
Chapter 1: Introduction and Methodology

These guidelines were developed by an expert panel composed of health care professionals with expertise in family medicine, general internal medicine, adult and pediatric hematology, psychiatry, transfusion medicine, obstetrics and gynecology, emergency department nursing, and evidence-based medicine. Panel members were selected by the National Heart, Lung, and Blood Institute's (NHLBI's) leadership.

The purpose of these guidelines is to help people living with sickle cell disease (SCD) receive appropriate care by providing the best science-based recommendations to guide practice decisions. The target audience is primary care providers and other clinicians, nurses, and staff who provide emergency or continuity care to individuals with SCD.

NHLBI sponsored the development of these guidelines to assist health care professionals in the management of common issues, including routine health maintenance, the recognition and treatment of common acute and chronic complications and comorbidities of SCD, as well as the indications for and monitoring of hydroxyurea and blood transfusion therapy. The guidelines address the care of infants, children, adolescents, and adults with SCD, with the goal of facilitating high-quality and appropriate care for all individuals with this disease.

Historical Perspective, Epidemiology, and Definitions

SCD was first reported in the literature in November 1910 by James B. Herrick, who referred to “peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia.”¹ We have gained substantial knowledge about SCD since that first description. Today there is hope for a cure using hematopoietic stem cell transplantation (HSCT).² However, at present, the procedure is infrequently performed and very expensive.³⁻⁵ Additional research regarding patient and donor selection and the specific transplantation procedure is required before this potentially curative therapy will become more widely available. Two effective disease-modifying therapies for SCD—hydroxyurea and chronic transfusion—are potentially widely available but remain underutilized.⁶⁻¹¹

The sickle cell mutation results in substitution of the amino acid valine for glutamic acid at the sixth position of the beta globin chain, causing formation of hemoglobin S.¹² More than 2 million U.S. residents are estimated to be either heterozygous or homozygous for the genetic substitution. Most of those affected are of African ancestry or self-identify as Black; a minority are of Hispanic or southern European, Middle Eastern, or Asian Indian descent.¹³ It is estimated that between 70,000 and 100,000 Americans have SCD. Although SCD is associated with major morbidity, currently more than 90 percent of children with SCD in the United States and the United Kingdom survive into adulthood.¹⁴⁻¹⁶ However, their lifespan remains shortened by two or three decades compared to the general population.^{17,18}

The most prevalent SCD genotypes (exhibit 1) include homozygous hemoglobin SS (HbSS) and the compound heterozygous conditions hemoglobin S β^0 -thalassemia (HbS β^0 -thalassemia), hemoglobin S β^+ -thalassemia (HbS β^+ -thalassemia), and hemoglobin SC disease (HbSC). HbSS and HbS β^0 -thalassemia are clinically very similar and therefore are commonly referred to as sickle cell anemia (SCA); these genotypes are associated with

the most severe clinical manifestations. These guidelines are not applicable to individuals with sickle cell trait (HbAS), the carrier state.

Exhibit 1a. Typical Laboratory Findings in Sickle Cell Disease

Genotype	Hb* (g/dL) [†]	HbS (%)	HbA (%)	HbA ₂ (%)	HbF (%)	HbC (%)
SS	6–9	>90	0	<3.5	<10	0
Sβ ⁰ -thalassemia	7–9	>80	0	>3.5	<20	0
Sβ ⁺ -thalassemia	9–12	>60	10–30	>3.5	<20	0
SC	9–14	50	0	<3.5	≤1.0	45

* Definitions for abbreviations are as follows: Hb = hemoglobin; HbS = sickle hemoglobin; HbA = normal adult hemoglobin; HbA₂ = minor variant of adult hemoglobin; HbF = fetal hemoglobin; HbC = hemoglobin variant that causes manifestations of SCD when paired with HbS

[†] The hemoglobin values in this exhibit apply in the absence of a blood transfusion in the last 4 months, are not absolute, and are applicable to adults and children only (not newborns).

Exhibit 1b. Typical Laboratory Findings in Sickle Cell Trait (Provided for Comparison)

Genotype	Hb* (g/dL) [†]	HbS (%)	HbA (%)	HbA ₂ (%)	HbF (%)	HbC (%)
AS	normal	≤40	>60	<3.5	≤1.0	0

* Definitions for abbreviations are as follows: Hb = hemoglobin; HbS = sickle hemoglobin; HbA = normal adult hemoglobin; HbA₂ = minor variant of adult hemoglobin; HbF = fetal hemoglobin; HbC = hemoglobin variant that causes manifestations of SCD when paired with HbS

[†] The hemoglobin values in this exhibit apply in the absence of a blood transfusion in the last 4 months, are not absolute, and are applicable to adults and children only (not newborns).

