Question 1

Should transfusion vs. no transfusion or hydroxyurea therapy be used for children aged 2 to 16 years or younger with HbSS or HbSß^0 thalassemia genotypes and abnormal non-imaging transcranial ultrasonography?	
POPULATION:	Children aged 2 to 16 years or younger with HbSS or HbSß^0 thalassemia genotypes and abnormal non-imaging transcranial ultrasonography.
INTERVENTION:	Transfusion
COMPARISON:	No transfusion or hydroxyurea therapy
MAIN OUTCOMES:	Stroke; Recurrence of cerebral infarction; Acute chest syndrome; Painful crisis; Transient ischemic attack; Infection; Total adverse events
CONFLICT OF INTEREST:	Drs. King and McKinstry were recused.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	STOP Trial- Transfusion when compared to observation was associated with significant reduction in the risk of recurrence of cerebral infarction (clinical stroke) in patients with abnormal transcranial Doppler measurement compared to those with an abnormal transcranial Doppler measurement without regular blood transfusion therapy. TWITCH Trial- Hydroxyurea therapy at maximum tolerated dose when compared to regular blood transfusion was non-inferior for preventing strokes in children with abnormal transcranial Doppler measurement and normal MRA (no evidence of intracranial cerebral vasculopathy).	STOP Trial- A 92% relative risk reduction in strokes when treated with regular blood transfusion[1] TWITCH Trial- Trial was stopped prematurely because compelling evidence that hydroxyurea at maximum tolerated dose was non-inferior when compared to regular blood transfusions. Children with MRA defined vasculopathy and abnormal TCD were excluded from the TWITCH Trial. For children with MRA defined vasculopathy and abnormal TCD measurements, no current evidence exist to change this group from regular blood transfusion to hydroxyurea at maximum tolerated dose [2].

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	For regular blood transfusion as the primary prevention therapy, there is an increase in the total body iron content. The rise in total body iron content requires daily oral chelation therapy after the first or second year of monthly blood transfusions. In high-income countries, there is a very low risk of blood borne infection. There is a low rate of red blood cell allo-immunization if the recipient receives blood matched for minor red blood cell antigens C, E, Kell. Iron chelation is associated with specific toxicities, such as visual loss, hearing deficits and abnormal kidney function. These events must be monitored routinely. For hydroxyurea therapy as the primary therapy, there are limited risks. These risks include myelosuppresion and anemia, that are reversible after cessation of therapy.	Transfusion burdens are markedly more than HU.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ● Moderate ○ High ○ No included studies	*See Appendix 1*	Quality of evidence is moderate for transfusion; very low for hydroxyrurea vs transfusion for a prolonged period.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	**RESEARCH EVIDENCE**	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	There is important uncertainty among both, patients and providers. Discordance between providers and families in terms of values is likely. Despite the established benefit of blood transfusion to prevent strokes for abnormal TCD measurements, some families will elect to initially not receive monthly blood transfusion and elect to receive hydroxyurea, potentially an initial inferior option. There is clear evidence of benefit from the intervention, but not all individuals with an abnormal TCD measurement will elect to be treated.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	A 92% relative risk reduction in an initial stroke in the transfusion group favors the treatment group over the observation group for children with abnormal TCD measurements.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	A red blood cell transfusion for primary stroke prevention in children with abnormal TCD is associated with cost savings (considering cost of stroke care and indirect costs). Hydroxyurea is less costly than regular blood transfusion and eventual iron chelation therapy, but perhaps less effective as the initial treatment for primary stroke prevention. Hydroxyurea therapy for primary stroke prevention for abnormal TCD is also likely associated with cost savings.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ● Low ○ Moderate ○ High ○ No included studies	Resource are highly variable depending on the hospital setting or blood bank where regular blood transfusions are provided. Typical resources require a hematologist, transfusion medicine expert and an extensive blood bank for minor red blood cell matching. Regular blood transfusion also requires skilled pediatric nurses for monthly intravenous access or a pediatric surgeon for central catheter placement. Resources required for hydroxyurea therapy include knowledge about how to administer the medication and skills required to monitor for the toxicities associated with hydroxyurea.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ No included studies	Preventing strokes in children will always be less expensive than the treatment of regular blood transfusion therapy with chelation, or hydroxyurea therapy.	Regular red cell transfusion with chelation for life after 2 abnormal TCDs would likely have a similar cost to the same management strategy after stroke, but the SCD patient whose stroke and associated cognitive deterioration is prevented is more likely to complete education to a higher level and to work. This enhances the cost-effectiveness of prophylactic transfusion for abnormal TCD.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ● Increased ○ Varies ○ Don't know	There are clear health disparities affecting children with stroke. These disparities include, but are not limited, to access to education specific to offset specific cognitive deficits. Both regular blood transfusion and hydroxyureas will likely reduce these disparities.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The intervention, regular blood transfusion, is acceptable to many, but not all parents and children with abnormal TCD measurements. Patient representatives on the panel disclosed that transfusion is less acceptable or not acceptable to some individuals they know.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Regular blood transfusion therapy is more feasible in high-resourced settings than low resourced-settings. Few low-resourced settings have introduced primary stroke prevention programs due to the lack of the ability for safe regular red blood cell transfusions.	Available data from low-income and high-income settings shows that hydroxyurea reduces time averaged maximum velocity to normal ranges in children aged 2-16 years old with sickle cell anemia, but randomized controlled trial data on the effect on stroke outcome in children with sickle cell disease has not been published

Summary of judgements

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		**Varies**	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	**Increased**	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

CONCLUSIONS

Recommendation

1.1 In children with HbSS or HbSß^0 thalassemia (age 2-16 years) and repeated and confirmed abnormal transcranial Doppler results, ASH guideline panel recommends long-term transfusion therapy (over no transfusion) with a goal to keep maximum hemoglobin S concentration less than 30% to reduce the risk of stroke. (Strong recommendation, moderate certainty evidence)

Technical remarks:

-This recommendation is applicable to countries or settings in which chronic transfusion is feasible and acceptable

-Suggested threshold for treatment non-imaging transcranial Doppler ultrasound (TCD) techniques is (equivalent to TAMMV ≥200 cm/s) and for imaging is (equivalent to TAMX ≥185 cm/s) and should be based on time averaged velocity (not peak systolic velocity).

- Two TCD measurements greater than 200 cm/s or a single more than 220 cm/s using non-imaging technique and greater than 185 cm/sec or 205 cm/sec using imaging technique.

- Measurements should be done at the terminal portions of ICA and proximal portion of MCA. The predictive values of the TCD measurements in the intracranial arteries has not been rigorously addressed and should not be used to stratify into high and low risk groups for future strokes.

-Regular blood transfusion is defined as having the intent of the transfusion to maintain hemoglobin above 9-9.5gm/dl, Hemoglobin S < 30% with the hemoglobin S level determined prior to every transfusion. Some patients who will be difficult to transfuse effectively to keep the hemoglobin S percentage less than 30% on a consistent basis. In the event that the hemoglobin S percentage cannot be consistently kept less than 30% with modified exchange transfusion or apheresis, but transfusions have been performed at a reasonable period of every three to four weeks, individuals will be considered effectively transfused.

- This recommendation requires that a MRI and MRA of the brain be done to exclude silent cerebral infarcts (see PICO #10) and MRA defined cerebral vasculopathy in abnormal TCD measurements prior to switching to hydroxyurea.

1.2 In children with HbSS or HbSß0 thalassemia (age 2-16 years) and repeated and confirmed abnormal TCD results in settings where chronic transfusion is not available or not acceptable, ASH guideline panel suggests HU as an alternative to no therapy for primary stroke prevention.

- A minimum dose of HU 20 mg/kg/day

(Conditional recommendation, low certainty evidence)

1.3 In children with HbSS or HbSß^0 thalassemia (age 2-16 years) and abnormal transcranial Doppler results who are receiving transfusion therapy for at least one year and are interested in stopping transfusion, ASH guideline panel suggests risk stratification with an MRI and MRA:

- In children without MRA-defined vasculopathy or silent cerebral infarcts who have received at least 1 year of transfusions, ASH guideline panel suggests HU treatment at maximum tolerated dose can be considered to substitute for chronic transfusions- conditional recommendation, low certainty evidence.

- In children with MRA-defined vasculopathy or silent cerebral infarcts, ASH guideline panel suggests continuing blood transfusions indefinitely-conditional recommendation, low certainty evidence.

Subgroup considerations

In the original STOP trial there was a very small event rate of stroke that does not justify conclusions based on subgroup analysis. Despite this small group, those with MRA-defined vasculopathy were thought to be at higher risk and were subsequently excluded from the TWITCH Trial. Panel is concerned that those with abnormal MRA may have higher risk for stroke and should not be switched from transfusion, but insufficient data is available to make a decision in either direction.

