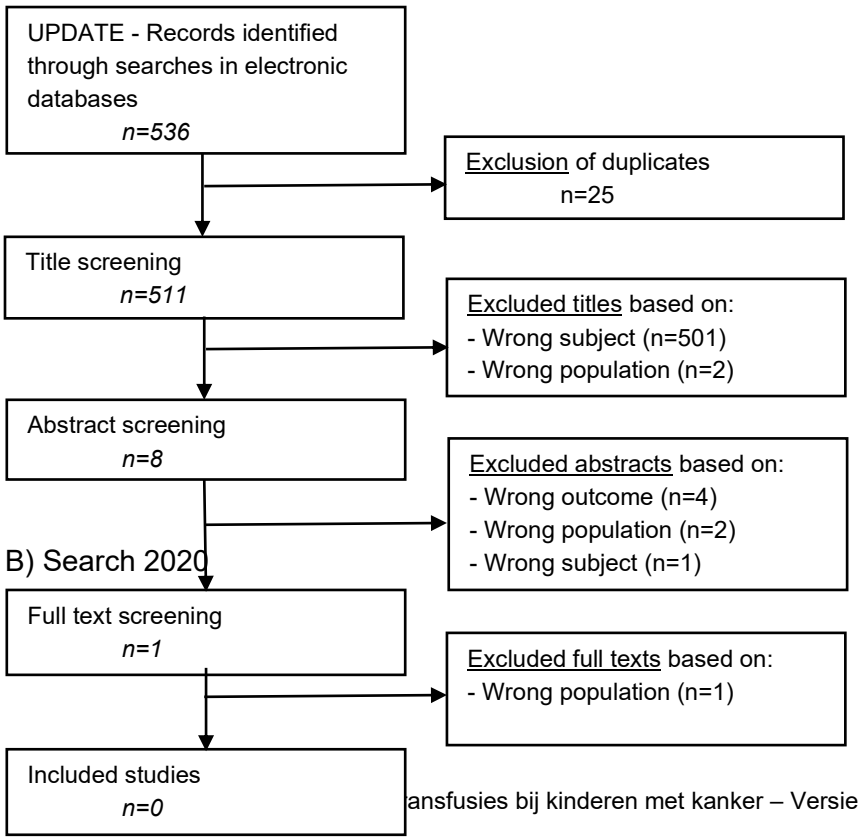
Embase P= kinderen met kanker = set 39
(3 varianten voor termen voor kanker of stamcel transplantatie= set 29)
2. leeftijd = set 37
3. bloedtransfusie =set 53
4. resultaat = P + bloedtransfusie= set 54

NB geen case reports nodig en daarom na aftrekken hiervan en beperking tot specifieke embase artikelen = gevonden aantal set 66

Bijlage 4: Inclusie en exclusie flowchart (2019 & 2020)

A) Search 2019





B) Search 2020

Bronvermelding:

1. FMS Federatie Medisch Specialisten, Bloedtransfusiebeleid. 2019.
2. NICE Guideline NCGC. Blood transfusion. 2015.
3. Schiffer CA, Bohlke K, Delaney M, Hume H, Magdalinski AJ, McCullough JJ, et al. Platelet Transfusion for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2018;36(3):283-99.
4. Loeffen EAH, Kremer LCM, Mulder RL, Font-Gonzalez A, Dupuis LL, Sung L, et al. The importance of evidence-based supportive care practice guidelines in childhood cancer-a plea for their development and implementation. Support Care Cancer. 2017;25(4):1121-5.
5. Higgins JPT GS (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. [updated M. The Cochrane Collaboration; 2011.
6. 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.
7. Dupuis LL, Robinson PD, van de Wetering MD, Tissing W, Seelisch J, Digout C, et al. Lexicon for guidance terminology in pediatric hematology/oncology: A White Paper. Pediatr Blood Cancer. 2020;67(4):e28170.
8. Murphy S, Litwin S, Herring LM, Koch P, Remischovsky J, Donaldson MH, et al. Indications for platelet transfusion in children with acute leukemia. Am J Hematol. 1982;12(4):347-56.
9. Stanworth SJ, Estcourt LJ, Powter G, Kahan BC, Dyer C, Choo L, et al. A no-prophylaxis platelet-transfusion strategy for hematologic cancers. N Engl J Med. 2013;368(19):1771-80.
10. Wandt H, Schaefer-Eckart K, Wendelin K, Pilz B, Wilhelm M, Thalheimer M, et al. Therapeutic platelet transfusion versus routine prophylactic transfusion in patients with haematological malignancies: an open-label, multicentre, randomised study. Lancet. 2012;380(9850):1309-16.
11. Crighton GL, Estcourt LJ, Wood EM, Trivella M, Doree C, Stanworth S. A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation. Cochrane Database Syst Rev. 2015(9):CD010981.
12. Estcourt LJ, Stanworth SJ, Doree C, Hopewell S, Trivella M, Murphy MF. Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation. Cochrane Database Syst Rev. 2015(11):CD010983.
13. Mats Heyman LB, André Baruchel, Marc Bierings, Manuel Brito, Jochen Büchner, Valerie de Haas, Barbara De Moerloose, Joaquin Duarte, Christina Halsey, Gabriele Escherich, Karin Flood, Carine Halfon-Domenech, Helene Hallböök, Jeremy Hancock, Martin Horstmann, Rachael Hough, Marianne Ifversen, Jenny Juhlin,Andrea Malone, Hanne Marquart, Vitor Mendes Costa, Veerle Mondelaers, Anthony Moorman, John Moppett, Rob Pieters, Sujith Samarasinghe, Kjeld Schmiegelow, Heidi Segers, Inge van der Sluis, Owen Smith, Marion Strullu, Mervi Taskinen, Ajay Vora, Martin Zimmermann. ALLTOGETHER. 2021.
14. NOPHO-DBH-AML. 2012.
15. Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Intensive Care Med. 2020;46(Suppl 1):10-67.
16. DENTISTRY AAP. Guideline on Dental Management of Pediatric Patients Receiving Chemotherapy, Hematopoietic Cell Transplantation, and/or Radiation Therapy. 2013.
17. https://hematologienederland.nl/covid-19/

18. Howard SC, Gajjar A, Ribeiro RC, Rivera GK, Rubnitz JE, Sandlund JT, et al. Safety of lumbar puncture for children with acute lymphoblastic leukemia and thrombocytopenia. JAMA. 2000;284(17):2222-4.
19. Foerster MV, Pedrosa Fde P, da Fonseca TC, Couceiro TC, Lima LC. Lumbar punctures in thrombocytopenic children with cancer. Paediatr Anaesth. 2015;25(2):206-10.