Currently in the United States, there are no comprehensive, systematically reviewed, evidence-based guidelines to assist health care professionals in the management of individuals with SCD. Providing care to these individuals can be challenging. As a result of the condition's relative rarity, there are few health care professionals who are prepared to deliver continuity care or expert consultation for patients with serious acute or chronic SCD complications. These guidelines are therefore being made available to help provide the latest evidence-based recommendations to manage this condition and to help engage health care professionals in supporting their implementation at the practice level.

Overview of the SCD Guidelines Chapters

This report begins with a chapter on comprehensive health maintenance. Many children and adults with chronic diseases such as SCD do not receive the recommended preventive care provided to other children and adults. Therefore, the guidelines summarize recommendations for health maintenance screening, testing, and immunizations as they apply to infants, children, adolescents, and adults with SCD. Generally speaking, recommendations for screening to facilitate primary and secondary prevention (e.g., asking a teen about smoking behavior or an adult woman about mammography, respectively) are often confused with recommendations for evaluating early symptoms of a disease or condition. For this and most other documents such as the recommendations of the U.S. Preventive Services Task Force (USPSTF), screening is considered testing or evaluation for a relatively common condition for which there is effective therapy prior to symptom recognition or during an asymptomatic phase.¹⁹ Generalized or universal screening is not recommended when existing therapies have not been shown to improve patient outcomes when implemented in this early

presymptomatic phase. Information on screening and preventive care is important for all clinicians who work with individuals with SCD, including specialists who may serve as the continuity health care source for them.

Acute complications are common at all ages in individuals with SCD and are addressed in the chapter, [“Managing Acute Complications of Sickle Cell Disease.”](#) Recurrent acute pain crises (also known as vaso-occlusive crises) are the most common manifestation of SCD. These crises occur, usually without warning, when obstructed blood flow results in ischemic tissue injury and pain. The vascular occlusion, generally at the level of capillaries and post-capillary venules, results not only from an accumulation of adherent and sickled erythrocytes, but also from alterations involving the vascular endothelium and adhesive proteins in the plasma and on white blood cells and platelets. The management of acute pain is central to the care of individuals with SCD, yet pain is often poorly or inadequately addressed in all types of health care settings.

These guidelines include recommendations for rapid and effective pain management in people with SCD who present with such pain crises. Other significant acute complications addressed in this chapter include acute chest syndrome (ACS), stroke, splenic sequestration, acute renal failure, and cholecystitis. Neuropsychological, educational, and vocational impairment as well as common mental health issues such as depression and anxiety, which often accompany chronic illness, were considered beyond the scope of this guideline work.

Chronic complications of SCD may occur as a result of acute episodes or as chronic or recurrent events. Several of the most common of the chronic complications—including chronic pain, cholelithiasis, renal dysfunction, pulmonary hypertension, and retinal problems—are addressed in the fourth chapter, [“Managing Chronic Complications of Sickle Cell Disease.”](#)

Each of the two major therapies used in individuals with SCD—hydroxyurea and chronic blood transfusions—are described in separate chapters (see [“Hydroxyurea Therapy in the Management of Sickle Cell Disease.”](#) and [“Blood Transfusion in the Management of Sickle Cell Disease”](#)). These are the only currently proven disease-modifying treatments for people with SCD. Both therapies are used in primary and secondary stroke prevention. Although neither has been shown to prevent all SCD-related organ damage, these treatment modalities can improve the quality of life for individuals with SCD. Treatment with hydroxyurea is underutilized for many people with SCA who could benefit from it. Blood transfusion therapy has at times been underutilized, overutilized, or prescribed inappropriately for both acute and chronic complications. These two chapters provide guidance regarding the appropriate use of these therapies for SCD.

Process and Methodology

The expert panel first convened in the spring of 2009 to establish the vision and purpose of the panel, discuss the process and schedule for producing the guidelines, and determine the critical areas to be addressed. Prior to this meeting, the expert panel participated in a conference call to introduce the panel’s work and discuss the overarching questions that should be answered by the guidelines. Before beginning the writing of the guidelines report, the expert panel divided its work into sections dealing with preventive care or health maintenance, recognition and management of acute SCD-related complications, recognition and management of chronic SCD-related complications, and the two most broadly assessed and available disease-modifying therapies for SCD, hydroxyurea and chronic blood transfusions.

