SECTION I.
BASIC MEASURE INFORMATION

I.A. Measure Name

Anticipatory Guidance Regarding Hydroxyurea Treatment for Children with Sickle Cell Disease

I.B. Measure Citation Information

Dombkowski KJ, Madden B, Shevrin CA, McCormick J, Freed GL for the Quality Measurement, Evaluation, Testing, Review, and Implementation Consortium. Anticipatory Guidance Regarding Hydroxyurea Treatment for Children with Sickle Cell Disease. National Quality Measures Clearinghouse (NQMC). Rockville (MD): Agency for Healthcare Research and Quality (AHRQ). Published March 23, 2015.

I.C. Measure Description

Please provide a non-technical description of the measure that conveys to a broad audience what it measures.

This measure assesses the percentage of children younger than 18 years of age identified as having sickle cell anemia (Hb SS or Hb S beta-zero thalassemia [SCA]) who received anticipatory guidance regarding the risks and benefits of treatment with hydroxyurea as part of outpatient care during the measurement year. This measure uses medical record data to find evidence of the provision of anticipatory guidance. A higher proportion indicates better performance as reflected by appropriate testing. There are no existing quality measures for anticipatory guidance regarding the risks and benefits of treatment with hydroxyurea in children with SCD.

Approximately 2,000 infants are born with SCD in the United States each year, a condition that occurs predominantly in people of African and Hispanic descent. SCD is a chronic blood disorder, characterized by the presence of hemoglobin S (HbS). From infancy onward, the presence of this hemoglobin variant can lead to an array of serious medical conditions. Hydroxyurea is a drug that increases the percentage of fetal hemoglobin (HbF) in the blood, a variant that is protective against the clinical severity of SCA, which is caused by HbS. Hydroxyurea is indicated for pediatric patients with SCA who have recurrent vaso-occlusive events, including frequent pain episodes and acute chest syndrome. While abundant evidence has been gathered over the years supporting its efficacy in children and its low toxicity, the drug is currently only approved by the US Food and Drug Administration for use in adults. Although off-label use in children with SCA is supported by the National Institutes of Health (NIH) and the National Heart, Lung and Blood Institute (NHLBI), use of hydroxyurea therapy in children with SCA remains low. Possible reasons for this include inadequate knowledge among health care providers, financial challenges for patients, and lack of capacity in medical delivery system to support the volume of patient encounters necessary for sustained use of the drug. For patients receiving anticipatory guidance, the two most important long-term concerns

to discuss with families are potential treatment-related infertility (no major relationship yet seen) and cancer (anecdotes exist but there are no assumptions of causality). As patient years of treatment accumulate, concerns about serious long-term consequences are abating at many academic programs. While barriers remain, evidence suggests that hydroxyurea treatment is of substantial benefit to many young children with SCA and that treatment should begin before the onset of substantial organ damage.

This measure uses medical record data and is calculated as the percentage of eligible children who received anticipatory guidance regarding the risks and benefits of treatment with hydroxyurea as part of outpatient care (numerator divided by denominator).

I.D. Measure Owner

The Quality Measurement, Evaluation, Testing, Review, and Implementation Consortium (Q-METRIC)

I.E. National Quality Forum (NQF) ID (if applicable)

Not applicable

I.F. Measure Hierarchy

Please use this section to note if the measure is part of a measure hierarchy or is part of a measure group or composite measure. The following definitions are used by AHRQ's National Quality Measures Clearinghouse and are available at http://www.qualitymeasures.ahrq.gov/about/hierarchy.aspx:

I.F.1. Please identify the name of the **collection** of measures to which the measure belongs (if applicable). A Collection is the highest possible level of the measure hierarchy. A Collection may contain one or more Sets, Subsets, Composites, and/or Individual Measures.

This measure is part of the Q-METRIC Sickle Cell Disease Measures collection.

I.F.2. Please identify the name of the measure **set** to which the measure belongs (if applicable). A Set is the second level of the hierarchy. A Set may include one or more Subsets, Composites, and/or Individual Measures.

This measure is part of the Q-METRIC Sickle Cell Disease Medical Record Data set.

I.F.3. Please identify the name of the **subset** to which the measure belongs (if applicable). A Subset is the third level of the hierarchy. A Subset may include one or more Composites and/or Individual Measures.

Not applicable

I.F.4. Please identify the name of the **composite** measure to which the measure belongs (if applicable). A Composite is a measure with a score that is an aggregate of scores from other measures. A Composite may include one or more other Composites and/or Individual Measures. Composites may comprise component measures that can or cannot be used on their own.

Not applicable

I.G. Numerator Statement

The eligible population for the numerator is the number of children younger than 18 years of age with SCA who received anticipatory guidance regarding the risks and benefits of treatment with hydroxyurea as part of outpatient care during the measurement year (January 1-December 31). Eligible children are restricted to those diagnosed with SCA, determined by hemoglobin variants identified in Table 1, with the appropriate ICD-9 codes documented in the medical record. Codes to identify outpatient care are listed in Table 2.

Anticipatory guidance is any written or face-to-face verbal communication regarding the risks and benefits of treatment with hydroxyurea as part of outpatient care with patient, parent, or family member. Evidence of anticipatory guidance is determined through medical record review. Documentation in the medical record must include, at minimum, a note containing the date on which verbal or written anticipatory guidance was provided.

Table 1: Codes to Identify Sickle Cell Anemia

Condition Name	Hemoglobin Screening Result	ICD-9 Code(s)
Hb beta zero-thalassemia	Hb F only	282.49
Hb SS-disease (sickle cell anemia)	Hb F,S	282.6, 282.61, 282.62

Table 2: Codes to Identify Outpatient Care

Description	CPT	HCPCS	ICD-9-CM Diagnosis
Office or other outpatient services	99201-99205, 99211-99215, 99241-99245		
Preventive medicine	99381-99385, 99391-99395, 99401-99404, 99411-99412, 99420, 99429	G0438, G0439	
General medical examination			V20.2, V70.0, V70.3, V70.5, V70.6, V70.8, V70.9

I.H. Numerator Exclusions (as appropriate)

1. Inpatient stays, emergency department visits, and urgent care visits are excluded from the calculation.

2. Children with a diagnosis in the sampled medical record indicating one of the sickle cell disease variants listed in Table 3 should not be included in the eligible population *unless* there is also a diagnosis for a sickle cell variant listed in Table 1.

Table 3: Excluded Sickle Cell Disease Diagnosis Codes

Condition Name	Hemoglobin Screening Result	ICD-9 Code(s)
Hb S beta-thalassemia	Hb F,S,A	282.41, 282.42
Hb C-disease	Hb F,C	282.7
Hb SC-disease	Hb F,S,C	282.63, 282.64
Hb SD-disease	Hb F,S,D	282.68, 282.69
Hb SE-disease	Hb F,S,E	282.68, 282.69
Hb C beta-thalassemia	Hb F,C,A	282.49
Hb D beta-thalassemia	Hb F,D,A	282.49
Hb E beta-thalassemia	Hb F,E,A	282.49
Hb E-disease	Hb F,E	282.7
Hb H-disease	Hb F,H	282.49
Hb C-carrier	Hb F,A,C	282.7
Hb D-carrier	Hb F,A,D	282.7
Hb E-carrier	Hb F,A,E	282.7
Hb S (sickle)-carrier	Hb F,A,S	282.5

I.I. Denominator Statement

The eligible population for the denominator is the number of children younger than 18 years of age with SCA who received outpatient care during the measurement year (January 1-December 31). Eligible children are restricted to those diagnosed with SCA, determined by hemoglobin variants identified in Table 1, with the appropriate ICD-9 codes documented in the medical record. Codes to identify outpatient care are listed in Table 2.

I.J. Denominator Exclusions (as appropriate)

1. Inpatient stays, emergency department visits, and urgent care visits are excluded from the calculation.
2. Children with diagnosis in the sampled medical record indicating one of the sickle cell disease variants listed in Table 3 should not be included in the eligible population *unless* there is also a diagnosis for a sickle cell variant listed in Table 1.

I.K. Data Sources

Check all the data sources for which the measure is specified and tested.

Data Source	
1. Administrative Data (e.g., claims data)	
2. Paper Medical Record	**x**
3. Survey – Health care professional report	
4. Survey – Parent/caregiver report	
5. Survey – Child report	
6. Electronic Medical Record	**x**
7. Other (If other, please list all other data sources in the field below.)	

SECTION II.
DETAILED MEASURE SPECIFICATIONS

Provide sufficient detail to describe how a measure would be calculated from the recommended data sources, either by uploading a separate document or by providing a link to a URL in the field below. Examples of detailed measure specifications can be found in the CHIPRA Initial Core Set Technical Specifications Manual 2011 published by the Centers for Medicare & Medicaid Services.[1] Although submission of formal programming code or algorithms that demonstrate how a measure would be calculated from a query of an appropriate electronic data source are not requested at this time, the availability of these resources may be a factor in determining whether a measure can be recommended for use.

Please see the specification, *Q-METRIC Sickle Cell Disease Measure 10, Anticipatory Guidance Regarding Hydroxyurea Treatment for Children with Sickle Cell Disease,* at the end of this document. The SCD codebook used for medical record data abstraction is also included as a separate file.