Implementation considerations

- Definition of vasculopathy from the TWITCH trial

- TCD screening after switching to maximum tolerated dose of hydroxyurea remains a reasonable option. For individuals with abnormal TCD measurements, there is no established benefit for risk stratification with serial TCD measurements. Elevated TCD measurements after starting transfusion are expected and not established as a clear risk factor for a future stroke.

Appendices

Question 1. Evidence Profile

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with No transfusion	Risk with Transfusion				
Stroke	Study population		**RR 0.13** (0.03 to 0.56)	130 (1 RCT)[1,3-6]	⨁⨁⨁◯ MODERATE[a]	
	11 events in 102.18 patient years 11 per 100 PY	1 events in 110.25 patient years 1 per 100PY				
Recurrence of cerebral infarction	Transfusion was associated with a non-statistically significant reduction in the risk of cerebral infarction (clinical stroke or new or enlarged silent infarction) in patients with no abnormality on MRI at baseline (RR: 0.24, 95% [0.06, 1.07]).		-	(1 RCT)[1,3-6]	⨁⨁◯◯ LOW[b]	
Cerebral infarction	Transfusion was associated with significant reduction in the risk of recurrence of cerebral infarction (clinical stroke or new or enlarged silent infarction) in patients who had silent infarcts at baseline (RR: 0.05 95% [0.00, 0.80]).		-	(1 RCT)[1,3-6]	⨁⨁⨁◯ MODERATE[a]	
Acute chest syndrome	Transfusion was associated with significant reduction in the risk of acute chest syndrome (RR: 0.30 95%CI [0.11, 0.87]).		-	(1 RCT) [1,3-6]	⨁⨁⨁◯ MODERATE[a]	
Painful episodes	Transfusion was associated with nonsignificant reduction in the risk of painful crisis (RR: 0.90 95%CI [0.44, 1.86]).		-	(1 RCT) [1,3-6]	⨁⨁◯◯ LOW[b]	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with No transfusion	**Risk with Transfusion**				
	Transfusion	Hydroxyurea				
Transient ischemic attack	50 per 1,000	**51 per 1,000** (11 to 242)	**RR 1.02** (0.21 to 4.84)	121 (1 RCT)[2]	⨁◯◯◯ VERY LOW[b,c]	
Painful episodes	No significant difference between interventions		5.08 95%CI [0.61, 42.23]	(1 RCT) (1 RCT)[2]	⨁◯◯◯ VERY LOW[b,c]	
Acute Chest syndrome episodes	No significant difference between interventions.		2.03 95%CI [0.39, 10.69]	(1 RCT) (1 RCT)[2]	⨁◯◯◯ VERY LOW[b,c]	
Infection	No significant difference between interventions.		4.07 95%CI [0.47, 35.34]	(1 RCT) (1 RCT)[2]	⨁◯◯◯ VERY LOW[b,c]	
Total adverse events	No significant difference between interventions.		1.53 95%CI [0.58, 4.02]	(1 RCT) (1 RCT)[2]	⨁◯◯◯ VERY LOW[b,c]	

a. Imprecision due to a few number of patients
b. Serious concern about Imprecision due to small number of events and confidence intervals that include appreciable benefits and harms)
c. Increased risk of bias and stopping early

Question 2

Between 2 and 16 years of age should children with Hb ß$^{+}$ thalassemia, Hb Lepore disease, HbE disease, HbO Arab disease, HbD disease genotypes or other compound SCD heterozygotes other than hemoglobin SC or hemoglobin Sß^{0}thalassemia have transcranial-Doppler screening?	
POPULATION:	Children between 2 and 16 years of age with Hb ß$^{+}$ thalassemia, Hb Lepore disease, HbE disease, HbO Arab disease, HbD disease genotypes or other compound SCD heterozygotes other than hemoglobin SC or hemoglobin Sß^{0}thalassemia should have transcranial-Doppler screening?
INTERVENTION:	Transfusion
COMPARISON:	No transfusion or hydroxyurea therapy
MAIN OUTCOMES:	No studies were identified. Evidence is extrapolated from PICO 1 (Patients with SS or Sβ^{0}), clinical experience with children with compound heterozygotes for SCD, red blood cell physiology, and stakeholder input.
CONFLICT OF INTEREST:	Drs. King and McKinstry were recused.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No direct evidence from the literature because of the low number of children that fit into this category in high-resource settings that have been routinely screened for abnormal TCDs measurements. Further, compound heterozygotes for SCD were excluded from the STOP Trial.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Same as PICO #1	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	Same as PICO #2	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	The lack of direct evidence is challenging; however, we have indirect evidence suggesting that children who are compound heterozygotes for SCD and have evidence of hemolysis similar in magnitude to children with hemoglobin SS would benefit from primary stroke prevention via surveillance and treatment if an abnormal TCD measurement was detected.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Same response as PICO #1	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	Same as PICO #1	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Same as PICO #1	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Same as PICO #1	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ● Increased ○ Varies ○ Don't know	Same as PICO #1	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes	Same as PICO #1	

○ Varies ○ Don't know		

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Same as PICO #1	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		**Varies**	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know

	JUDGEMENT						
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	**Increased**	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

2. For children with compound heterozygous genotype sickle cell disease other than hemoglobin SC or HbSß^{0}thalassemia who have evidence of hemolysis in the same range as those with hemoglobin SS, ASH Guideline Panel suggests TCD screening and chronic transfusion to reduce the risk of stroke. (Conditional recommendation, very low certainty evidence).

Justification

Extrapolation of evidence from the STOP trial is justified by high stroke rate in these individuals and also by the demonstration of an association between abnormal physiologic parameters (such as anemia and reticulocytosis) and stroke.

Implementation considerations

Technical remarks:

-The threshold for hemolysis to obtain TCD should be determined based on the clinical setting

-Anemia, hemolysis and reticulocytosis parameters to be used for TCD recommendation

Appendices

Question 2. No Evidence Profile.

Question 3

Should annual screening with transcranial Doppler ultrasonography and subsequent treatment for abnormal screening results vs. no annual screening with transcranial Doppler ultrasonography be used for children between 2 and 16 years of age HbSS or HbSß^0 thalassemia genotypes from low-income to middle-income countries?	
POPULATION:	Children with between 2 and 16 with HbSS or HbSß^0 thalassemia genotypes and abnormal transcranial ultrasonography from low-income to lower-middle income countries according to the World Bank
INTERVENTION:	Annual screening with transcranial ultrasonography and subsequent treatment for abnormal screening results
Comparison:	No annual screening with transcranial ultrasonography.
MAIN OUTCOMES:	Mortality; Stroke
CONFLICT OF INTEREST:	No recusals.

Assessment

Problem

Is the problem a priority?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Evidence is limited to the biological plausibility and a few studies demonstrating that strokes do occur in all children with hemoglobin with HbSS or HbSß^0 thalassemia; however primary stroke prevention detection strategies have for the most part been limited to high-resources settings where less than 10% of 300,000 children born with SCD every year live. Given the evidence that the prevalence of strokes in children with SCD is primarily independent of where they are born, strategies should be undertaken to prevent strokes in regions of the world where the majority of children with SCD live.	

Desirable Effects

How substantial are the desirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know		

Undesirable Effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	Depends on the intervention. In most low-resource settings, regular blood transfusion therapy for primary stroke prevention in children with abnormal TCD measurements is not feasible. If transfusions are offered, the prevalence of undesirable effects will be at least similar PICO #1.	Available data from low income settings shows that hydroxyurea reduces time averaged maximum velocity in children aged 2-16 years old with sickle cell disease but randomized controlled trial data on the effect on stroke outcome has not yet been published. Hydroxyurea has less adverse effects than blood transfusion

Certainty of evidence

What is the overall certainty of the evidence of effects?

Judgement	Research evidence	Additional considerations

● Very low ○ Low ○ Moderate ○ High ○ No included studies	*See Appendix 1*	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence	Additional considerations
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability		

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The benefits of initial treatment with hydroxyurea may be less than for initial treatment with regular blood transfusion. The benefit of hydroxyurea therapy is clearly superior to no therapy for children with abnormal TCD measurements with approximately a 10% incidence rate of strokes per year. We do not know the optimal dose of hydroxyurea therapy for primary stroke prevention, but we would not recommend any therapy less than 20 mg/kg/day unless in a clinical trial setting.	

Resources required

How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	Hydroxyurea therapy, the only alternative to regular blood transfusion for primary stroke prevention, will require at least the same resources in a low- and middle-income setting as those in high-income settings. In addition, children need access to hydroxyurea therapy, for primary stroke prevention, and must receive laboratory surveillance at the same interval in high-income setting (initially every 2 weeks and eventually ever 2 or 3 months). Given the financial challenges in low-income settings, the state or federal government should offer hydroxyurea therapy free or at a reduced cost.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ○ Moderate ○ High ● No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	As an example, in Nigeria, the cost to prevent a stroke with fixed moderate dose hydroxyurea is approximately $0.16 per day (Thirty 500 mg capsule per day). The cost of $0.16 per day may still be too much for many families in low and middle-income countries where the majority of children with sickle cell disease live. The cost of a stroke associated with lost work productivity and decreased quality of life is significantly more than the cost of preventing a stroke with fixed moderate dose of hydroxyurea.	