With the assistance of the methodology team and the supporting evidence center, the panel then developed key questions and literature search terms to identify evidence. The field of SCD has a limited number of randomized controlled trials (RCTs) or large prospective cohort studies to guide clinical decisionmaking; therefore, few of the recommendations in this document are based on this highest quality evidence. For

common health issues, the panel included the evidence-based recommendations of the USPSTF²⁰ as well as vetted recommendations of other groups. These recommendations include the SCD reproductive-related recommendations of the World Health Organization (WHO),²¹ the immunization recommendations of the Advisory Committee on Immunization Practices (ACIP),²² and the acute and chronic pain management recommendations of the American Pain Society (APS).^{23,24} These recommendations are denoted as “Consensus–Adapted.”

Recognizing the need to provide practical guidance for common problems that may lie outside of the panel’s evidence reviews or available science, in many areas the published evidence was supplemented by the expertise of the panel members, who have many years of experience in managing and studying individuals with SCD. Recommendations based on the opinions of the expert panel members are labeled as “Consensus–Panel Expertise.” Each is clearly labeled with the strength of the recommendation and the quality of evidence available to support it.

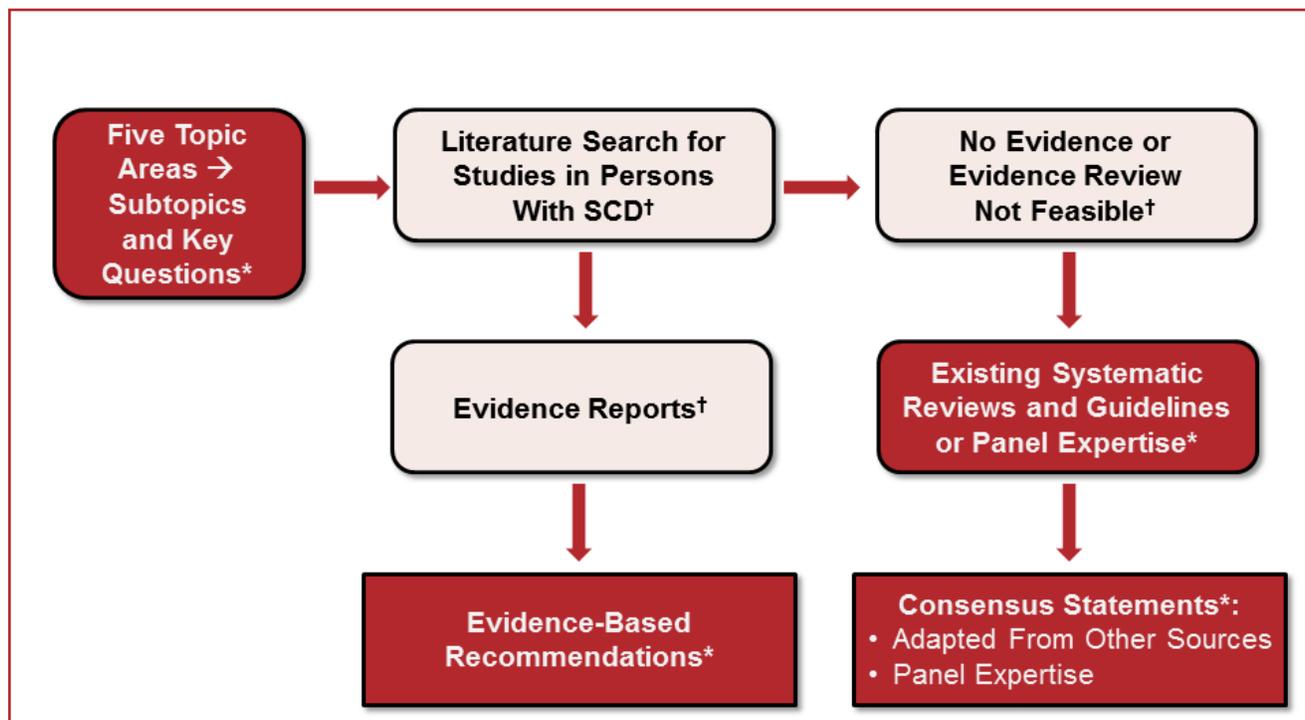
Evidence Review and Synthesis

Beginning in April 2010, the expert panel collaborated with an independent evidence synthesis group (hereafter referred to as the methodology team) that included methodologists, librarians, and research staff with expertise in conducting systematic reviews and meta-analyses and appraising and summarizing evidence for the purpose of guideline development. The methodology team used the overarching questions, the key questions, and a list of specific guideline topics to draft an initial list of PICOS^c-formatted critical questions for literature searches and formal evidence appraisal and vetting (see [appendix B](#)). The methodology team developed search strategies and then conducted literature searches and prepared the evidence tables and a summary of the body of the evidence (see <http://www.nhlbi.nih.gov/guidelines/scd/index.htm>).