[1] Initial Core Set of Children's Health Care Quality Measures: Technical Specifications and Resource Manual for Federal Fiscal Year 2011 Reporting. Available at http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Quality-of-Care/Downloads/InitialCoreSetResourceManual.pdf and http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Quality-of-Care/CHIPRA-Initial-Core-Set-of-Childrens-Health-Care-Quality-Measures.html.

SECTION III.
IMPORTANCE OF THE MEASURE

In the following sections, provide brief descriptions of how the measure meets one or more of the following criteria for measure importance (general importance, importance to Medicaid and/or CHIP, complements or enhances an existing measure). Include references related to specific points made in your narrative (not a free-form listing of citations).

III.A. Evidence for General Importance of the Measure

Provide evidence for all applicable aspects of general importance, including but not limited to the following:

- Addresses a known or suspected quality gap or disparity in quality (e.g., addresses a socioeconomic disparity, a racial/ethnic disparity, a disparity for Children with Special Health Care Needs (CSHCN) and/or a disparity for limited English proficiency (LEP) populations.

- Potential for quality improvement (i.e., there are effective approaches to reducing the quality gap or disparity in quality).

- Prevalence of condition among children under age 21 and/or among pregnant women.

- Severity of condition and burden of condition on children, family, and society (unrelated to cost).

- Fiscal burden of measure focus (e.g., clinical condition) on patients, families, public and private payers, or society more generally, currently and over the life span of the child.

- Association of measure topic with children's future health—for example, a measure addressing childhood obesity may have implications for the subsequent development of cardiovascular diseases.

- The extent to which the measure is applicable to changes across developmental stages (e.g., infancy, early childhood, middle childhood, adolescence, young adulthood).

Sickle Cell Disease Prevalence and Incidence

SCD is one of the most common genetic disorders in the United States (Kavanagh et al., 2011). The National Heart, Lung and Blood Institute estimates that 2,000 infants are born with SCD in the United States each year (NHLBI, 2002). SCD affects 70,000-100,000 children and adults in the United States, predominantly those of African and Hispanic descent (Hassell et al., 2010). The condition is chronic,

lifelong and associated with a decreased lifespan.

Sickle Cell Disease Pathology and Severity

Vaso-occlusion (the sudden blockage of a blood vessel caused by the sickle shape of abnormal blood cells) is responsible for most complications of SCD, including pain episodes, sepsis, stroke, acute chest syndrome, priapism, leg ulcers, osteonecrosis and renal insufficiency (Steinberg, 1999). In addition, SCD can have hemolytic and infectious complications that result in morbidity and mortality in children with SCD (Kavanagh et al., 2011).

Sickle Cell Disease Burden in Daily Life

The effect of SCD on children and families is significant; severe pain episodes and hospitalizations restrict daily activities and reflect negatively on school attendance and performance, as well as on sleep and social activities (Lemanek et al., 2009; Alvim et al., 2005). Although medical management of SCD continues to improve over time, 196 US children died from SCD-related causes between 1999 and 2002 (Yanni et al., 2009).

Sickle Cell Disease Cost

In a study of health care utilization among low income children with SCD between 2004 and 2007, 27% of these children required inpatient hospitalization and 39% used emergency care during a year. Of these children, 63% averaged one well-child visit per year and 10% had at least one outpatient visit with a specialist (Raphael et al., 2009). Patients with SCD use many parts of the health care system, incurring significant costs. In 2009, mean hospital charges for children with SCD and a hospital stay were $23,000 for children with private insurance and $18,200 for children enrolled in Medicaid (AHRQ, 2012). Kauf et al. estimate the lifetime cost of health care per patient with SCD to be approximately $460,000 (Kauf et al., 2009).

Hydroxyurea use may reduce medical expenses for children with SCA. In a subanalysis of 159 pediatric patients taking hydroxyurea drawn from a North Carolina Medicaid claims database, 41% of patients were classified as adherent compared with 29% of patients older than 18 (Candrilli et al., 2011). Among the pediatric patients, treatment adherence in the 12 months following hydroxyurea initiation was associated with a significant reduction in all-cause and SCD-related inpatient, emergency, and total costs. (SCD-related costs were $5,772 for adherent pediatric patients vs. $8,631 for those who were not.). The authors suggest that the decreases in mortality, stroke, and end-stage organ damage likely to result from hydroxyurea adherence may lead to greater cost savings (Candrilli et al., 2011).

Wang and colleagues analyzed financial data collected during the BABY HUG clinical trial, which assessed hydroxyurea use in very young children with SCA (Wang et al., 2013). In this study, hydroxyurea was associated with significant medical cost savings because of reduced hospitalization expenses. Total estimated annual costs for young children (aged 1 to 3 years) receiving hydroxyurea were 21% lower than costs for those on placebo ($11,072 vs. $13,962, respectively). This occurred because inpatient savings more than compensated for the greater outpatient care expenses resulting from additional clinic visits, lab monitoring, and the cost of the medication. The authors

suggest that savings could be even more pronounced in older children with SCA, as they are hospitalized more often for the pain events that hydroxyurea addresses (Wang et al., 2013).

Outcomes of Anticipatory Guidance Regarding Hydroxyurea Treatment

While hydroxyurea therapy is currently approved only for use in adults, pediatric hematologists are enthusiastic about its use in the children with SCA, who are the sickest of young sickle cell patients. SCA is a chronic and progressively debilitating medical condition characterized by ongoing hemolytic anemia and recurrent acute vaso-occlusive events (pain crises, splenic sequestration, acute chest syndrome, and stroke) with considerable morbidity from insidious but inexorable organ damage. Early treatment in young patients who have developed serious or irreversible organ damage is an appropriate goal (Ware, 2010).

With support from both the NHLBI guidelines (2002) and an NIH Consensus Development Conference statement (Brawley et al., 2008), which notes that hydroxyurea is the only treatment for SCD that modifies the disease process, clinicians are pressing ahead with administration of hydroxyurea in children with SCA. Reasons cited include:

- Hydroxyurea is a single agent; it is inexpensive, orally administered, and taken as a single daily dose.
- Hydroxyurea increases both fetal hemoglobin (HbF) and total hemoglobin, thus reducing the amount of sickle hemoglobin (HbS), which causes the damage associated with SCD. The drug also beneficially reduces white blood cell count and reticulocytes and lowers lactic dehydrogenase (LDH).
- Hydroxyurea therapy ameliorates anemia, leading to fewer vaso-occlusive events and hospitalizations, and decreases hemolysis.
- Hydroxyurea works in all age groups to prevent acute events and chronic organ dysfunction.
- Benefits of hydroxyurea therapy continue over time without medication resistance or tolerance.
- No major short-term toxicities or known long-term chronic effects or complications have been associated thus far with hydroxyurea use in children, though research about adverse effects is continuing (Ware, 2010).

Research has further shown that despite disease severity, children with SCD taking hydroxyurea have higher self-reported overall health-related quality of life (HRQoL) and better physical HRQoL than children not taking the medication (Thornburg et al., 2011).

The decision to start hydroxyurea treatment in a child with SCD should be deliberate and thoughtful. The medical history of the patient should be reviewed carefully to document the number and severity of acute vaso-occlusive events and any evidence of chronic organ damage. Also, previous compliance with outpatient clinic visits should be reviewed, along with neurocognitive status and psychosocial environment. The decision to treat should be discussed openly with patients and families (Heeney et al., 2008).

This measure assesses the percentage of children identified as having sickle cell anemia who received anticipatory guidance regarding the risks and benefits of treatment with hydroxyurea as part of

outpatient care during the measurement year. The measure does not change across developmental stages.

Performance Gap

Several concerns have been raised about the underuse of hydroxyurea therapy in children with SCA. In many cases, clinical care tends to be supportive (e.g., transfusions, intravenous fluids, analgesics, antibiotics) rather than addressing underlying causes (McGann et al., 2011). Because the effects of SCA are insidious and progressive, it should be viewed as a chronic medical condition that merits early and aggressive therapy. To say that pediatric patients with SCA are doing well in the absence of pain or if not hospitalized is an inadequate assessment. Ongoing therapy is necessary to prevent complications and to treat these children before they develop debilitating organ damage (Ware 2010).

Concern exists, too, that hydroxyurea therapy is being administered predominantly to severely ill pediatric patients, many of whom have already started to develop organ-specific complications. In a review of Medicaid medical and pharmacy claims for 1996 through 2006 for children in South Carolina, Tripathi and colleagues (2011) report that fewer than 10% of pediatric patients with SCD received hydroxyurea treatment. They also found great variability in the use of hydroxyurea therapy, possibly indicating that providers are using it to control exaggerated vaso-occlusive episodes and acute chest syndrome, rather than as a long-term treatment to mitigate organ damage. This limited and inconsistent use raises concern that the drug is not being used to its full potential in pediatric patients with SCA in routine practice (Tripathi et al., 2011).

Adherence with treatment is also a problem. Because children may miss occasional doses without ill effect, they may skip subsequent days not understanding that ongoing red blood cell production requires daily doses of the medication (Heeney et al., 2008). Health care providers who administer hydroxyurea need to anticipate barriers and create personal solutions, such as showing erythrocyte changes, emphasizing regular dosing times, and reminding parents that they are responsible for ensuring that the medication is taken daily (Strouse et al., 2012).