Equity

What would be the impact on health equity?

Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ○ Yes	Based on prior studies in low and middle-income settings, we have significant evidence that parents	

● Varies ○ Don't know	of children at risk for strokes with abnormal TCD measurements are likely to agree to treatment with hydroxyurea.	

Feasibility

Is the intervention feasible to implement?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	Based on preliminary data from several primary stroke prevention trials and other trials, there is sufficient evidence to indicate that primary stroke prevention programs with hydroxyurea are a reasonable strategy to implement with appropriate resource allocation. Resources, must include, but should not be limited to health care providers well educated about toxicities associated with hydroxyurea, laboratory surveillance, and free hydroxyurea or hydroxyurea at a significant reduced cost when compared in high-income settings.	

Summary of judgements

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		**Varies**	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		**Varies**	Don't know
Certainty of evidence	**Very low**	Low	Moderate	High			No included studies
Values	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			

	Judgement						
Balance of effects	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention

○	○	○	●	○

Conclusions

Recommendation

In children with HbSS, HbSß^0 thalassemia (age 2-16 years) , or compound heterozygote for SCD with evidence of hemolysis similar to hemoglobin SS (PICO #2) and repeated and confirmed abnormal TCD results living in low-middle income countries, the ASH guideline panel suggests hydroxyurea therapy for primary stroke prevention. Conditional recommendation, low certainity evidence.

Technical remarks:

-This recommendation is applicable to countries or settings in which regular blood transfusion is not feasible or acceptable

-Suggested threshold for treatment with non-imaging TCD techniques is equivalent to TAMMV ≥200 cm/s and for imaging is equivalent to TAMX ≥185 cm/s and should be based on time averaged velocity (not peak systolic velocity).

- Two TCD measurements greater than 200 cm/s or a single more than 220 cm/s using non-imaging technique and greater than 185 cm/sec or 205 cm/sec using imaging technique.

- Measurements should be done at the terminal portions of ICA and proximal portion of MCA

-Adequate regular blood transfusion is defined as having a maximum hemoglobin S level greater less than 30% immediately prior to the next schedule blood transfusion.

-What has not been determined when initiating such a program is the optimal hydroxyurea therapy dose, and the appropriate infrastructure support required to safely administer hydroxyurea and to follow the patients for expected toxicities.

- A minimum dose of HU 20 mg/kg, which typically does not require frequent full blood count monitoring, up to a maximum tolerated dose monitored with monthly full blood counts

Appendices

Question 3. Evidence Profile

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Mortality	Patients who were screened and had an abnormal TCD measurement and received hydroxyurea did not show a statistically reduction in mortality compared to patients who had normal TCD measurements and underwent observation (RR: 1.68 95%CI [0.39, 7.23]).	(1 observational study)[7]	⨁◯◯◯ VERY LOW[a,b]
Stroke	Patients who were screened and had an abnormal TCD measurement and received hydroxyurea did not show statistically reduction in the risk of stroke compared to patients who had normal TCD measurements and underwent observation (RR: 2.70 95%CI [0.11, 64.70]).	(1 observational study)[7]	⨁◯◯◯ VERY LOW[a,b]

a. Imprecision due to non-significant result and small number of patients
b. Overall risk of bias is high

Question 4

Should simple blood transfusion vs. exchange transfusion be used for Patients with SCD and suspected acute symptomatic stroke?	
POPULATION:	Patients with SCD and suspected acute symptomatic stroke.
INTERVENTION:	Simple blood transfusion
COMPARISON:	Exchange transfusion
MAIN OUTCOMES:	Recurrent stroke
CONFLICT OF INTEREST:	Dr. Telfer was recused.

Assessment

Problem

Is the problem a priority?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Yes, prevention of stroke recurrence in children with sickle cell disease.	

Desirable Effects

How substantial are the desirable anticipated effects?

Judgement	Research evidence	Additional considerations

○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Prevention of a stroke recurrence is considered important priority for the health care of a child	

Undesirable Effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		

Certainty of evidence

What is the overall certainty of the evidence of effects?

Judgement	Research evidence	Additional considerations
○ Very low ● Low ○ Moderate ○ High ○ No included studies	*See Appendix 1*	Low for simple vs exchange. High for any transfusion vs no transfusion.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence	Additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability		Exchange red blood transfusion is more complicated and requires a high level of expertise within the medical center. In suspected acute symptomatic stroke, it is usually possible to undertake simple transfusion relatively quickly to improve the oxygen carrying capacity of the patient's blood. Exchange transfusion is costly in terms of manpower: manual exchange requires hours of one healthcare worker's time and it Is difficult to mobilize the erythrocytaphersis team as an emergency for automated exchange transfusion

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Exchange is more expensive in terms of manpower and equipment, but is negligible in cost when compared to simple transfusions.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ○ Moderate ○ High ● No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

Judgement	Research evidence	Additional considerations

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies		

Equity

What would be the impact on health equity?

Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	Prevention of stroke recurrence would decrease the magnitude of stroke disability in children with SCD when compared to children without SCD.	Exchange red blood transfusion is more complicated and requires a high level of expertise within the medical center; erythrocytaphersis may not be readily available at all centers without a high level of expertise and it may be difficult for a healthcare worker to undertake an emergency manual exchange

Acceptability

Is the intervention acceptable to key stakeholders?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Line infections can be challenging for implementation. Exchange requires ICU and central line placement (can be done peripherally in some places)	

Feasibility

Is the intervention feasible to implement?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Exchange is less available even in academic centers	

Summary of judgements

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	**Large**		Varies	Don't know
Undesirable Effects	Large	Moderate	**Small**	Trivial		Varies	Don't know
Certainty of evidence	Very low	**Low**	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
Resources required	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			**No included studies**

	Judgement						
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

Conclusions

Recommendation

4.1 In patients with sickle cell disease and an acute neurologic deficit or transient ischemic attack, the ASH guideline panel suggests prompt transfusion.

(Strong recommendation, high certainty evidence).

Technical remarks:

- **If the hemoglobin is less than ~ 8.5 g/dl a simple red blood cell transfusion should be performed urgently without delaying for subspecialty consults or definitive MRI diagnosis.**
- **If the hemoglobin > ~ 8.5 g/dl, then strong consideration must be given for the initial transfusion to be an exchange transfusion.**

4.2 In patients with sickle cell disease and an acute neurologic deficit or transient ischemic attack, the ASH guideline panel suggests exchange transfusion over simple transfusion (see details for exceptions). When exchange transfusion is not readily available, simple transfusion should be performed to avoid delays in treatment while planning a manual exchange transfusion or an automated pheresis.

(Conditional recommendation, low certainty evidence).

Implementation considerations

Technical remarks:

- Prompt transfusion within 2 hours of presentation to medical care is suggested in patients with sickle cell disease presenting with an acute neurologic deficit or transient ischemic attack within 72 hours of symptom onset.

- In patients presenting with a new neurologic deficit or TIA > 72 hours after onset and without recent worsening, we suggest an assessment for anemia and percentage of sickle hemoglobin with consideration of transfusion on a case-by-case basis

Appendices

Question 4. Evidence Profile

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Recurrent stroke	1st episode: Patients who presented within 24h of stroke symptom onset (n=52) and received simple transfusion had greater incidence of recurrent stroke compared to patients who received exchange transfusion (RR: 5.0 95%CI [1.3 -18.6]). 2nd episode: Of the patients who initially received exchange transfusion within 24h (n=38), those who received chronic exchange transfusion had fewer second strokes than patients who received simple chronic transfusion (RR: 0.61 95%CI [0.42 -0.88]).	(1 observational study)[8]	⨁⨁◯◯ LOW

Question 5

Should Red blood cell transfusion targeted to keep hemoglobinS <30%. vs. no treatment, red blood cell transfusion targeted to keep hemoglobinS >30% or HU (Hydroxyurea) be used for children with sickle cell disease with a history of stroke?	
POPULATION:	Children with sickle cell disease with a history of stroke
INTERVENTION:	Red blood cell transfusion targeted to keep hemoglobin S <30%.
COMPARISON:	No treatment, red blood cell transfusion targeted to keep hemoglobin S >30% or HU (Hydroxyurea)
MAIN OUTCOMES:	Overt stroke; Silent stroke; Strokes in patients with cerebral vasculopathy vs no vasculopathy; Strokes in patients with acute precipitating events vs no acute precipitating events; Transient ischemic attack
CONFLICT OF INTEREST:	Dr. King was recused.

Assessment

Problem

Is the problem a priority?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	This is a common question with important consequences.	