Exhibit 2 outlines the overall process for the evidence search, evidence synthesis, and recommendation development.

^c PICOS is a framework for developing a structured research question. It includes the following components in the statement of the critical question: P = Population; I = Intervention, exposure; C = Comparator; O = Outcome; S = Setting.

Exhibit 2. Evidence Review Process



Note: Exhibit 2 shows the evidence review process. Boxes marked with an * symbol represent work conducted by the expert panel; boxes marked with a † symbol represent work conducted by the methodology team.

Literature Search

Due to the comprehensive scope of the guidelines, the search strategies for the systematic reviews were designed to have high sensitivity and low specificity; hence, the strategies were often derived from population and condition terms (e.g., people with SCD who have priapism) and not restricted or combined with outcome or intervention terms. To be inclusive of the available literature in the field, searches included randomized trials, nonrandomized intervention studies, and observational studies. Case reports and small case series were included only when outcomes involved harm (e.g., the adverse effects of hydroxyurea) or when rare complications were expected to be reported.

Literature searches involved multiple databases (e.g., Medline[®] In-Process & Other Non-Indexed Citations, MEDLINE[®], Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature (CINAHL[®]), TOXLINE[®], and Scopus) and used controlled vocabulary (prespecified) terms supplemented with keywords to define concept areas.

Evidence Synthesis

The initial literature searches performed to support these guidelines yielded 12,532 references. The expert panel also identified an additional 1,231 potentially relevant references. An updated search of randomized controlled trials (RCTs) added eight trials.^d All abstracts were reviewed independently by two reviewers using an online reference management system (DistillerSR—<http://systematic-review.net>) until reviewers reached adequate agreement ($\kappa \geq 0.90$). A total of 1,575 original studies were included in the evidence tables. Methodologists developed evidence tables to summarize individual study findings and present the quality of

^d An updated search was performed to span the time from June 1, 2010 through July 11, 2014. Eight additional RCTs were identified, and a supplemental table reflecting these additions was added to the evidence table document.

evidence (i.e., confidence in the estimates of effect). The tables included descriptions of study population, SCD genotypes, interventions, and outcomes. Additional methodological details are discussed in each evidence table, including the search question, search strategy, study selection process, and list of excluded studies (see <http://www.nhlbi.nih.gov/guidelines/scd/index.htm>).

Evidence Framework

The methodology team used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework²⁵ to grade the quality of evidence, and, in concert with the panel, determine the strength of recommendations. The GRADE framework is accepted by more than 75 national and international organizations (see exhibit 3). It provides the advantages of: (a) separately judging the quality of supporting evidence and strength of recommendations, and (b) incorporating factors other than evidence in decisionmaking (e.g., the balance of benefits and harms; the perceived values and preferences of those with SCD; resources; and clinical and social context). GRADE emphasizes the use of patient-important outcomes (i.e., outcomes that affect the way patients feel, function, or survive)²⁶ over laboratory and physiologic outcomes.

Exhibit 3. Steps in the GRADE Process

1. Quality of evidence for each patient-important outcome is rated individually and then across outcomes
2. Randomized trials start as high quality and observational studies start as low quality
3. Quality of evidence is rated down for increased risk of
 - a. Risk of bias
 - b. Publication bias
 - c. Imprecision
 - d. Indirectness
 - e. Inconsistency
4. Quality of evidence is rated up for
 - a. Large effect
 - b. Dose response effect
 - c. When plausible confounding increases the association
5. Consider balance of benefits and harms, resources and patient's values and preferences in addition to quality of the body of evidence to determine strength of recommendations
6. The strength of recommendation is either strong or weak*

Source: Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol.* 2011 Apr;64(4):401–6.²⁷

* In these guidelines, an intermediate category of recommendation (moderate) was also used.