Barriers to the use of hydroxyurea therapy and possible solutions were detailed in the NIH Consensus Development Conference statement (Brawley et al., 2008). At the patient level, poverty and public insurance status make access and adherence difficult, as does immigrant status. System-level barriers identified in the statement include 1) financing (lack of insurance, type of insurance, underinsurance, scope of coverage, co-pays, reimbursements, payment structures); 2) geographic isolation; 3) lack of coordination between academic centers and community-based clinicians; 4) limited access to comprehensive care centers and comprehensive care models; 5) problems in transitioning from pediatric to adult care; 6) limited access (e.g., the geographic distribution, recruitment, and retention of clinicians competent in the provision of comprehensive care to patients who have SCD; 7) inadequate government, industry, and philanthropic support for the care of patients with SCD; 8) slow development and promotion of hydroxyurea because of lack of commercial interest; 9) lack of visibility and empowerment of SCD advocacy groups; 10) cultural and language barriers to the provision of appropriate care; and 11) inadequate information technology systems to support the long-term care of for patients with SCD.

Proposed solutions from the NIH Consensus Development Conference statement include: 1) promote models of care across the patient lifespan that support quality of care and improved access; 2) provide multidisciplinary care to improve patient mental and physical health; 3) provide support for community health worker models; 4) support care coordination with telemedicine; 5) use culturally or language-sensitive educational materials; 6) implement health promotion models to foster adherence to therapies; 7) support community-based education about the benefits and risks of hydroxyurea; 8) improve federal, state, and local coordination of SCD activities; 9) provide support for cultural competency training across the interdisciplinary SCD treatment team; 10) improve insurance coverage for SCD; 11) eliminate barriers restricting access to public insurance; 12) support ongoing training for health providers to achieve and maintain competence in caring for patients with SCD, including the provision of hydroxyurea therapy; 13) increase funding for SCD from government, industry, and philanthropic organizations; 14) encourage partnership and support of SCD advocacy groups; and 15) develop better info systems to coordinate care delivery (Brawley et al., 2008).

III.B. Evidence for Importance of the Measure to Medicaid and/or CHIP

Comment on any specific features of this measure important to Medicaid and/or CHIP that are in addition to the evidence of importance described above, including the following:

- The extent to which the measure is understood to be sensitive to changes in Medicaid or CHIP (e.g., policy changes, quality improvement strategies).
- Relevance to the Early and Periodic Screening, Diagnostic and Treatment benefit in Medicaid (EPSDT).[2]
- Any other specific relevance to Medicaid/CHIP (please specify).

Sickle Cell Disease and Medicaid/CHIP

The majority of children with SCD are enrolled in Medicaid. In 2009, 67% of children with SCD discharged from the hospital were covered by Medicaid, while 25% had private insurance (AHRQ, 2012). Several concerns about the underuse of hydroxyurea therapy detailed in the Performance Gap section above are applicable to the Medicaid pediatric population. In South Carolina, only a small percentage of children on Medicaid had access to subspecialty care; this may indicate lack of access to care that is both appropriate for the severity of their disease and offered by knowledgeable providers (Tripathi et al., 2011). The NIH Consensus Development Conference statement raised similar concern that limited access to centers providing comprehensive care raised a barrier to adherence (Brawley et al., 2008). All patients with SCD should be treated in clinics specializing in the disorder,

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[2] The EPSDT is a comprehensive set of benefits available to children and youth under age 21 who are enrolled in Medicaid. For more information, see http://www.healthlaw.org/images/stories/epsdt/3-ESDPT08.pdf.

the statement noted, and should have a principal health care provider who, if not a hematologist, consults frequently with one. This is especially relevant for hydroxyurea therapy, because its use should be directed by a knowledgeable pediatric hematologist (AAP, 2002). Obtaining specialty care is further complicated for patients enrolled in Medicaid by the limited and declining numbers of health care professionals trained to treat the disease (Brawley et al., 2008).

Successful adherence to hydroxyurea therapy requires a commitment to both daily dosing and frequent clinic visits to monitor blood levels. For children living in poverty, the stability and resources necessary to ensure successful hydroxyurea treatment may not exist in their daily lives. Patients with SCD who have access only to primary care providers or who depend on the emergency department for treatment will not receive care that is focused on the underlying issues of SCA.

On a positive note, because hydroxyurea treatment has been shown to reduce the cost of care, addressing issues of underuse could well result in cost savings for Medicaid.

III.C. Relationship to Other Measures (if any)

Describe, if known, how this measure complements or improves on an existing measure in this topic area for the child or adult population, or if it is intended to fill a specific gap in an existing measure category or topic. For example, the proposed measure may enhance an existing measure in the initial core set, it may lower the age range for an existing adult-focused measure, or it may fill a gap in measurement (e.g., for asthma care quality, inpatient care measures).

There are currently no quality measures for the diagnosis, assessment or treatment of pediatric SCD.

References for Section III

Agency for Healthcare Research and Quality. Welcome to HCUPnet: Healthcare Cost and Utilization Project (HCUP). 2012; http://hcupnet.ahrq.gov/.

Alvim RC, Viana MB, Pires MA, et al. Inefficacy of piracetam in the prevention of painful crises in children and adolescents with sickle cell disease. *Acta Haematol* 2005; 113(4):228-233.

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Wang WC, Oyeku SO, Luo Z, et al. Hydroxyurea is associated with lower costs of care of young children with sickle cell anemia. *Pediatrics* 2013; 132(4):677-683.

Ware RE. How I use hydroxyurea to treat young patients with sickle cell anemia. *Blood* 2010; 115(26): 5300-5311.

Yanni E, Grosse SD, Yang Q, Olney RS. Trends in pediatric sickle cell disease-related mortality in the United States, 1983-2002. *J Pediatr* 2009; 154(4):541-545.

SECTION IV.
MEASURE CATEGORIES

CHIPRA legislation[3] requires that measures in the initial and improved core set, taken together, cover all settings, services, and topics of health care relevant to children. Moreover, the legislation requires the core set to address the needs of children across all ages,[4] including services to promote healthy birth. Regardless of the eventual use of the measure, we are interested in knowing all settings, services, measure topics, and populations that this measure addresses. These categories are not exclusive of one another, so please indicate "Yes" to all that apply.

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3 Children's Health Insurance Program Reauthorization Act of 2009. Public Law No. 111-3, 123 Stat. 8 (2009). Available at: http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=111_cong_public_laws&docid=f:publ003.111.

4 Under Section 214 of CHIPRA, States may elect to cover the following groups under Medicaid only or under both Medicaid and CHIP: pregnant women and children up to age 19 for CHIP or up to age 21 for Medicaid.

	Does the measure address this category [Yes/No drop-down]	
a. Care Setting – ambulatory	**YES**	
b. Care Setting – inpatient	**No**	
c. Care Setting – other—please specify	**No**	**[Add the following choices: home, school, other community and public health settings, long-term care, other---drop-down or radio buttons]**
d. Service – preventive health	**Yes**	
e. Service – care for acute conditions	**No**	
f. Service - care for children with special health care needs/chronic conditions	**Yes**	
g. Service – health promotion and services to promote healthy birth	**No**	
h. Service-other (please specify)	**No**	
i. Measure Topic -duration of enrollment	**No**	
j. Measure Topic – clinical quality	**Yes**	
k. Measure Topic – patient safety	**No**	
l. Measure Topic – family experience with care	**No**	
m. Measure Topic – care in the most integrated setting	**No**	
n. Measure Topic – other (please specify)		n/a
o. Population – pregnant women		n/a
p. Population – neonates (28 days after birth) (specify age range) [	**Yes**	Birth – 28 days
q. Population – infants (29 days to 1 year) (specify age range)	**Yes**	Children ages 29 days to 1 year
r. Population – pre-school age children (1 year through 5 years) (specify age range)	**Yes**	All ages in this range
s. Population – school-age children (6 years through 10 years) (specify age range)	**Yes**	All ages in this range
t. Population – adolescents (11 years through 20 years) (specify age range)	**Yes**	Adolescents 11 through 17 years

SECTION V.
EVIDENCE OR OTHER JUSTIFICATION FOR THE FOCUS OF THE MEASURE

The evidence base for the focus of the measures will be made explicit and transparent as part of the public release of CHIPRA deliberations; thus, it is critical for submitters to specify the scientific evidence or other basis for the focus of the measure in the following sections.

V.A. Research Evidence

Research evidence should include a brief description of the evidence base for valid relationship(s) among the structure, process, and/or outcome of health care that is the focus of the measure. For example, evidence exists for the relationship between immunizing a child or adolescent (process of care) and improved outcomes for the child and the public. If sufficient evidence existed for the use of immunization registries in practice or at the State level and the provision of immunizations to children and adolescents, such evidence would support the focus of a measure on immunization registries (a structural measure).

Describe the nature of the evidence, including study design, and provide relevant citations for statements made. Evidence may include rigorous systematic reviews of research literature and high-quality research studies.

This measure focuses on a clinical process (anticipatory guidance regarding hydroxyurea treatment for children with SCA), that, if followed, results in a desirable clinical outcome (increased amounts of HbF, leading to a reduction in the occurrence of vaso-occlusive events, such as frequent pain episodes and acute chest syndrome, as well as less frequent hospitalizations and transfusions). The measure highlights where providers or health systems are falling short in providing maintenance health care for children with SCD.