Desirable Effects

How substantial are the desirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	**Stroke incidence per 100 patient years with different treatment options** Blood transfusion to maintain HBS ≤30%- 2.29 (1.01, 5.19) Hydroxyurea 3.8 -(95% CI, 1.9-5.7) No treatment 29.1- (95% CI, 19.2-38.9)	

Undesirable Effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		

Certainty of evidence

What is the overall certainty of the evidence of effects?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ● Moderate ○ High ○ No included studies	**Stroke incidence per 100 patient years with different treatment options** Blood transfusion to maintain HBS ≤30%- 2.29 (1.01, 5.19) Hydroxyurea 3.8 -(95% CI, 1.9-5.7) No treatment 29.1- (95% CI, 19.2-38.9) *See Appendix 1*	

Values Is there important uncertainty about or variability in how much people value the main outcomes?		
Judgement	Research evidence	Additional considerations
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability		
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know		
Resources required How large are the resource requirements (costs)?		
Judgement	Research evidence	Additional considerations

○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know		A study was undertaken to evaluate the financial impact of chronic transfusion for stroke prevention in patients with sickle cell anemia. Charges ranged from $9828 to $50 852 per patient per year. Uniform Bill (UB-92), chelation, and physician-related charges accounted for 53%, 42%, and 5% of total charges, respectively. Of UB-92 charges, 58% were associated with laboratory fees and 16% were related to the processing and administration of blood. Charges for patients who required chelation therapy ranged from $31 143 to $50 852 per patient per year (mean, $39 779; median, $38 607). Deferoxamine accounted for 71% of chelation-related charges, which ranged from $12 719 to $24 845 per patient per year (mean, $20 514; median, $21 381). The financial impact of chronic transfusion therapy for sickle cell disease is substantial with charges approaching $400 000 per patient decade for patients who require deferoxamine chelation.[9]

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Very low ● Low ○ Moderate ○ High ○ No included studies		Another study appraised regular blood transfusion therapy and assessed its feasibility as an option for stroke prevention in a setting of limited resources. Five (10%) of the caregivers of the 50 children who had an indication for CBT for stroke prevention consented to the treatment. They all had homozygous sickle cell anemia and had suffered a stroke. None of the children with abnormal TCD velocities consented to CBT. Two children experienced transfusion reactions, fatal in one. The mean annual cost of chronic transfusion (without chelation) was $3,276 (SD = 1,168). Major reasons given for declining regular blood transfusions were high costs of blood transfusion, unavailability of blood, the need to regularly seek for blood donors, and the indefinite duration of blood transfusions. [10]

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies		

Equity

What would be the impact on health equity?

Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	Reduction of stroke in children will improve equity because of the racial health disparities affecting this condition.	

Acceptability

Is the intervention acceptable to key stakeholders?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		Patient representatives expressed dissatisfaction about transfusion and its impact on quality of life. They acknowledged the lack of other good alternatives. HU was considered by them much more acceptable.

Feasibility

Is the intervention feasible to implement?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	A study appraised regular blood transfusion therapy to keep hemoglobin S level < 30% and assessed its feasibility as an option for stroke prevention in a low-resource setting. Five (10%) of the caregivers of the 50 children who had an indication for regular blood transfusion for stroke prevention consented to the treatment. They all had homozygous sickle cell anemia and had suffered a stroke. None of the children with abnormal TCD velocities consented to regular blood transfusion. Two children experienced transfusion reactions, fatal in one. The mean annual cost of chronic transfusion (without chelation) was $3,276 (SD = 1,168). Major reasons given for declining regular blood transfusion were high costs of blood transfusion, unavailability of blood, the need to regularly seek for blood donors, and the indefinite duration of blood transfusions.	Jehovah's witness refusing transfusion for stroke prevention requires court order for minors

Summary of judgements

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	**Large**		Varies	Don't know
Undesirable Effects	Large	Moderate	**Small**	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	**Moderate**	High			No included studies
Values	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know

	Judgement						
Resources required	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	**Low**	Moderate	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

Conclusions

Recommendation

5. In children with SCD and a history of prior ischemic stroke, the ASH guideline panel recommends that transfusion goals for secondary stroke prevention are to increase the hemoglobin above 9 gm/dL and to maintain the percent HbS to <30% of total Hb until the time of the next transfusion. (Strong recommendation, moderate certainty evidence)

Implementation considerations

-In patients who cannot be transfused or refuse transfusion, HU is an inferior alternative for chronic transfusion for secondary stroke prevention.

-Adolescents who had a stroke as a child should continue transfusion into adulthood for secondary stroke prevention.

-Adults who suffer their first stroke as an adult should receive the recommended evaluation for stroke modifiable risk factors according to American Heart Association (AHA) guidelines. Secondary stroke prevention should include chronic transfusion and other AHA recommended measures.

Appendices

Question 5. Evidence Profile

Outcomes	**Anticipated absolute effects*** **(95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with No treatment, red blood cell transfusion targeted to keep hemoglobin S >30% or Hydroxyurea (HU)	**Risk with Red blood cell transfusion targeted to keep hemoglobin S <30%.**				
Overt stroke	Study population		**RR 0.060** (0.003 to 1.160)	133 (1 RCT)[11]	⨁⨁◯◯ LOW[a]	
	Rates for blood transfusion are 2.2 events per 100 patient years vs 29 per 100 patient years					
Silent stroke	Study population		**RR 0.3383** (0.0140 to 8.1580)	133 (1 RCT)[11]	⨁⨁◯◯ LOW[a]	
	15 per 1,000	**5 per 1,000** (0 to 122)				

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with No treatment, red blood cell transfusion targeted to keep hemoglobin S >30% or Hydroxyurea (HU)	**Risk with Red blood cell transfusion targeted to keep hemoglobin S <30%.**				
Strokes in patients with cerebral vasculopathy vs no vasulopathy	Not reported		-	(studies)	-	
Strokes in patients with acute precipitating events vs no acute precipitating events	Not reported		-	(studies)	-	
Transient ischemic attack	Study population		**RR 1.520** (0.574 to 4.039)	133 (1 RCT)[11]	⨁⨁◯◯ LOW[a]	
	90 per 1,000	**136 per 1,000** (51 to 362)				

a. Very serious imprecision, also stopped early for lack of improvement in liver iron content

Question 6

Should cerebral revascularization surgery (including encephalo-duro-arterio-synangiosis (EDAS), encephalo-duro-arterio-myo-synangiosis (EDAMS), pial synangiosis, direct) plus transfusion therapy. vs. transfusion therapy alone be used for patients with sickle cell disease and moyamoya syndrome?	
POPULATION:	Patients with sickle cell disease and moyamoya syndrome
INTERVENTION:	Cerebral revascularization surgery [including encephalo-duro-arterio-synangiosis (EDAS), encephalo-duro-arterio-myo-synangiosis (EDAMS), pial synangiosis, or direct anastomosis] plus transfusion therapy.
COMPARISON:	Transfusion therapy alone
MAIN OUTCOMES:	New clinical stroke; All cause death; Silent stroke; Transient ischemic Neurologic events; Post-operative subdural hygroma; Seizure; Cerebral edema; Subarachnoid; Non-fatal interventricular hemorrhage
CONFLICT OF INTEREST:	No recusals.

Assessment

Problem

Is the problem a priority?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		

Desirable Effects

How substantial are the desirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know		

Undesirable Effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know		

Certainty of evidence

What is the overall certainty of the evidence of effects?

Judgement	Research evidence	Additional considerations
● Very low ○ Low ○ Moderate ○ High ○ No included studies	*See Appendix 1*	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence	Additional considerations
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	Probable variability in how much people value the risk of peri-operative and post-operative complications versus possible risk reduction of long-term outcome (stroke). Burden of long-term transfusion and risk of stroke despite transfusion makes patients seek a moyamoya surgery because with regular blood transfusion therapy, the risk of recurrent stroke is approximately 50% over 5.5 years.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ Don't know	.	Probably favors the intervention, evidence is limited, but can be beneficial, requires formal evaluation.

Resources required

How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations

○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know		Patients denied a cerebral revascularization procedure may go to another center to get surgery Unintended harm is potential for additional procedures such as catheter angiogram for surgical planning with associated procedural risk and radiation exposure

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ○ Moderate ○ High ● No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies		

Equity

What would be the impact on health equity?		
Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know		Prevention of stroke recurrence will likely improve health equity.

Acceptability

Is the intervention acceptable to key stakeholders?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know		The panel had a wide range of views. Patient representative expressed concern about acceptability in light of uncertainty about benefit.

Feasibility

Is the intervention feasible to implement?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know		Travel is a challenge. Intervention is feasible in specialty centers (requires neurosurgeon, hematologist, neurologist). Different surgeons and centers may offer different procedures to the same patient.

Summary of judgements

	Judgement						
Problem	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	**Moderate**	Large		Varies	Don't know
Undesirable Effects	Large	**Moderate**	Small	Trivial		Varies	Don't know
Certainty of evidence	**Very low**	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
Certainty of evidence of required resources	Very low	Low	Moderate	High			**No included studies**
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
Acceptability	No	Probably no	Probably yes	Yes		**Varies**	Don't know
Feasibility	No	Probably no	Probably yes	Yes		**Varies**	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

Conclusions

Recommendation

6. In adults and children with sickle cell disease, moyamoya syndrome and a history of stroke or TIAs, ASH Guideline Panel suggests evaluation for revascularization surgery in addition to standard transfusion. (Conditional recommendation, very low certainty evidence).