Determining Evidence Quality

In the GRADE framework, the quality of evidence (in this case, the body of evidence) is rated as high, moderate, low, or very low.²⁸ The quality of evidence derived from randomized trials starts as “high,” and the quality of evidence derived from observational studies starts as “low.” The quality of evidence can then be lowered due to methodological limitations in individual studies (risk of bias), inconsistency across studies (heterogeneity), indirectness (the extent to which the evidence fails to apply to the specific clinical question in terms of the patients, interventions, or outcomes), imprecision (typically due to a small number of events or wide confidence intervals), and the presence of publication and reporting biases. Conversely, the quality of evidence can be upgraded in certain situations such as when the treatment effect is large or a dose-response relationship is evident.

Determining the Strength of Recommendations

The GRADE framework rates the strength of recommendations as “strong” or “weak.” However, the panel modified the GRADE system and used a third category—moderate—when they determined that patients would be better off if they followed a recommendation, despite there being some level of uncertainty about the magnitude of benefit of the intervention or the relative net benefit of alternative courses of action. The panel intends for these moderate-strength recommendations to be used to populate protocols of care and provide a guideline based on the best available evidence. The panel does not intend for weak- or moderate-strength recommendations to generate quality-of-care indicators or accountability measures or affect insurance reimbursement. Variation in care in the areas of weak- or moderate-strength recommendations may be acceptable, particularly in ways that reflect patient values and preferences. Conversely, strong recommendations represent areas in which there is confidence in the evidence supporting net benefit, and the recommendations likely apply to most individuals with SCA. For more information, see exhibit 4.

Exhibit 4. GRADE Recommendations—A Closer Look

Grade of Recommendation	Clarity of Risk/Benefit	Quality of Supporting Evidence	Implications
Strong recommendation High-quality evidence	Benefits clearly outweigh harms and burdens, or vice versa	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies*	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect.
Strong recommendation Moderate-quality evidence	Benefits clearly outweigh harms and burdens, or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise evidence), or unusually strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research (if performed) is likely to have an impact on our confidence in the estimate of effect and may change the estimate.
Strong recommendation Low-quality evidence	Benefits clearly outweigh harms and burdens, or vice versa	Evidence for at least one critical outcome from observational studies, from RCTs with serious flaws, or indirect evidence	Recommendation may change when higher quality evidence becomes available. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Strong recommendation Very low-quality evidence (very rarely applicable)	Benefits clearly outweigh harms and burdens, or vice versa	Evidence for at least one of the critical outcomes from unsystematic clinical observations or very indirect evidence	Recommendation may change when higher quality evidence becomes available; any estimate of effect, for at least one critical outcome, is very uncertain.
Weak recommendation High-quality evidence	Benefits closely balanced with harms and burdens	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	The best action may differ depending on circumstances or patient or societal values. Further research is very unlikely to change our confidence in the estimate of effect.

Grade of Recommendation	Clarity of Risk/Benefit	Quality of Supporting Evidence	Implications
Weak recommendation Moderate-quality evidence	Benefits closely balanced with harms and burdens	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise evidence), or unusually strong evidence from unbiased observational studies	Alternative approaches likely to be better for some patients under some circumstances. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Weak recommendation Low-quality evidence	Uncertainty in the estimates of benefits, harms, and burdens; benefits may be closely balanced with harms and burdens	Evidence for at least one critical outcome from observational studies, from RCTs with serious flaws, or indirect evidence	Other alternatives may be equally reasonable. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Weak recommendation Very low-quality evidence	Major uncertainty in the estimates of benefits, harms, and burdens; benefits may or may not be balanced with harms and burdens	Evidence for at least one critical outcome from unsystematic clinical observations or very indirect evidence	Other alternatives may be equally reasonable. Any estimate of effect, for at least one critical outcome, is very uncertain.

Source: Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. Schünemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Soh AA, Ernst A, Fahy BF, Gould MK, Horan KL, Krishnan JA, Manthous CA, Maurer JR, McNicholas WT, Oxman AD, Rubenfeld G, Turino GM, Guyatt G; ATS Documents Development and Implementation Committee. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. *Am J Respir Crit Care Med.* 2006 Sep 1;174(5):605-14. Official Journal of the American Thoracic Society.²⁹

* Exceptionally strong evidence from unbiased observational studies includes: (1) evidence from studies that yield estimates of the treatment effect that are large and consistent; (2) evidence in which all potential biases may be working to underestimate an apparent treatment effect, and therefore, the actual treatment effect is likely to be larger than that suggested by the study data; and (3) evidence in which a dose-response gradient exists