Hydroxyurea is an FDA-approved drug available to treat SCA. Its use is currently approved only in adults, though NHLBI guidelines issued in 2002 support the off-label use of hydroxyurea in children with SCA, as does an NIH Consensus Development Conference statement issued in 2008 (Strouse et al., 2012; NHLBI, 2002; Brawley et al., 2008). In the mid-1990s, the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (the pivotal MSH clinical trial; Charache et al., 1995) tested hydroxyurea in adults and adolescents (though the latter were not separated out in analyses). The trial was halted early because of the clear beneficial effects of hydroxyurea. The trial's striking findings regarding the reduction of pain events, acute chest syndrome, hospitalizations, and transfusions prompted clinicians and researchers to press ahead with several clinical trials designed to investigate the use of hydroxyurea in younger children. The reasoning: because SCA is progressive disease, greater benefit from the drug will accrue from early use in children before organ damage occurs. While findings have been positive, results in children have been less pronounced than those of the MSH trial in adults. Researchers are also moving with care so not to miss any major toxicity issues associated with long-term use in children. However, as the years of observation accumulate, using hydroxyurea in children with SCA to treat a disease marked by severe symptoms and progressive organ damage is accepted among clinicians as reasonably safe strategy (Ware, 2010).

Table 4 summarizes several key sources of evidence for this measure, using the US Preventive Services Task Force (USPSTF) rankings (criteria denoted in Table 4).

Table 4: Evidence Supporting Hydroxyurea Treatment for Children with Sickle Cell Disease

TYPE OF EVIDENCE	KEY FINDINGS	LEVEL OF EVIDENCE (USPSTF RANKING*)	CITATIONS
Randomized controlled trial	The Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH), a randomized, double-blind, placebo-controlled clinical trial, found that hydroxyurea therapy ameliorated the clinical course of SCA in some adults with three or more painful crises per year. Reductions in the frequency of acute chest syndrome and transfusions were also noted. Long-term safety of hydroxyurea in patients with SCA is uncertain. The trial was stopped before treatment was completed because of the beneficial effects observed. (Note: adolescents were included among the participants, but not reported as a separate group.)	I	Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. *N Engl J Med* 1995; 332(20):1317-1322.
Randomized controlled trial	The HUG-KIDS study was a Phase I/II trial of hydroxyurea in children, ages 5 to 15 years, with SCA. The study showed that hydroxyurea significantly increases hemoglobin concentration, mean corpuscular volume, HbF, and F-cell percentage above pretreatment values. In addition, study results showed that pediatric and adult patients had similar hematologic toxicities. Finally, no adverse effect on growth was observed during the treatment period.	I	Kinney TR, Helms RW, O'Branski EE, et al. Safety of hydroxyurea in children with sickle cell anemia: Results of the HUG-KIDS Study, a phase I/II trial. *Blood* 1999; 94:1550-1554.
Randomized controlled trial	The Hydroxyurea Safety and Organ Toxicity Study (HUSOFT) was an NIH-funded pilot trial in which very young children, ages 6 to 28 months old, with a median age of 15 months with SCA tolerated a liquid hydroxyurea formulation (20 mg/kg/day) and had improved blood counts and HbF concentrations compared with predicted age-specific levels.	I	Wang WC, Wynn LW, Rogers ZR, et al. A two-year pilot trial of hydroxyurea in very young children with sickle-cell anemia. *J Pediatr* 2001; 139(6): 790-796.
Randomized controlled trial	The Hydroxyurea to Prevent Organ Damage in Children with Sickle Cell Anemia trial (BABY HUG) was an NIH-funded multicenter randomized double-blinded trial of hydroxyurea in children aged 9 to 18 months at enrollment and receiving hydroxyurea or placebo for 2 years. While it failed to show significant differences in its primary endpoints of renal and spleen function, subjects receiving the drug had few episodes of pain, acute chest	I	Wang WC, Ware RE, Miller ST, et al. Hydroxycarbamide* in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). *Lancet* 2011; 377(9778): 1663-1672.*

TYPE OF EVIDENCE	KEY FINDINGS	LEVEL OF EVIDENCE (USPSTF RANKING*)	CITATIONS
	syndrome, and dactylitis; less frequent hospitalizations and transfusions; plus higher hemoglobin and HbF levels and lower while blood cell and reticulocyte counts. It was not associated with significant toxicity other than expected mild to moderate neutropenia. Given the demonstrated benefits, clinicians should consider shifting their practice to prescribe hydroxyurea therapy to all very young children with SCA, rather than just treating only those most severely affected.		Thornburg CD, Files BA, Luo Z, et al. (2012). Impact of hydroxyurea on clinical events in the BABY HUG trial. *Blood* 2012; 120(22): 4304-4310. *Hydroxycarbamide is the British approved name for hydroxyurea.
Clinical guidelines (from agencies or groups)	NHLBI guidelines suggest that indications for hydroxyurea therapy in children and adolescents are HbSS (SCA) or SCD-S β^0-thalassemia and frequent pain episodes, history of acute chest syndrome, other severe vaso-occlusive events, or severe symptomatic anemia. After baseline evaluation, hydroxyurea can be initiated at 10-15 mg/kg/day in a single daily dose for 6 to 8 weeks, with regular testing for complete blood count, percent Hb F, and serum chemistries. If no major toxicity occurs, dose may be escalated every 6 to 8 weeks until the desired endpoints are reached; regular blood counts should continue. Endpoints include less pain, an increase in HbF to 15%-20%, increased hemoglobin level if severely anemic, improved well-being, and acceptable myelotoxicity. Caution should be taken in patients with compromised hepatic or renal function. (p 165).	III	National Heart Lung and Blood Institute. The Management of Sickle Cell Disease. National Institutes of Health. Bethesda, MD, 2002.
Clinical guidelines (from agencies or groups)	The AAP sections on Hematology/Oncology and the Committee on Genetics suggest that daily oral administration of hydroxyurea increases HbF levels, decreases leukocyte counts, and decreases the frequency of episodes of pain and acute chest syndrome. Hydroxyurea may be appropriate for selected children and adolescents, accompanied by frequent monitoring for myelotoxicity and other drug-related complications by a physician with expertise in SCD and chemotherapy.	III	American Academy of Pediatrics Section on Hematology/Oncology and Committee on Genetics. Health supervision for children with sickle cell disease. *Pediatrics* 2002; 109(3):526-535.
Clinical guidelines (from agencies or groups)	The NIH Consensus Development Conference stated that "Strong evidence supports the efficacy of hydroxyurea in adults to decrease severe painful episodes, hospitalizations, number of blood transfusions, and the acute chest syndrome. Although the evidence for efficacy of hydroxyurea treatment for children	III	Brawley OW, Cornelius LJ, Edwards LR, et al. National Institutes of Health Consensus Development Conference statement: Hydroxyurea treatment

TYPE OF EVIDENCE	KEY FINDINGS	LEVEL OF EVIDENCE (USPSTF RANKING*)	CITATIONS
	is not as strong, the emerging data are encouraging." (p. 938) "… the evidence in children does not contradict the findings in adults that hydroxyurea improves hematologic variables and decreases hospitalization rates." (p. 933)		for sickle cell disease. *Ann Intern Med* 2008; 148(12): 932-938.
Comprehensive literature review	After synthesizing the published literature on the efficacy, effectiveness, and toxicity of hydroxyurea in children with SCD, the authors wrote, "Although not approved in children for the treatment of SCD, hydroxyurea is the only readily available agent that improves both hematologic and clinical outcomes. Its known and potential toxicities should be interpreted in this context, because it is indicated for treating a disease with tremendous morbidity and early mortality. Co-management by the primary care provider and a pediatric hematologist/ oncologist may be helpful in expanding access to hydroxyurea, because the distance to a referral center and need for frequent monitoring for hematologic toxicity may be a barrier to treatment." (p. 1338)	III	Strouse JJ, Lanzkron S, Beach MC, et al. Hydroxyurea for sickle cell disease: a systematic review for efficacy and toxicity in children. *Pediatrics* 2008; 122(6):1332-1342.
Clinical overview and guidelines	"In lieu of curative therapy, one approach given considerable effort over the past 25 years has been the pharmacological induction of HbF beyond the fetal and infant periods. … Hydroxyurea … has a long and growing track record in inducing HbF in patients with SCD. In addition, hydroxyurea has a variety of salutary effects on other aspects of the pathophysiology of SCD, such as increased erythrocyte hydration, improved rheology, and reduced adhesiveness. Hydroxyurea also decreases leukocyte count, and releases nitric oxide. … Hydroxyurea may be an ideal therapeutic agent for use in children with SCD." (pp. 484-485)	III	Heeney MM, Ware RE. Hydroxyurea for children with sickle cell disease. *Pediatr Clin North Am* 2008; 55(2):483-501.
Clinical overview and guidelines	Hydroxyurea can be offered to children with pain or acute chest syndrome as young as 2 years old. The drug should be considered for young patients with few acute clinical events but abnormal lab parameters. Another emerging category for treatment consideration is early evidence of organ dysfunction, such as hypoxemia, microalbuminuria, or elevated TCD velocities.	III	Ware RE. How I use hydroxyurea to treat young patients with sickle cell anemia. *Blood* 2010; 115(26): 5300-5311.
Clinical overview	"… hydroxyurea should now be considered for every patient with SCA, regardless of symptoms, since we know that all patients with	III	McGann PT, Ware RE. Hydroxyurea for sickle cell anemia: what have

TYPE OF EVIDENCE	KEY FINDINGS	LEVEL OF EVIDENCE (USPSTF RANKING*)	CITATIONS
	SCA experience sickle-related vaso-occlusion and subsequent organ damage starting at a very early age. Ideally the time to intervene is early in life, just as fetal hemoglobin production declines in the first year." (p. 164)		we learned and what questions still remain? *Curr Opin Hematol* 2011; 18(3): 158-165.
Clinical guidelines	"Indications for hydroxyurea therapy are not universally agreed upon, but with greater evidence of long-term efficacy and safety, the threshold is lowering." (p. 368) The authors identify two strong potential indications for hydroxyurea therapy: frequent painful events and dactylitis. Moderate indications are acute chest syndrome, elevated transcranial Doppler velocities, stroke prophylaxis, and parental request.	III	Strouse JJ, Heeney MM. Hydroxyurea for the treatment of sickle cell disease: efficacy, barriers, toxicity, and management in children. *Pediatr Blood Cancer* 2012; 59(2): 365-371.