Technical remarks- A multidisciplinary team including a hematologist, neurologist, neuroradiologist and neurosurgeon is essential for evaluation for surgery, as well as for the preparation and optimization of patients' health before, during and after surgery. For individuals that undergo this procedure, standardized care protocols and a registry are encouraged to carefully track long-term outcomes of greater than 1 year.

Implementation considerations

-The type of revascularization approach that is most effective is unclear and depends on the patient clinical context and availability of surgical expertise.

-Some patients with sickle cell disease and symptomatic moyamoya syndrome (progressive silent infarct or cognitive decline) without stroke may also benefit from revascularization.

Research priorities

Appendices

Question 6. Evidence Profile

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Transfusion therapy alone	**Risk with Cerebral revascularization surgery (including encephalo-duro-arterio-synangiosis (EDAS), encephalo-duro-arterio-myo-synangiosis (EDAMS), pial synangiosis, direct) plus transfusion therapy.**				
New clinical stroke (>70% of patients had prior stroke. Therefore, the rate per 100 PY of this outcome approximates the rate of stroke recurrence)	**2.29 (1.01, 5.19) per100 patient-years** assuming that average study follow up applies to all individuals included in the study. This rate is not derived from the 4 small observational studies but rather from a meta-analysis of larger transfusion studies.	**2.03 per 100 patient-years (0.65-4.73)** assuming that average study follow up applies to all individuals included in the study. This rate is derived from 4 small observational studies with follow up 2.1-4.7 years. **EDAS plus transfusion:** 1.92 per 100 patient-years (0.23-6.94) **Pial synangiosis plus transfusion:** 2.10 per 100 patient-years (0.43-6.15)	**OR 0.19** (0.05 to 0.74)	78 (4 observational studies)[12-15]	⨁⨁◯◯ LOW	
All cause death	0.68 Per 100 patient-years	0.69 Per 100 patient-years (0.083-2.48). **EDAS plus transfusion:** 0.61 (0.015-3.41) Per 100 patient-years **Pial synangiosis plus transfusion:** 0.78 Per 100 patient-years (0.02-4.356)	**OR 1.40** (0.08 to 25.14)	26 (1 observational study)[13]	⨁◯◯◯ VERY LOW[a]	

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Transfusion therapy alone	**Risk with Cerebral revascularization surgery (including encephalo-duro-arterio-synangiosis (EDAS), encephalo-duro-arterio-myo-synangiosis (EDAMS), pial synangiosis, direct) plus transfusion therapy.**				
Silent stroke	No silent strokes were reported in the surgical group during 331 available patient-years		-	(9 observational studies)[13,14,16-21]	⨁◯◯◯ VERY LOW[b]	
Transient ischemic	Incidence rate in the surgical group is 3.50 per 100 patient-years (1.68-6.441)		-	(4 observational studies)[13,14,21,22]	⨁◯◯◯ VERY LOW[c]	
Other adverse outcomes	• Post-operative subdural hygroma: 1/14 patients (7.1%) had post-operative subdural hygroma that required evacuation • Seizures: 1/14 patients (7.1%) • Cerebral edema that required delayed cranioplasty: 1/14 patients (7.1%) • Subarachnoid hemorrhage: 1/10 patients (10%) • Interventricular hemorrhage: In the chronic transfusion group, 1/16 (6.25%) patients had non-fatal interventricular hemorrhage		-	(1 observational study)[23]	⨁◯◯◯ VERY LOW[c]	

a. Imprecision due to small number of patients and wide confidence interval.
b. No events, severe imprecision
c. No reliable comparative data

Question 7

Should intravenous thrombolysis with tissue plasminogen activator (tPA) vs. no treatment with tPA be used for adults with sickle cell disease presenting with acute ischemic stroke having had a CT scan excluding hemorrhage within 4.5 hours of onset of symptoms or signs and without contraindications for thrombolysis?	
POPULATION:	Adults with sickle cell disease presenting with acute ischemic stroke having had a CT scan excluding hemorrhage within 4.5 hours of onset of symptoms/signs without contraindications for thrombolysis.
INTERVENTION:	Intravenous thrombolysis with tissue plasminogen activator (tPA)
COMPARISON:	No treatment with tPA
MAIN OUTCOMES:	Symptomatic intracerebral hemorrhage; Life-threatening systemic hemorrhage; Any serious complication; neurologic outcome at 90 days
CONFLICT OF INTEREST:	Dr. Telfer was recused.

Assessment

Problem

Is the problem a priority?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Dilemma whenever SCD patients present with stroke; to give or not give tPA	

Desirable Effects

How substantial are the desirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know		Reduced disability after stroke: In adults in the general population, IV tPA improves functional outcome at three months to 6 months when given within 4.5 hours of ischemic stroke onset, but unsure about added value in adults with sickle cell disease with a SCD related ischemic stroke, versus a non SCD related ischemic stroke.

Undesirable Effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know		In adults in the general population, IV tPA within 4.5 hours of ischemic stroke onset is associated with an increased early risk of intracerebral hemorrhage, but this risk is offset by later benefit in the form of reduced disability. A potential undesirable effect is delay in transfusion therapy; unknown how substantial this undesirable effect may be.

Certainty of evidence

What is the overall certainty of the evidence of effects?

Judgement	Research evidence	Additional considerations

● Very low ○ Low ○ Moderate ○ High ○ No included studies	*See Appendix 1*	Certainty of evidence is high in the general adult population, but very low certainty of evidence of effects in the specific subgroup of patients with sickle cell disease.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence	Additional considerations
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability		

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The available studies likely included patients with sickle cell trait (perhaps the majority of included patients). Hence, adverse effects of tPA cannot be reliably determined.	

Resources required

How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know		

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ○ Moderate ○ High ● No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

Judgement	Research evidence	Additional considerations

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies		In the general adult population, IV tPA in the 0-4.5 hour window is a cost-effective strategy compared to stroke treatment without IV tPA. There are no included studies specific to patients with sickle cell disease.

Equity

What would be the impact on health equity?

Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know		Shared decision making tools are needed for this decision.

Feasibility

Is the intervention feasible to implement?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		Patients may be sent directly to stroke team and miss opportunity for transfusion or cause delays in starting transfusion therapy. Stroke and SCD need to have joint protocols for management of patients with SCD so that they can benefit from acute treatments to include tPa and transfusion EMT and prehospital caregivers often direct patients to certain facilities focusing on stroke care. A proxy with power of attorney (POA) is often needed for shared decision making in the setting of acute stroke. tPA protocols require 2 large bore IVs which can facilitate simple transfusion and possibly exchange transfusion.

Summary of judgements

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	**Don't know**
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	**Don't know**
Certainty of evidence	**Very low**	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			

	Judgement						
Balance of effects	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
Certainty of evidence of required resources	Very low	Low	Moderate	High			**No included studies**
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
Equity	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		**Varies**	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

Conclusions

Recommendation

7. In patients with sickle cell disease presenting with symptoms of acute ischemic stroke and being considered for intravenous tPA (age ≥18 years, no hemorrhage on CT scan, within 4.5 hours of onset of symptoms/signs and without contraindications for thrombolysis), ASH guideline panel suggests management using a shared decision making approach that follows these principles:

a. In all patients, the administration of tPA should not delay prompt simple or exchange blood transfusion therapy

b. Patients should be considered for intravenous tPA based on its established inclusion and exclusion criteria detailed in stroke management algorithms

c. The following factors suggest likely benefit from IV tPA: older age, atrial fibrillation, diabetes, hypertension and hyperlipidemia. Management of younger patients without these risk factors should emphasize early transfusion.

d. There is no validated risk stratification or reliable age cutoff criteria to guide choice of initial therapy. Intravenous tPA is not recommended for children with sickle cell disease (<18 years of age).

(Conditional recommendation, very low certainty evidence).

Appendices

Question 7. Evidence Profile

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Symptomatic intracerebral hemorrhage	A total of 3 out of 61 (4.9%) patients and 9 out of 290 (3.2%) patients developed symptomatic intracerebral hemorrhage in the sickle cell disease and non-sickle cell disease respectively during 7 years of follow-up.	(1 observational study)[24]	⨁◯◯◯ VERY LOW[a]
Life-threatening systemic hemorrhage	None of the patients in the SCD group developed life-threatening systemic hemorrhage. On the other hand, 2 (0.7%) patients in the non-SCD group developed life-threatening systemic hemorrhage during 7 years of follow-up.	(1 observational study)[24]	⨁◯◯◯ VERY LOW[a]
Any serious complication	A total of 4/61 (6.6%) patients in the SCD group developed any type of serious complication. However, 17/290 (6.0%) patients in the non SCD group developed any type of serious complication during 7 years of follow-up.	(1 observational study)[24]	⨁◯◯◯ VERY LOW[a]

a. Indirectness: some patients in the studies may have had SCD trait

Question 8

Should clinicians perform or refer for screening for developmental delay and cognitive impairment. vs. no screening be used in patients with SCD (adults and children)?	
POPULATION:	Patients with SCD (adults and children)
INTERVENTION:	Perform or refer for screening for developmental delay and cognitive impairment.
OMPARISON:	No screening
MAIN OUTCOMES:	Intelligent quotient/cognitive impairment/developmental delay/school performance;
CONFLICT OF INTEREST:	No recusals.