Existing Systematic Reviews and Clinical Practice Guidelines

The expert panel and methodology team identified existing systematic reviews and clinical practice guidelines that were relevant to the topics of this guideline, even though they were not necessarily specific to people with SCD. If the methodological quality of these resources was found to be appropriate by the methodology team, they were used. Using this external evidence was considered helpful because well-conducted systematic reviews made the process of identifying relevant studies more feasible. In addition, using existing guidelines developed by professional organizations enabled the panel to develop more comprehensive recommendations that addressed specific aspects of care in individuals with SCD. Usually, this external evidence was derived from studies in non-sickle cell patient cohorts because it was felt that they offered more precise and useful inferences than evidence derived from sickle cell patient studies. For example, comparative evidence in the area of pain management in people with SCD was sparse. In this situation, pain management guidelines from individuals with other pain-related conditions proved to be helpful.

The methodology team used the AMSTAR tool to assess the methodological quality of systematic reviews.³⁰ Recent well-conducted systematic reviews were identified that addressed hydroxyurea therapy in pediatric and adult patients.⁶⁻⁸ The expert panel and methodology team appraised these reviews and conducted additional searches to update the existing systematic review through May 2010 to find evidence for the benefits, harms,

and barriers of using hydroxyurea. Regarding the management of children with SCD complications, the panel also used recent evidence that had been systematically reviewed.³¹

Existing clinical practice guidelines were considered acceptable if they had prespecified clinical questions, were developed after a comprehensive literature search, had explicit and clear criteria for the inclusion of evidence, and included recommendations that were explicitly linked to the quality of supporting evidence. The expert panel and methodology team used relevant recommendations from the USPSTF,²⁰ the Advisory Committee on Immunization Practices (ACIP),²² the Centers for Disease Control and Prevention's (CDC) adaptation of the World Health Organization's (WHO's) "Medical Eligibility Criteria for Contraceptive Use,"²¹ and the American Pain Society's "Guideline for the Management of Acute and Chronic Pain in Sickle-Cell Disease," and "Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain."^{23,24}

Consensus Statements

The panel believed that, for this guideline document to be most helpful to primary care providers and specialty health care professionals, it needed to be comprehensive. This required that, in areas with minimal existing direct evidence, the panel would provide recommendations based on their and others' expert opinions. Those recommendations are labeled as "consensus." Several different situations, outlined below, led to the use of consensus statements.

Consensus–Panel Expertise

- Systematic reviews conducted by the methodology team revealed minimal or no supporting evidence (e.g., management of acute hepatic sequestration).
- An adequate systematic review of the literature was not feasible because of anticipated low yield or no yield (e.g., comparative effectiveness of management approaches for individuals with SCD presenting with fever or worsening anemia).
- Recommendations were based on the panel's expert knowledge, practice experience, and ability to extrapolate evidence from non-SCD populations (e.g., management of chronic opioid therapy in chronic SCD pain).

Consensus–Adapted

- These recommendations were based on the panel's expert knowledge to adapt recommendations derived from existing guidelines and synthesized evidence developed by other professional societies (e.g., management of acute and chronic pain in SCD).

The panel clearly identified these statements as consensus recommendations and acknowledges that these areas represent gaps in the evidence base and areas for future research.

Prior to publication, these guidelines were reviewed by the NHLBI Advisory Council, a separate panel of SCD experts, and the National Blood Disorders Program Coordinating Committee. The guidelines were also posted to the NHLBI Web site for an extensive public review and comment period, which resulted in the submission of more than 1,300 comments from individuals and professional societies. The expert panel and NHLBI staff reviewed each comment or recommendation, many of which resulted in a revision to the guidelines. The guidelines were then reviewed by SCD experts representing three professional societies.

Clinical Practice Guidelines and the Institute of Medicine

In April 2011, 12 months after the start of the first of the expert panel report's systematic reviews, the Institute of Medicine (IOM) published "Clinical Practice Guidelines We Can Trust."³² Although at that point, the panel's processes were already identified and in progress, it was determined that the panel's report was well aligned with the main points that the IOM standards identified as critical to trustworthy guidelines (establishing transparency, managing conflict of interest, guideline development group composition, clinical practice guidelines-systematic review intersection, establishing evidence foundations for and rating strength of recommendations, articulation of recommendations, external review, and updating). Because the panel's work began prior to the release of the IOM standards, it did not include a patient representative, the questions considered were not disseminated for public comment, and at this time, no updates are planned for this guideline document.