Note: USPSTF criteria for assessing evidence at the individual study level are as follows: I) Properly powered and conducted randomized controlled trial (RCT); well-conducted systematic review or meta-analysis of homogeneous RCTs. II) Well-designed cohort or case-control analytic study. III) Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees.

Other clinical trials have investigated hydroxyurea therapy:

- Stroke With Transfusions Changing to Hydroxyurea (SWiTCH) was a phase 3 multicenter trial comparing transfusions and chelation with hydroxyurea and phlebotomy for children with SCA, stroke, and iron overload. NHLBI stopped the trial after interim analysis showed the primary endpoint of a reduced iron load was not achievable. An imbalance of strokes between the treatment arms was also observed; 10% of hydroxyurea recipients experienced recurrent stroke versus none for those in the transfusion arm (Ware et al., 2011 and Ware et al., 2012)
- TCD With Transfusions Changing to Hydroxyurea (TWiTCH), which grew out of the SWiTCH work, is a Phase III trial currently comparing hydroxyurea with transfusions for children with abnormally elevated TCD velocities but no primary stroke (Ware et al., 2012).
- The BABY-HUG follow-up cohort is planned through 2016 when participants will be 9 to 13 years old; the study will provide valuable data for longer-term safety and effectiveness of hydroxyurea (Thornburg et al., 2012, Wang et al., 2011)
- Hydroxyurea to Prevent CNS Complications of SCD in Children Study (HU Prevent) is a randomized Phase II pilot study in young children (12 to 48 months old) without stroke or stroke risk, to study the effect of hydroxyurea on stroke, silent cerebral infarct, and abnormal TCD velocity (Strouse et al., 2012)
- Long Term Effects of Hydroxyurea Therapy in Children with Sickle Cell Disease (HUSTLE) is a prospective observational and longitudinal cohort study gathering data on hydroxyurea pharmacokinetics, genotoxicity, and long-term effects on organ function (Ware, 2010).

- Evaluating the Safety and Effectiveness of Hydroxyurea and Magnesium Pidolate to Treat People with Hemoglobin Sickle Cell Disease (CHAMPS). This study focused on the hydroxyurea-magnesium pidolate drug combination for patients with HbSC disease but was terminated in late 2008 because of inadequate enrollment (Ware, 2010)

V.B. Clinical or Other Rationale Supporting the Focus of the Measure (optional)

Provide documentation of the clinical or other rationale for the focus of this measure, including citations as appropriate and available.

Initially synthesized in Germany in 1869, hydroxyurea was developed 50 years ago as an anti-cancer drug. It was first tested in patients with SCD in 1984 to address the hemoglobin deficiencies that define this blood disorder (Brawley et al., 2008).

In infants born with SCD, the presence of healthy fetal hemoglobin (HbF) is gradually compromised by the increasing presence of sickle hemoglobin (HbS). This hemoglobin variant becomes depleted of oxygen, which causes it to become dehydrated and assume a crescent or sickle shape. The misshapen and sticky HbS cells clump together and adhere to the walls of the blood vessels. This aggregation blocks blood flow to the organs and limbs, causing painful episodes and permanent damage to the eyes, brains, heart, lungs, kidneys, liver, bones, and spleen. Infections and lung disease are the leading cause of death in patients with SCD (McGann et al., 2011; Ware, 2010)

Hydroxyurea is an effective therapy for SCA, the most acute form of SCD, because it induces the development of HbF and reduces marrow production of neutrophils and reticulocytes, which promote vaso-occlusion through adhesion. Having a higher percentage of HbF decreases hemolysis and is protective against clinical severity of the disease; it increases total hemoglobin concentration, and improves blood flow — leading to a decrease in pain events, acute chest syndrome, hospitalization, and transfusion (McGann et al., 2011; Strouse et al., 2012; Ware, 2010) These effects were first documented in adults in the MSH clinical trial (Charache et al., 1995). Hydroxyurea also reduces white blood cell count, which is associated with morbidity and mortality in patients with SCA; it may also support local release of nitric oxide (McGann et al., 2011; Ware, 2010).

Usually, most children with good hydroxyurea adherence have impressive clinical improvement within weeks of starting therapy. Because laboratory effects (e.g., HbF induction, lower white blood cell count) are dose dependent, it may take 4 to 6 months to reach maximum effect. The initial suggested dose of hydroxyurea, 20 mg/kg/day, should be escalated by approximately 5 mg/kg/day every 8 weeks until a maximum tolerated dose is achieved, usually within 6 months. This dose should not exceed 35 mg/kg/day (Heeney et al., 2008; Strouse et al., 2012).

Fixed-dose hydroxyurea in young children, with dose escalation in older children, is safe, provided regular monitoring occurs for myelosuppression (Strouse et al., 2012). This decrease in bone marrow activity is transient, reversible, and actually reflects the desired marrow suppression that creates fewer neutrophils, thus lowering the white blood cell count (Ware, 2010). Other reported side effects include occasional headache, gastrointestinal symptoms (usually addressed by switching the dose from morning to evening), and dermatologic changes such as darkening of skin and nails. Regular

clinic visits to monitor the patient's adherence to hydroxyurea therapy, overall health, and lab values are crucial (Heeney et al., 2008; Strouse et al., 2008; Ware, 2010).

In summary, hydroxyurea:

- reduces morbidity and mortality in children and adults with SCA;
- is well -tolerated in children and adults with SCA without significant short-term toxicities or long-term safety concerns;
- is supported by a large body of evidence demonstrating its safety and efficacy as a disease modifying therapy for patients with SCA (McGann et al., 2011).

Because some children will begin taking hydroxyurea at a very young age and for an indefinite period of time, investigation of the drug's long-term safety profile should continue. Concerns to be definitively resolved include any related development of infertility or cancer (Ware, 2010). Varying opinions exist as to whether hydroxyurea therapy should be extended to younger children with SCA but few symptoms in order to gain protective effects (Thornburg et al., 2012) or to children with other SCD variations (Strouse and Heeney, 2012).

References for Section V

Brawley OW, Cornelius LJ, Edwards LR, et al. National Institutes of Health Consensus Development Conference statement: Hydroxyurea treatment for sickle cell disease. *Ann Intern Med* 2008; 148(12): 932-938.

Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. N Engl J Med 1995; 332(20):1317-1322.

Heeney MM, Ware RE. Hydroxyurea for children with sickle cell disease. *Pediatr Clin North Am* 2008; 55(2):483-501.

McGann PT, Ware RE. Hydroxyurea for sickle cell anemia: what have we learned and what questions still remain? *Curr Opin Hematol* 2011; 18(3): 158-165.

Strouse JJ, Heeney MM. Hydroxyurea for the treatment of sickle cell disease: efficacy, barriers, toxicity, and management in children. *Pediatr Blood Cancer* 2012; 59(2): 365-371.

Strouse JJ, Lanzkron S, Beach MC, et al. Hydroxyurea for sickle cell disease: a systematic review for efficacy and toxicity in children. *Pediatrics* 2008; 122(6):1332-1342.

Thornburg CD, Files BA, Luo Z, et al. Impact of hydroxyurea on clinical events in the BABY HUG trial. *Blood* 2012; 120(22): 4304-4310.

Wang WC, Ware RE, Miller ST, et al. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). *Lancet* 2011; 377(9778): 1663-1672.

Ware RE. How I use hydroxyurea to treat young patients with sickle cell anemia. *Blood* 2010; 115(26): 5300-5311.

Ware RE, Schultz WH, Yovetich N, et al. Stroke With Transfusions Changing to Hydroxyurea (SWiTCH): A phase III randomized clinical trial for treatment of children with sickle cell anemia, stroke, and iron overload. *Pediatr Blood Cancer* 2011; 57(6): 1011-1017.

Ware RE, Helms RW. Stroke With Transfusions Changing to Hydroxyurea (SWiTCH). *Blood* 2012; 119(17): 3925-3932.

SECTION VI.
SCIENTIFIC SOUNDNESS OF THE MEASURE

Explain the methods used to determine the scientific soundness of the measure itself. Include results of all tests of validity and reliability, including description(s) of the study sample(s) and methods used to arrive at the results. Note how characteristics of other data systems, data sources, or eligible populations may affect reliability and validity.