Assessment

Problem

Is the problem a priority?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Developmental delays in children and cognitive impairment in adults are quite common in individuals with SCD and are due to silent infarcts and subsequent overt strokes. These individuals have difficulty accessing state and federal resources and can be misdiagnosed with other mental health conditions or learning disabilities.	

Desirable Effects

How substantial are the desirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Screening may allow children to be put on effective chronic transfusion program and allow adults and children to access resources to support improved quality of life. Transfusion adverse effects are the undesirable effects.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	Screening may allow children to be put on management strategies such as effective chronic transfusion program and allow adults and children to access educational and other resources to support improved quality of life. Transfusion adverse effects are the undesirable effects.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ○ Moderate ● High ○ No included studies	*See Appendix 1*	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence	Additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability		Strong teamwork and collaboration between primary care physician and hematologist is possible and not aspirational (it has been the case for one patient representative). Stake holders had significant concerns that the results of screening will remain without action (ie, hematologist will keep asking the question about developmental delay every visit and document in their notes that it is getting worse, but no action). Some may attribute child's delay to parents having no higher education, or to race or SES rather than considering neurologic causes.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	There is value of knowing why a child is impaired or why an adult cannot perform instrumental daily activities.	

Resources required

How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know		Extremely difficult to identify specialists and primary care health care providers for adults with sickle cell. Many top tier centers do not have either hematologists or primary care providers focused on the medical care of adults with sickle cell disease.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ● Moderate ○ High ○ No included studies		A large body of evidence exists on the societal costs and consequences of a drop in 5 points in IQ with no associated intervention, including loss of job, being in jail, not graduating high school, etc. Financial cost per IQ drop is extrapolated from studies of environmental exposures.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

Judgement	Research evidence	Additional considerations

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies		Screening adults and children for cognition and development is likely cost saving if we assume that our end goal is to have a healthy adult who is productive and able to hold a job. Screening may be cost effective because it will eventually lead to better compliance with medical care and better outcomes.

Equity

What would be the impact on health equity?

Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ● Increased ○ Varies ○ Don't know		Important implication to minorities' education and social consequences due to the reduced stigma when academic or functional deficits are linked with their medical condition. Without input from health care providers, misattribution of disease-related impacts on neurocognitive functioning to other causes of academic/functional deficits is common.

Acceptability

Is the intervention acceptable to key stakeholders?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		Screening will help with relationship with schools and teachers as the in-school behavior of children with disease-related impacts on development is better understood and supported Some parents are very involved with children's' education, and some are unfortunately are not; therefore, information from

		health care provides can help facilitate a better understanding of the child's abilities and needs.

Feasibility

Is the intervention feasible to implement?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	For toddlers, positive screenings for language delays predicted lower academic performance (p = .023). For older children, positive screenings for cognitive delays predicted more frequent academic/attentional problems at school (p = .0003), grade retention (p = .007), and lower academic performance (p = .001). Positive screenings were associated with an earlier onset of school problems and lower QOL. Positive screenings for language/ cognitive delays predicted increased stroke risk (both p's < .05). [25]	Resources or referral sources for developmental/cognitive screenings are likely more available in medical centers with comprehensive sickle cell care than for patients only seen in primary care settings. Resources and tools for these screenings have been designed for primary care settings and are widely available; however, practitioners need to prioritize this screening as part of routine health care. Patients may have to travel long ways to get appropriate neurocognitive and developmental screening, particularly in managed care settings.

Summary of judgements

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable Effects	Trivial	Small	**Moderate**	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	**Trivial**		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	**High**			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			

	Judgement						
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	**Moderate**	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	**Increased**	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

Conclusions

Recommendation

***8.1 Given the high prevalence of developmental delay* and cognitive deficits and coupled with the guidelines set by the American Academy of Pediatrics, ASH guideline panel recommends that clinicians supervising pediatric sickle cell care should conduct surveillance using simplified signaling questions for:**

- Concerns about developmental delays in preschool-age children,

- Concerns about neurodevelopmental disorders in school age children, such as academic or behavioral problems, or symptoms of inattention, hyperactivity, or impulsivity

(Strong recommendation, high certainty evidence)

8.2. In children with sickle cell disease who have abnormal surveillance results suggesting increased risk for developmental delay or cognitive deficits, the ASH guideline panel recommends performing or referral for formal screening by a psychologist or a pediatrician able to perform screening with the available validated tools

(Strong recommendation, high certainty evidence)

8.3 *Given the high prevalence of* cognitive impairment and coupled with the guidelines set by the American Academy of Neurology, the ASH guideline panel recommends that clinicians supervising adult sickle cell care should conduct surveillance *for* cognitive impairment using simplified signaling questions

(Strong recommendation, high certainty evidence)

8.4. In adults with sickle cell disease who have abnormal surveillance results suggesting cognitive impairment, the ASH guideline panel recommends performing or referring for formal screening by a psychologist or a primary care physician able to perform screening with the available validated tools

(Strong recommendation, high certainty evidence)

Appendices

Question 8. Evidence Profile

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Intelligent quotient/cognitive impairment/developmental delay/school performance	1) None of the included studies compared screening to no screening. However, some studies were identified that evaluated screening without a comparison group and reported outcomes of intelligence quotient score, the prevalence of cognitive impairment, developmental delay or school performance. 2) 39 studies reported a mean overall IQ score (82.75± 16.38) that ranged from 24.5 to 101.25 which included 1752 patients with sickle cell disease. 3) 15 studies reported data about the frequency of cognitive	Several observational noncomparative studies[26-39]	No comparative evidence; however high quality evidence supporting high prevalence of developmental delay and cognitive deficits

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
	impairment. 4) Academic Performance: One study reported that 20% (CI: 12%-32%) of the patients with SCD had poor academic performance.		

Question 9

Should cognitive rehabilitation therapy vs. no rehabilitation be used for Patients with sickle cell disease and cognitive deficit?	
POPULATION:	Patients with sickle cell disease and cognitive deficit
INTERVENTION:	Cognitive Rehabilitation Therapy
COMPARISON:	No rehabilitation
MAIN OUTCOMES:	Reading ability; Mathematics-related ability; Spelling ability; Verbal short-term memory; Verbal working memory; Visuospatial short-term memory; Visuospatial working memory; Short-term memory; Long-term memory;
CONFLICT OF INTEREST:	No recusals.

Assessment

Problem

Is the problem a priority?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	see previous question	

Desirable Effects

How substantial are the desirable anticipated effects?

Judgement	Research evidence	Additional considerations

○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know		Extrapolated evidence from other conditions (such as environmental exposures, lead toxicity) shows that cognitive rehabilitation is beneficial.

Undesirable Effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		Extrapolated evidence from other conditions (such as environmental exposures, lead toxicity) shows that cognitive rehabilitation is beneficial.

Certainty of evidence

What is the overall certainty of the evidence of effects?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ○ Moderate ○ High ● No included studies	*See Appendix 1*	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence	Additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	Screening and intervention on those with impaired development (children) or adults (cognitive impairment) will help the families in managing the condition and allow access to federal, state educational and social resources.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations

○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know		

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ○ Moderate ○ High ● No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies		

Equity

What would be the impact on health equity?

Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ● Increased ○ Varies ○ Don't know		Many children and adults with neurologic impacts from SCD, such as silent cerebral infarction, do not receive the same rehabilitation services typically provided to those with traumatic brain injury, overt stroke, or other brain injuries that produce a similar magnitude of cognitive deficit.

Acceptability

Is the intervention acceptable to key stakeholders?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Input from patients' representatives supports acceptability of the intervention.	

Feasibility

Is the intervention feasible to implement?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ● Probably yes ○ Yes	Parents or caregivers reported that the computerized working memory program was easy to use, including very easy or somewhat easy to login (92.9%), start the games (85.7%), use the mouse (100%) and carry out the tasks procedurally (64.3%).	