VI.A. Reliability

Reliability of the measure is the extent to which the measure results are reproducible when conditions remain the same. The method for establishing the reliability of a measure will depend on the type of measure, data source, and other factors. Explain your rationale for selecting the methods you have chosen, show how you used the methods chosen, and provide information on the results (e.g., the Kappa statistic). Provide appropriate citations to justify methods.

This measure is based on medical record data. Reliability testing is described below.

Data and Methods

Our testing data consisted of an audit of medical records from the three largest centers serving SCD patients in Michigan during 2012: Children's Hospital of Michigan (CHM, Detroit), Hurley Medical Center (Hurley, Flint), and the University of Michigan Health System (UMHS, Ann Arbor). Combined, these sites treat the majority of children with SCD in Michigan. Medical records for all children with SCD meeting the measure specification criteria during the measurement year were abstracted at each site. Abstracting was conducted in two phases; during Phase 1, 435 records were abstracted among the three sites. In Phase 2, an additional 237 cases were abstracted at one site. In total, 672 unique records were reviewed for children with SCD to test this measure.

Reliability of medical record data was determined through re-abstraction of patient record data to calculate the inter-rater reliability (IRR) between abstractors. Broadly, IRR is the extent to which the abstracted information is collected in a consistent manner. Low IRR may be a sign of poorly executed abstraction procedures, such as ambiguous wording in the data collection tool, inadequate abstractor training, or abstractor fatigue. For this project, the medical record data collected by two nurse abstractors were compared.

Measuring IRR at the beginning of the abstraction is imperative to identify any misinterpretations early on. It is also important to assess IRR throughout the abstraction process to ensure that the collected data maintain high reliability standards. Therefore, the IRR was evaluated during Phase 1 at each site to address any reliability issues before beginning data abstraction at the next site.

IRR was determined by calculating both percent agreement and Kappa statistics. While abstraction was still being conducted at each site, IRR assessments were conducted for 5% of the total set of unique patient records that were abstracted during Phase 1 of data collection. Two abstractors reviewed the same medical records; findings from these abstractions were then compared, and a list of discrepancies was created.

Three separate IRR meetings were conducted, all of which included a review of multiple SCD measures that were being evaluated. Because of eligibility criteria, not all patients were eligible for all measures. Therefore, records for IRR were not chosen completely at random; rather, records were selected to maximize the number of measures assessed for IRR at each site.

Results

For this measure, 16 of 435 unique patient records (4%) from Phase 1 of the abstraction process were assessed for IRR across the three testing sites.

Table 5 shows the percent agreement and Kappa statistic for the measure numerator for each site and across all sites. The agreement for this measure is 100% and the Kappa is 1.00, indicating that a perfect IRR level was achieved.

Table 5: Agreement and Kappa Statistics for Sickle Cell Disease for Inter-Rater Reliability at Three Sites

Site	Total Records	N Agreed (%)	Kappa Statistic
Hospital #1	2	100%	1.00
Hospital #2	4	100%	1.00
Hospital #3	10	100%	1.00
All Sites	16	100%	1.00

Discrepancies

There was perfect agreement among the sample of records selected for IRR and no discrepancies were noted.

VI.B. Validity

Validity of the measure is the extent to which the measure meaningfully represents the concept being evaluated. The method for establishing the validity of a measure will depend on the type of measure, data source, and other factors. Explain your rationale for selecting the methods you have chosen, show how you used the methods chosen, and provide information on the results (e.g., R^2 for concurrent validity). Provide appropriate citations to justify methods.

The validity of this measure was determined from two perspectives: face validity and validity of medical record data.

Face Validity

Face validity is the degree to which the measure construct characterizes the concept being assessed. The face validity of this measure was established by a national panel of experts and advocates for families of children with SCD convened by Q-METRIC. The Q-METRIC expert panel included nationally recognized experts in SCD, representing hematology, pediatrics, and SCD family advocacy. In addition, measure validity was considered by experts in state Medicaid program operations, health plan quality measurement, health informatics, and health care quality measurement. In total, the Q-

METRIC SCD panel included 14 experts, providing a comprehensive perspective on SCD management and the measurement of quality metrics for states and health plans.

The Q-METRIC expert panel concluded that this measure has a high degree of face validity through a detailed review of concepts and metrics considered to be essential to effective SCD management and treatment. Concepts and draft measures were rated by this group for their relative importance. This measure was highly rated, receiving an average score of 8.9 (with 9 as the highest possible score).

Validity of Abstracted Data

This measure was tested using medical record data which is considered the gold standard for clinical information and had a high degree of face validity and reliability. This measure was tested among a total of 310 children younger than 18 years of age with sickle cell disease (Table 6). Overall, 23% of children with sickle cell disease received anticipatory guidance regarding the risks and benefits of treatment with hydroxyurea as part of outpatient care (range: 17%-51%).

Table 6: Anticipatory Guidance Regarding Hydroxyurea Treatment for Children with Sickle Cell Disease

Site	Rate	Numerator	Denominator
Hospital #1	51%	18	35
Hospital #2	39%	12	31
Hospital #3	17%	42	244
All Sites	23%	72	310

SECTION VII.
IDENTIFICATION OF DISPARITIES

CHIPRA requires that quality measures be able to identify disparities by race, ethnicity, socioeconomic status, and special health care needs. Thus, we strongly encourage nominators to have tested measures in diverse populations. Such testing provides evidence for assessing measure's performance for disparities identification. In the sections below, describe the results of efforts to demonstrate the capacity of this measure to produce results that can be stratified by the characteristics noted and retain the scientific soundness (reliability and validity) within and across the relevant subgroups.

VII.A. Race/Ethnicity

The measure was tested using medical records from the three largest centers serving SCD patients in Michigan during 2012: Children's Hospital of Michigan, Hurley Medical Center, and the University of Michigan Health System. Combined, these centers serve the vast majority of SCD patients in Michigan. While race and ethnicity data were not abstracted as part of the medical record review process, information is available from the state of Michigan for its entire population of births with an initial newborn screening result indicating SCD from 2004 to 2008. Table 7 summarizes the distribution across race and ethnicity groups for all SCD births in Michigan during that time period.

Table 7: Race/Ethnicity for Newborns with SCD in Michigan, 2004-2008 (n=294)

White			Black			Asian or Pacific Islander			Other	Total
Non-Hispanic	Hispanic	Total	Non-Hispanic	Hispanic	Total	Non-Hispanic	Hispanic	Total	Unknown	
2%	1%	3%	81%	1%	82%	1%	0%	1%	15%	100%

VII.B. Special Health Care Needs

The medical records data abstracted for this study does not include indicators of special health care needs.

VII.C. Socioeconomic Status

The medical records data abstracted for this study does not include indicators of socioeconomic status.

VII.D. Rurality/Urbanicity

The medical records data abstracted for this study does not include indicators of urban/rural residence.

VII.E. Limited English Proficiency (LEP) Populations

The medical records data abstracted for this study does not include indicators of LEP.

SECTION VIII.
FEASIBILITY

Feasibility is the extent to which the data required for the measure are readily available, retrievable without undue burden, and can be implemented for performance measurement.[5] Using the following sections, explain the methods used to determine the feasibility of implementing the measure.

VIII.A. Data Availability

VIII.A.1. What is the availability of data in existing data systems? How readily are the data available?

This measure is based on review of medical record data. The medical chart audit included records from the three largest centers serving SCD patients in Michigan during 2012: Children's Hospital of Michigan, Hurley Medical Center, and the University of Michigan Health System. Data were abstracted from medical record systems at two sites that use EHRs (both Epic systems) and from one site using paper charts.

Medical records for 100% of children with SCD meeting the measure specification criteria during the measurement year were abstracted from each hospital. In total, 672 unique records were reviewed; 310 records (46%) met denominator criteria for this measure.

Based on the abstracted chart data, the rate was calculated as the percentage of children younger than 18 years of age identified as having sickle cell anemia (Hb SS or Hb S beta-zero thalassemia [SCA]) who received anticipatory guidance regarding the risks and benefits of treatment with hydroxyurea as part of outpatient care (23%). Measure numerator (72) divided by denominator (310). (See Table 6 in the Validity section above).

Medical record abstraction for this measure was accomplished with a data-collection tool developed using LimeSurvey software (version 1.92, formerly PHPSurveyor). LimeSurvey is an open-source online application based in MySQL that enables users to develop and publish surveys, as well as collect responses. The tool was piloted to determine its usability and revised as necessary. The technical specification for this measure also underwent revisions following pilot testing.

Data abstraction was completed by experienced nurse abstractors who had undergone training for each medical record system used, electronic and paper. Abstractors participated in onsite training during which the measure was discussed in length to include the description, calculation, definitions,

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[5] The definition is adapted from: Centers for Medicare & Medicaid Services Quality Measurement and Health Assessment Group glossary, as part of the Measures Management System Measure Development Overview. Available at: http://www.cms.gov/MMS/19_MeasuresManagementSystemBlueprint.asp#TopOfPage. Accessed February 6, 2012.

eligible population specification, and exclusions. Following training, abstractors were provided with a coded list of potentially eligible cases from each of the sites. To abstract all pertinent data, two nurse abstractors reviewed the electronic and paper medical records. In addition to the specific data values required for this measure, key patient characteristics, such as date of birth and hemoglobin variant type, were also collected.

Abstraction Times

In addition to calculating IRR, the study team assessed how burdensome it was to locate and record the information used to test this measure by having abstractors note the time it took to complete each record. During Phase 1, on average, the abstractors spent 14 minutes per eligible SCD case abstracting the data for this measure, with times ranging from 3-45 minutes.

VIII.A.2. If data are not available in existing data systems or would be better collected from future data systems, what is the potential for modifying current data systems or creating new data systems to enhance the feasibility of the measure and facilitate implementation?

The proposed measure was determined to be feasible by Q-METRIC using medical record data from the three largest centers serving SCD patients in Michigan during 2012. Although paper charts were used at one of the sites, this was not found to be a barrier. In fact, the average time spent abstracting records for paper charts (13 minutes) was less than the average time spent abstracting data from electronic medical records at the other two sites (14 minutes and 19 minutes).

VIII.B. Lessons from Use of the Measure

VIII.B.1. Describe the extent to which the measure has been used or is in use, including the types of settings in which it has been used, and purposes for which it has been used.

To our knowledge, this measure is not currently in use anywhere in the United States.

VIII.B.2. If the measure has been used or is in use, what methods, if any, have already been used to collect data for this measure?

Not applicable

VIII.B.3. What lessons are available from the current or prior use of the measure?

Not applicable

SECTION IX.
LEVELS OF AGGREGATION

CHIPRA states that data used in quality measures must be collected and reported in a standard format that permits comparison (at minimum) at State, health plan, and provider levels. Use the following table to provide information about this measure's use for reporting at the levels of aggregation in the table.

For the purpose of this section, please refer to the definitions for provider, practice site, medical group, and network in Section XVI. Glossary of Terms.

If there is no information about whether the measure could be meaningfully reported at a specific level of aggregation, please write "Not available" in the text field before progressing to the next section. Table IX-1 shows the questions (in columns) about the measure's use at different levels of aggregation for quality reporting (in rows) included in the CHIPRA PQMP Candidate Measure Submission Form (CPCF).

Table IX-1. Questions about the measure's use at different levels of aggregation for quality reporting

Level of aggregation (Unit) for reporting on the quality of care for children covered by Medicaid/CHIP†	**Intended use: Is measure intended to support meaningful comparisons at this level? (Yes/No)**	**Data Sources: Are data sources available to support reporting at this level?**	**Sample Size: What is the typical sample size available for each unit at this level? What proportion of units at this level of aggregation can achieve an acceptable minimum sample size?**	**In Use: Have measure results been reported at this level previously?**	**Reliability & Validity: Is there published evidence about the reliability and validity of the measure when reported at this level of aggregation?**	**Unintended consequences: What are the potential unintended consequences of reporting at this level of aggregation?**
State level*: Can compare States	☐Yes ☒No	No	Not applicable	No	No	Not applicable.
Other geographic level: Can compare other geographic regions (e.g., MSA, HRR)	☐Yes ☒No	No	Not applicable	No	No	Not applicable.
Medicaid or CHIP Payment model: Can compare payment models (e.g., managed care, primary care case management, FFS, and other models)	☐Yes ☒No	No	Not applicable	No	No	Not applicable
Health plan*: Can compare quality of care among health plans.	☐Yes ☒No	No	Not applicable	No	No	Not applicable
Provider-level* Individual practitioner: Can compare individual health care professionals	☐Yes ☒No	No	Not applicable	No	No	Not applicable
Hospital: Can compare hospitals that serve SCD patients.	☒Yes ☐No	Yes.	The sample would include all children with clinical documentation of sickle cell anemia ([see Table 1]).	No.	No.	None identified.
Practice, group, or facility:** Can compare: (i) practice sites; (ii) medical or other professional groups; or (iii) integrated or other delivery networks	☐Yes ☒No	No	Not applicable	No	No	Not applicable

† There could be other levels of reporting that could be of interest to Medicaid agencies such as markets and referral regions.

* Required in CHIPRA legislation.

** There is no implication that measures that are applicable at one level are automatically applicable at all three of the levels listed in this row.

SECTION X.
UNDERSTANDABILITY

CHIPRA states that the core set should allow purchasers, families, and health care providers to understand the quality of care for children. Please describe the usefulness of this measure toward achieving this goal. Describe efforts to assess the understandability of this measure (e.g., focus group testing with stakeholders).

This measure provides families with a straightforward measure to assess how well basic levels of comprehensive care are being provided for children with SCD. Low rates for the provision of anticipatory guidance are easily understood to be unsatisfactory. The simplicity of the measure likewise makes it a straightforward guide for providers and purchasers to assess how well comprehensive care, including anticipatory guidance, is managed in children with SCD.

This measure has not been assessed for comprehension. The primary information needed for this measure comes from medical records data and includes basic demographics, diagnostic codes, and procedure codes, all of which are widely available. The nurse abstractors testing the measure provided feedback to refine the abstraction tool and thus the specifications. These changes are reflected in the final documentation.

SECTION XI.
HEALTH INFORMATION TECHNOLOGY

Please respond to the following questions in terms of any health information technology (health IT) that has been or could be incorporated into the calculation of the measure.

XI.A. Health IT Enhancement

Please describe how health IT may enhance the use of this measure.

In the short term, the predominant role of health IT in this measure is through displaying documentation templates and aggregating provider-captured anticipatory guidance information. Because most of this information is in one section of the EHR, it will be relatively easy to find and to use data mining techniques to extract for the purposes of this measure. Over time, two phenomena may improve the use of the measure. First, it should be possible, given standards regarding ages and stages for providing this guidance, to develop patient-specific templates for documentation. These templates have been shown to improve compliance with recommended care practices, which will result in improved anticipatory guidance discussion. Second, the role of the patient and of patient portals is only beginning to emerge. It will likely be the case that these issues, as well as tools to help patients manage their illness, will be available through applications (apps) or personal health records that then communicate back to EHRs (or care coordinators) to improve the behaviors that these measures address.

XI.B. Health IT Testing

Has the measure been tested as part of an electronic health record (EHR) or other health IT system?

Yes

If so, in what health IT system was it tested and what were the results of testing?

This measure was tested using electronic medical record review conducted at two major SCD treatment facilities in Michigan using the Epic electronic health records system. The third facility used paper medical records for outpatient visits.

XI.C. Health IT Workflow

Please describe how the information needed to calculate the measure may be captured as part of routine clinical or administrative workflow.

Anticipatory guidance in general comes in two forms: check box lists or "standardized" text created using documentation templates, or unstructured text arising from dictation or potentially scanned documents in an EHR. This will be the primary way these data are captured in routine clinical workflow. Another, though less common, approach is to ask patients to complete forms before a

visit. These forms, created by groups such as the American Academy of Pediatrics (Bright Futures) and customized for specialty-specific conditions, could be captured in any of the methods described above, and would be available to calculate the measure after neuro-linguistic programming techniques or data extraction in some other form took place.

XI.D. Health IT Standards

Are the data elements in this measure supported explicitly by the Office of the National Coordinator for Health IT Standards and Certification criteria (see: http://healthit.hhs.gov/portal/server.pt/community/healthit_hhs_gov__standards_ifr/1195)?

Yes

If yes, please describe.

The ONC's Health IT Standards explicitly address the ability to create patient-specific reminders for preventive services, broadly defined. While such reminders may be aimed at future appointments for services, they can also include prompts for patients to engage in activities to properly manage chronic conditions. In addition, these standards indicate the requirement for EHRs to track specific patient conditions, such as SCD. Consequently, patient reminders for activities to appropriately manage SCD could be achieved through these mechanisms, meeting the goals of anticipatory guidance preventive care. The ONC standards include the following specific requirements in the Certification criteria (Federal Register 2010) pertaining to Stage 2 Meaningful Use:

> (h) Generate patient lists. Enable a user to electronically select, sort, retrieve, and output a list of patients and patients' clinical information, based on user-defined demographic data, medication list, and specific conditions.

XI.E. Health IT Calculation

Please assess the likelihood that missing or ambiguous information will lead to calculation errors.

Missing or ambiguous information in the following areas could lead to missing cases or calculation errors:

1. Child's date of birth
2. ICD-9 codes selected to indicate sickle cell anemia
3. Date and time of anticipatory guidance
4. Care setting

XI.F. Health IT Other Functions

If the measure is implemented in an EHR or other health IT system, how might implementation of other health IT functions (e.g., computerized decision support systems in an EHR) enhance performance on the measure?

Performance on this measure could benefit from a number of health IT integration steps:

a. Documentation templates filled out by providers (or potentially scribes, in communication with providers during the visit) could improve provider behavior with respect to these issues during the visit.

b. Documentation templates created in specialty clinics could help with missed opportunities to provide this counseling in emergency departments, other clinic visits, home visits, or through patient-initiated contact with the health system via a patient portal or personal health application.

c. Active decision support before, during, or after the visit could prompt providers or patients about these issues.

d. EHRs could generate triggers to providers to provide this guidance (again) based on events that suggest a need to re-teach (such as after an emergency department visit for pain).

References for Section XI

Health information technology: Initial set of standards, implementation specifications, and certification criteria for electronic health record technology." Fed Regist **75**(8): 2013-2047.

Electronic Health Record Incentive Program—Stage 2 Fed Regist **77**(171): 53968- 54162.