○ Varies ○ Don't know	Youth participants reported that it was either very easy or somewhat easy to login (85.7%), start the games (85.7%), and use the mouse (76.9%). Children reported somewhat greater difficulty carrying out the tasks procedurally, however, with 42.9% of participants reporting that this was either somewhat or very easy, 35.7% reporting it was neither easy nor difficult and 21.4% reporting that it was somewhat or very hard. Children also reported that they sometimes (35.7%) or often/always (35.7%) experienced frustration while carrying out the tasks. [40]	

Summary of judgements

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable Effects	Trivial	Small	**Moderate**	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	**Trivial**		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			**No included studies**
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
Certainty of evidence of required resources	Very low	Low	Moderate	High			**No included studies**

	Judgement						
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	**Increased**	Varies	Don't know
Acceptability	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

Conclusions

Recommendation

9.1 In children with sickle cell disease and abnormal screening for developmental or cognitive status, ASH guideline panel recommends:

- a developmental/cognitive/medical evaluation to diagnose any related disorders and to identify modifiable risk factors for developmental delays or cognitive deficits

- following the disease specific evidence-based guidelines for these conditions to provide appropriate interventions.

(Strong recommendation, high certainty evidence)

9.2 In adults with sickle cell disease and abnormal screening for cognitive status, ASH guideline panel recommends:

- a developmental/cognitive/medical evaluation to diagnose any related disorders and to identify modifiable risk factors for cognitive deficits.

- following the disease specific evidence-based guidelines for these conditions to provide appropriate interventions.

(Strong recommendation, high certainty evidence)

Technical note-

The American Congress of Rehabilitation Medicine endorses behavioral strategies to support individuals with executive function impairments. Executive functions are a set of processes that all have to do with managing oneself and one's resources in order to achieve a goal, involving mental control and self-regulation[41]. Children and adults with sickle cell disease commonly have deficits in executive dysfunction [42]. These deficits correlate with the frequent injury to the frontal lobe, the most common area of the brain affected by silent cerebral infarcts [42,43].

After recognizing executive dysfunction, the person can be trained to use task specific approaches, problem solving strategies, external cues, and internalized strategies. Systematic reviews of randomized controlled trials support the use of goal management training, problem solving techniques and time pressure management [44]. Recently, evidence reveals that the intervention that makes the largest difference is the Cognitive Orientation to Daily Occupational Performance (CO–OP). [45]. CO-OP is a top-down approach that reduces impairments and improves health. Defined as "a client centered, performance-based, problem solving approach that enables skill acquisition through a process of strategy use and guided discovery" [46], CO–OP focuses treatments directly on improving performance in everyday life activity rather than treating the underlying impairments and hoping for secondary improvement in meaningful activities. Three RCTs have demonstrated that the CO-OP approach is more effective than impairment focused therapy delivered by Occupational Therapist [47-49].

Cognitive lapses, which occur most often in individuals with cognitive deficits, are the most common cause of poor medical adherence [10-11]. Aspects of executive function (e.g., mental flexibility, working memory) are the most common area of cognitive deficit associated with poor adherence [12]. Challenges with following through on plans of daily life that include medical appointments, medications, education and work are frequently underappreciated as cognitive deficits and are often labeled as problem behaviors or motivational problems by those around the affected individual. The actual patient is often unaware as well. Expert advice on improving adherence indicates a starting point is having a realistic understanding of the patient's knowledge, understanding, and capacity for following the medical regimen [13]. Formal assessments of cognition provide an objective understanding of the patient's cognitive capacities and are most commonly obtained after cerebral injury is diagnosed from MRI. The assessments allow both health care staff and the family to better understand the patient's need for information, support, and rehabilitation. The identification of neurocognitive deficits is the important first step in obtaining rehabilitation as recommended multiple national organizations for relevant disciplines, Figure 1 [14]. In addition, hematologists and other medical providers can make use of behavioral and family supports (e.g., CO-OP approaches) to better support adherence. [1,2,41-54]

Justification

See technical note -above

Implementation considerations

Despite endorsement from multiple different professional societies, implementing cognitive screening strategies in high risk children and adults with sickle cell disease will be challenging to implement without basic research strategies to identified barriers and facilitators within sickle cell care centers.

Question 9. Evidence Profile

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Reading ability	Patients with academic tutoring and memory rehabilitation improved their reading ability when compared to academic tutoring alone (p=0.046).	(1 RCT)[55]	⨁⨁◯◯ LOW[a,b]
Mathematics-related ability	Patients who received academic tutoring and memory rehabilitation did not show statistically improvement in this outcome compared to academic tutoring alone (p=0.4).	(1 RCT)[55]	⨁⨁◯◯ LOW[a,b]
Spelling ability	Patients did not show improvement in their spelling ability when they received academic tutoring and memory rehabilitation compared to academic tutoring (p=0.1).	(1 RCT)[55]	⨁⨁◯◯ LOW[a,b]
Verbal short-term memory	Cogmed completers did not show a statistically improvement in verbal short-term memory (measured as digit recall) compared to Cogmed non-completers (MD: 3.8 95%CI [-14.43, 22.02]).	(1 observational study)[56]	⨁◯◯◯ VERY LOW[a,b]
Verbal working memory	Cogmed completers showed a statistically improvement in Verbal working memory (measured as listening recall) compared to Cogmed non-completers (MD: 21.2 95%CI [3.95, 38.45]).	(1 observational study)[56]	⨁◯◯◯ VERY LOW[a,b]
Visuospatial short-term memory	Cogmed completers showed a statistically improvement in this outcome (measured as dot matrix) compared to Cogmed non-completers (MD: 21.4 95%CI [1.74, 41.06]).	(1 observational study)[56]	⨁◯◯◯ VERY LOW[a,b]
Visuospatial working memory	Cogmed completers showed a statistically improvement in this outcome (measured as spatial recall) compared to Cogmed non-completers (MD: 27.9 95%CI [12.11, 43.69]).	(1 observational study)[56]	⨁◯◯◯ VERY LOW[a,b]
Short-term memory	Academic tutoring and specific learning and memory strategies did not show a statistically improvement in short-term memory (measured as digit span) compared to academic tutoring alone (MD: 1.7 95%CI [-0.4, 3.7]).	(1 observational study)[57]	⨁◯◯◯ VERY LOW[a,b]
Long-term memory	Academic tutoring and specific learning and memory strategies did not show a statistically improvement in long-term memory, measured as free recall, compared to academic tutoring alone (MD: 14.0 95%CI [-15.4, 43.4]). However,	(1 observational study)[57]	⨁◯◯◯ VERY LOW[a,b]

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
	when it was measured as semantic clustering, long-term memory was statistically improved (MD: 24.3 95%CI [5.3, 43.4]		

a. Indirectness of the comparison
b. Imprecision due to small number of patients

Question 10

Should screening with MRI for silent cerebral infarcts vs. no screening be used for children and adults with HbSS or HbSß^0 thalassemia?	
POPULATION:	Patients with sickle cell disease (adults and children)
INTERVENTTION:	Screening with MRI for silent strokes
COMPARISON:	No screening
MAIN OUTCOMES:	Frequency of silent cerebral infarcts and strokes
CONFLICT OF INTEREST:	Dr. McKinstry was recused.

Assessment

Problem

Is the problem a priority?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		Consequences of low IQ and developmental delays in individuals with SCD can be grave from medical and societal perspectives.

Desirable Effects

How substantial are the desirable anticipated effects?

Judgement	Research evidence	Additional considerations

○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Outcomes from the SIT trial – Transfusion (n=99) vs. Observation group (n=97). All rates are based on intention to treat. (N Engl J Med 2014) **Efficacy outcomes** / Incidence rate ratio (95% CI) / P value Infarct recurrence: 0.41 (0.12 – 0.99); 0.04 All neurologic events (TIA and infarct recurrence): 0.36 (0.10 – 0.83); 0.02 **Adverse events** / **Incidence rate ratio (95% CI)** / P value Vaso-occlusive pain: 0.41 (0.20 – 0.75); 0.004 Acute chest syndrome: 0.13 (0.04 – 0.28); <0.001 Priapism: 0.13 (0.03 – 0.55); 0.02 Symptomatic avascular necrosis of the hip: 0.22 (0.05 – 0.85); 0.02 Headache: 0.78 (0.39 – 1.57); 0.40 Blood-transfusion reaction: 5.33 (1.67 – 23.52); 0.05 HRQOL data from SIT: Children's scores at exit for Physical Function were 11.50 points higher for those in the transfusion group compared to those in the observation group, $t = 3.25$, $p \leq 0.001$; on Bodily Pain, [$t = 2.93$, $p = 0.004$] and 0.47 points higher (on a 1–5 point scale) on Change in Health, t = 3.29, $p \leq 0.001$. Children in the transfusion group scored 5.99 points higher on Physical Summary Scores at exit than children in the observation group, $t = 3.06$, $p = 0.003$. The increase in change in Health, measured as the child's health being better, was significantly greater for the transfusion group than the observation group (difference estimate = -0.54, P ≤ 0.001). that children with SCA who received regular blood transfusion therapy felt better and had better overall HRQL than those who did not receive transfusion therapy. (Am J Hematol. 2015 Feb;90(2):139-43) See previous questions. Identification of silent cerebral infarcts can help in determining which children and adults will have an established diagnosis of developmental delay or cognitive impairment and facilitate access to treatment programs, transfusion therapy, cognitive rehabilitation, as well as state and federal resources. Screening framework from epidemiological principles is used.[43]	Our panel consisted of two sickle cell disease stakeholders directly impacted by the disease, three neurologists, two neuroradiologists, three hematologist (all of which provide medical care to children and adults), a psychologist, an education specialist (also a hematologist). All members of our panel strongly supportive identifying a silent cerebral infarct in a school age child and an adult with hemoglobin SS or SB^0thalassemia. Additional support for regular blood transfusions is based on the decreases in not only infarct recurrence, but also the substantial decrease in the major morbidities associated with sickle cell disease including, vaso-occlusion, pain, acute chest syndrome, symptomatic avascular necrosis of the hip, and headache. In addition, there was significant and clinically relevant improvement in patient centered quality of life for those receiving blood transfusion therapy when compared to those that did not. The barriers of regular blood transfusions therapy include, but not limited to accumulation of excessive iron stores, requirement for chelation therapy, increase in blood transfusion reactions, cost and inconvenience of monthly red blood cell transfusions. Given the pros and cons of transfusions, the committee strongly believed that screening for silent cerebral infarcts should be offered at least once to children and adults with HbSS or $HbS\beta^0$ thalassemia, but the decision to receive red blood transfusions, should be based on the family's values after weighing the clear benefits and risks.