SECTION XII.
LIMITATIONS OF THE MEASURE

Describe any limitations of the measure related to the attributes included in this CPCF (i.e., availability of measure specifications, importance of the measure, evidence for the focus of the measure, scientific soundness of the measure, identification of disparities, feasibility, levels of aggregation, understandability, health information technology).

This measure assesses the percentage of children younger than 18 years of age identified as having sickle cell disease (SCD) who received anticipatory guidance regarding the risks and benefits of treatment with hydroxyurea as part of outpatient care during the measurement year.

This measure is implemented with medical record data, and was tested with electronic and paper medical records. The primary information needed for this measure includes date of birth, diagnosis codes, and procedure codes and dates. These data are available, although obtaining them may require a restricted-use data agreement. It also required the development of an abstraction tool and the use of qualified nurse abstractors. Continuing advances in the development and implementation of electronic medical records may establish the feasibility of regularly implementing this measure with data supplied by electronic medical records.

SECTION XIII.
SUMMARY STATEMENT

Provide a summary rationale for why the measure should be selected for use, taking into account a balance among desirable attributes and limitations of the measure. Highlight specific advantages that this measure has over alternative measures on the same topic that were considered by the measure developer or specific advantages that this measure has over existing measures. If there is any information about this measure that is important for the review process but has not been addressed above, include it here.

This measure, *Anticipatory Guidance Regarding Hydroxyurea Treatment for Children with Sickle Cell Disease*, assesses the percentage of children younger than 18 years of age identified as having sickle cell anemia (Hb SS or Hb S beta-zero thalassemia [SCA]) who received anticipatory guidance regarding the risks and benefits of treatment with hydroxyurea as part of outpatient care during the measurement year. This measure was tested using medical record data. A higher proportion indicates better performance, as reflected by the appropriate provision of anticipatory guidance. There are no existing quality measures for anticipatory guidance regarding the risks and benefits of treatment with hydroxyurea in children with SCD.

Clinical guidelines suggest that while the evidence for efficacy of hydroxyurea treatment for children is not as strong as evidence supporting its use in adults, the emerging data are encouraging and do not contradict the adult findings that this medication improves hematologic variables and decreases hospitalization rates, pain episodes, number of blood transfusions, and acute chest syndrome. However, barriers exist to its use. At the patient level, poverty and public insurance status make access to the health system and adherence to medication difficult. System-level barriers include financing, geographic isolation, and limited access to comprehensive care centers and comprehensive care models.

This measure was tested among a total of 310 children younger than 18 years of age with sickle cell anemia. Overall, 23% of children received anticipatory guidance regarding the risks and benefits of treatment with hydroxyurea as part of outpatient care (range among the three hospitals was: 17%-51%).

This measure provides families, providers, and purchasers with a straightforward means of assessing how well basic levels of comprehensive care, including anticipatory guidance, are being provided for children with SCD. The primary information needed for this measure includes basic demographics, dates, diagnostic codes, and procedure codes, all of which are widely available. Continuing advances in the development and implementation of health information technology may establish the feasibility of regularly implementing this measure with data supplied by electronic medical records.

SECTION XIV.
IDENTIFYING INFORMATION FOR THE MEASURE SUBMITTER

Complete information about the person submitting the material, including the following:

a. Gary L. Freed, MD, MPH

b. Percy and Mary Murphy Professor of Pediatrics, School of Medicine; Professor of Health Management and Policy, School of Public Health

c. University of Michigan

d. 300 North Ingalls, Room 6E08, Ann Arbor, MI 48109

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g. Signed written statement guaranteeing that all aspects of the measure will be publicly available, as defined in the Public Disclosure Requirements.

Public Disclosure Requirements

Each submission must include a written statement agreeing that, should U.S. Department of Health and Human Services accept the measure for the 2014 and/or 2015 Improved Core Measure Sets, full measure specifications for the accepted measure will be subject to public disclosure (e.g., on the Agency for Healthcare Research and Quality [AHRQ] and/or Centers for Medicare & Medicaid Services [CMS] websites), except that potential measure users will not be permitted to use the measure for commercial use. In addition, AHRQ expects that measures and full measure specifications will be made reasonably available to all interested parties. "Full measure specifications" is defined as all information that any potential measure implementer will need to use and analyze the measure, including use and analysis within an electronic health record or other health information technology. As used herein, "commercial use" refers to any sale, license or distribution of a measure for commercial gain, or incorporation of a measure into any product or service that is sold, licensed or distributed for commercial gain, even if there is no actual charge for inclusion of the measure. This statement must be signed by an individual authorized to act for any holder of copyright on each submitted measure or instrument. The authority of the signatory to provide such authorization should be described in the letter (Section XIV: Identifying Information for the Measure Submitter).

This work was funded by the Agency for Healthcare Research and Quality (AHRQ) and the Centers for Medicare & Medicaid Services (CMS) under the CHIPRA Pediatric Quality Measures Program Centers of Excellence grant number U18 HS020516. AHRQ, in accordance to CHIPRA 42 U.S.C. Section 1139A(b), and consistent with AHRQ's mandate to disseminate research results, 42 U.S.C. Section 299c-3, has a worldwide irrevocable license to use and permit others to use products and materials from the grant for government purposes, which may include making the materials available for verification or replication by other researchers and making them available to the health care community and the public, if such distribution would significantly increase access to a product and thereby produce substantial or valuable public health benefits.

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Sickle Cell Disease

Measure 10: Anticipatory Guidance Regarding Hydroxyurea Treatment for Children with Sickle Cell Disease

Description

The percentage of children identified as having Sickle Cell Anemia who received anticipatory guidance regarding the risks and benefits of treatment with hydroxyurea as part of outpatient care during the measurement year. A higher proportion indicates better performance as reflected by appropriate guidance.

Calculation

This measure requires medical record data and is calculated as follows:

The percentage of eligible children who received anticipatory guidance regarding the risks and benefits of treatment with hydroxyurea (numerator divided by denominator).

Definitions

Intake period January 1 through December 31 of the measurement year.

Anticipatory guidance Any written or face-to-face verbal communication regarding the risks and benefits of treatment with hydroxyurea as part of outpatient care with patient, parent, or family member.

Outpatient care A Health Maintenance Exam (HME) or an Evaluation and Management (E&M) visit with primary care provider or a specialist (see Table 10-A).

Table 10-A: Codes to Identify Ambulatory or Preventive Care Visits

Description	CPT	HCPCS	ICD-9-CM Diagnosis
Office or other outpatient services	99201-99205, 99211-99215, 99241-99245		
Preventive medicine	99381-99385, 99391-99395, 99401-99404, 99411-99412, 99420, 99429	G0438, G0439	
General medical examination			V20.2, V70.0, V70.3, V70.5, V70.6, V70.8, V70.9

Eligible Population

The determination of eligible population for this measure requires medical record data.

Ages Younger than eighteen years of age during measurement year

Event/Diagnosis Diagnosed with Sickle Cell Anemia as documented in the medical record (see Table 10-B).

NOTE: See exclusions noted below; there are several sickle cell variants that may be recorded under the 282.49 ICD-9 code that do not qualify for inclusion (see Table 10-C). Medical records for cases with ICD-9 code 282.49 should not be reviewed unless a diagnosis of Hb beta zero-thalassemia can be confirmed.

Table 10-B: Codes to Identify Sickle Cell Anemia

Condition Name	Hemoglobin Screening Result	ICD-9 Code(s)
Hb beta zero-thalassemia	Hb F only	282.49
Hb SS-disease (sickle cell anemia)	Hb F,S	282.6, 282.61, 282.62

Specification

Denominator The eligible population for the denominator is the number of children younger than 18 years of age with SCA who received outpatient care during the measurement year.

Numerator The eligible population for the numerator is the number of children younger than 18 years of age with SCA who received anticipatory guidance regarding the risks and benefits of treatment with hydroxyurea as part of outpatient care during the measurement year.

Documentation in medical record must include, at a minimum, a note containing the date on which verbal or written anticipatory guidance was provided.

Exclusions

- Inpatient stays, emergency department visits, urgent care visits.
- Children with diagnosis in the sampled medical record indicating one of the sickle cell disease variants listed in Table 10-C should not be included in the eligible population *unless* there is also a diagnosis for a sickle cell variant listed in Table 10-B.

Table 10-C: Excluded Sickle Cell Disease Diagnosis Codes

Condition Name	Hemoglobin Screening Result	ICD-9 Code(s)
Hb S beta-thalassemia	Hb F,S,A	282.41, 282.42
Hb C-disease	Hb F,C	282.7
Hb SC-disease	Hb F,S,C	282.63, 282.64
Hb SD-disease	Hb F,S,D	282.68, 282.69
Hb SE-disease	Hb F,S,E	282.68, 282.69
Hb C beta-thalassemia	Hb F,C,A	282.49
Hb D beta-thalassemia	Hb F,D,A	282.49
Hb E beta-thalassemia	Hb F,E,A	282.49
Hb E-disease	Hb F,E	282.7
Hb H-disease	Hb F,H	282.49
Hb C-carrier	Hb F,A,C	282.7
Hb D-carrier	Hb F,A,D	282.7
Hb E-carrier	Hb F,A,E	282.7
Hb S (sickle)-carrier	Hb F,A,S	282.5