Undesirable Effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations

○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		See previous questions. Identification of silent cerebral infarcts can help in determining which children and adults will have an established diagnosis of developmental delay or cognitive impairment and facilitate access to treatment programs, transfusion therapy, cognitive rehabilitation, as well as state and federal resources. Screening framework from epidemiological principles is used.

Certainty of evidence

What is the overall certainty of the evidence of effects?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Possibly high *See Appendix 1*	In children, certainty is lower due to the lack of effective treatment whereas in children transfusion therapy is effective

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence	Additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	No important certainty about the value of screening for a silent stroke given its impact on cognition and activities of daily living. There is important uncertainty among both, patients and provider about treatment with blood transfusion therapy- To discuss, possibly discordance between providers and families in terms of values. Despite the established benefit of blood transfusion to prevent strokes or recurrent SCI measurements, some families will elect to initially not receive monthly blood transfusion, elect to receive hydroxyurea, potentially and unproven option. There is clear evidence of benefit from the intervention for treatment of silent strokes, but not all individuals with an abnormal TCD measurement will elect to be treated.	For adults and children, no important uncertainty existed about the importance of identifying silent cerebral infarcts because of increased risk of future neurological injury, potential rehabilitation strategies, and escalation medical care. Families may differ in the values about the pros and cons of blood transfusion therapy for secondary prevention of cerebral infarct recurrence. All members of the committee strongly believed that families should be informed about the presence of a silent cerebral infarct based on the screening results. They can subsequently make a decision if they would like regular blood

		transfusion or experimental therapy, including hematopoetic stem cell transplant in a clinical trial setting.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know		An over-arching principle of our recommendation to screen for silent cerebral infarcts in children and adults with hemoglobin SS or SB^0thalassemia is the disease is rare, and associated with progressive brain dysfunction and decreases quality of life.

Resources required

How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know		

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ○ Moderate ○ High ● No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies		In 114 children with a variety of neurological conditions, the cost/benefit ratio (lower values denote a more cost-effective study) for MRI was 1.6 and for MRA was 3.3. The cost/benefit ratio for sickle cell disease 3.0. The best MRA cost/benefit ratios were obtained in patients with Menkes' disease, vascular malformations, and sickle cell disease. A normal MRI usually forecasted a normal MRA. However, abnormal MRI findings did not always predict MRA abnormalities. Positive, cost-beneficial information is provided by MRA mostly in conditions known to involve the cerebral vasculature.

Equity

What would be the impact on health equity?

Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ● Increased		Issues of race and vulnerable populations affect this issue. Identification of injury to the brain has an impact on medical care and services provided. This is particularly for African American

○ Varies ○ Don't know		males, individuals in jail, and individuals with associated psychosocial, developmental delay or mental health conditions.

Acceptability

Is the intervention acceptable to key stakeholders?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		

Feasibility

Is the intervention feasible to implement?

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know		Access to MRI may be limited in some geographic area or low resource settings. Younger children will need sedation.

Summary of judgements

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know

	Judgement						
Desirable Effects	Trivial	Small	**Moderate**	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	**Trivial**		Varies	Don't know
Certainty of evidence	Very low	Low	**Moderate**	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
Certainty of evidence of required resources	Very low	Low	Moderate	High			**No included studies**
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	**Increased**	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	**Don't know**

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

Conclusions

Recommendation

10.1 In early school age children with HbSS or HbSß^0 thalassemia who can undergo a non-sedated MRI, the ASH guideline panel recommends a one-time MRI screening for silent cerberal infarcts. The rationale for screening is based on the fact that silent cerebral infarcts are common, affecting 1 in 3 children and at least 1 in 2 adults with SCD; associated with cognitive impairment and poor school performance; are risk factors for future strokes; and silent cerebral infarcts are present in children with normal TCD measurements. Silent cerebral infarcts can be treated with regular blood transfusion to substantially reduce the incidence of a new stroke, silent infarct recurrence or both. Identification of silent cerebral infarcts facilitates providing school-based resources, educational support and government mandated resources for children with disabilities and similar resources and supports for adults.

(For children with HbSS or HbSß^0 thalassemia-strong recommendation, moderate certainty evidence)

Technical note-

-Our committee valued maintaining cognitive function greater than being alive with minimal cognitive function (significantly less than baseline functioning).

Five independent reasons justify screening for silent cerebral infarcts in children and adults with hemoglobin SS or SB^{0}thalassemia.

1. Silent cerebral infarcts are prevalent, approximately, 39% in children and 50% of adults will have a silent cerebral infarct.
2. Silent cerebral infarcts are progressive in both children and adults. The presence of silent cerebral infarcts predicts future neurological injury to the brain at a rate that exceeds the accepted threshold for prevention of neurological injury in adults with atrial fibrillation not receiving anti-coagulation.
3. Silent cerebral infarcts are associated with at least a 5 point full scale IQ drop in children with SCD, and it is reasonable to believe that there a similar degree of neurological morbidity in adults with SCD.
4. Once silent cerebral infarcts are identified, children and adults are eligible for evaluation for IEP and ADA services, respectively.
5. Most silent cerebral infarcts occur in the border zone regions of the brain which disproportionately affects executive function. The American Congress of Rehabilitation Medicine has formally endorsed evidenced based strategies to support individuals with executive dysfunction.

A sixth reason justifies screening for specifically in school-age children with silent cerebral infarcts and hemoglobin SS or SB^{0}thalassemia.

6. For children with pre-existing silent cerebral infarcts, regular blood transfusion therapy when compared to observation alone is associated with a 56% relative risk reduction in progression of silent cerebral infarcts or strokes.

10.2 In adults with sickle cell disease HbSS or HbSß^0 thalassemia who can undergo a non-sedated MRI, the ASH guideline panel suggests a one-time MRI screening for silent cerebral infarcts. The rationale for screening is based on the fact that silent infarcts are common, affecting at least 50% of young adults; are associated with cognitive impairment, poor employment performance and decreased instrumental activities of daily living; are risk factors for future silent cerebral infarcts; and can facilitate providing occupational therapy and government mandated resources for persons with disability.

(For adults with HbSS or HbSß^0 thalassemia-conditional recommendation, low certainty evidence)

See above technical note for #1-5 for adults.

Justification

See above technical note for #1-5

Implementation considerations

- Definition of silent infarct and progressive silent infarct (an infarct-like lesion was defined as an MRI signal abnormality that was at least 3 mm in one dimension and that was visible in two planes on fluid-attenuated inversion recovery (FLAIR) T2-weighted images. After an infarct lesion is identified a pediatric neurologist or neurologist must examine the patient and determine whether there is normal neurologic examination or an abnormality on examination that could not be explained by the location of the brain lesion or lesions. A hematologist definition of silent cerebral infarct will mis-classify approximately 10% of the children as having a silent cerebral infarct, when in fact they had a stroke, and their clinical course is different.

In the presence of a silent infarct, annual surveillance with MRI is suggested to allow for increased therapeutic interventions

- A second screening MRI is suggested if new behavioral or cognitive impairment occurs or a change in academic performance is noted.

- An older child who cannot undergo an non-sedated MRI should be supported by child life services to attempt MRI without sedation

-Since adults have increased prevalence of surgically correctable aneurysms, MRA should be added in adults

Appendices

Question 10. Evidence Profile

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Frequency of SCI and Stroke	• None of the included studies were comparative (compared screening with magnetic resonance imaging to no screening) • Data were available from observational studies documenting high prevalence of silent cerebral infarction (SCI) and stroke identified on imaging. Frequencies estimates were stratified based on the population age, comorbidities or history of stroke and phenotypes. • Data from the SIT trial provided supportive evidence for this screening question as it showed benefit of intervening (transfusion) in patients with SCIs.	0	-

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