Public Meeting on Sickle Cell Disease Patient-Focused Drug Development

February 7, 2014

U.S. Food and Drug Administration
Protecting and Promoting Public Health
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Welcome

Sara Eggers, PhD
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February 7, 2014

Agenda

- **Setting the context**
  - Opening Remarks
  - Overview of FDA's Patient-Focused Drug Development Initiative
  - Background on Sickle Cell Disease and Treatment
  - Overview of Discussion Format

- **Discussion Topic 1**: The effects of sickle cell disease that matter most to patients

- **Discussion Topic 2**: Patients' perspectives on treatments for sickle cell disease

- **Open Public Comment**

- **Closing Remarks**

Opening Remarks

Ann T. Farrell, MD
Director, Division of Hematology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

February 7, 2014

Drug Development Overview

- Animal (preclinical) testing
- Investigational New Drug Application to FDA
- Human testing in clinical trials
- New Drug Application to the FDA
- Marketing (sales and distribution)

Patient Reported Outcome

- A patient's report of how they feel
- A patient can report on symptoms that are only known to them
  - Fatigue
  - Pain
  - Difficulty concentrating

FDA's Patient-Focused Drug Development Initiative

Theresa Mullin, PhD
Director, Office of Strategic Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Basic Observations

- Patients are uniquely positioned to inform FDA understanding of the clinical context
- FDA could benefit from a more systematic method of obtaining patients' point of view on the severity of a condition, and its impact on daily life, and their assessments of available treatment options
- Current mechanisms for obtaining patient input are often limited to discussions related to specific applications under review, such as Advisory Committee meetings

Patient-Focused Drug Development under PDUFA V

- **FDA is developing a more systematic way of gathering patient perspective on their condition and available treatment options**
  - Patient perspective helps inform our understanding of the context for the assessment of benefit-risk and decision making for new drugs
  - Input can inform FDA analysis both during and outside of review

- **Patient-Focused Drug Development is part of FDA commitments under the fifth reauthorization of the Prescription Drug User Fee Act (PDUFA V)**
  - FDA will convene at least 20 meetings on specific disease areas over the next five years
  - Meetings will help develop a systematic approach to gathering input

Which Disease Areas would be the Focus of PDUFA V Meetings? Criteria for Nomination

- Disease areas that are chronic, symptomatic, and affect functioning and activities of daily living
- Disease areas for which important aspects of that disease are not formally captured in clinical trials
- Disease areas for which there are currently no therapies or very few therapies, or the available therapies do not directly affects how a patients feels, functions, or survives
- Disease areas that reflect a range of severity
- Disease areas that have a severe impact on identifiable sub-populations (such as children or the elderly)
- Disease areas that represent a broad range in terms of size of the affected population

Identifying Disease Areas for the Patient-Focused Meetings

- **In September 2012, FDA announced a preliminary set of diseases as potential meeting candidates**
  - Public input on these nominations was collected through an online docket and at a public meeting held in October 2012
  - Over 4,500 comments were submitted, which addressed over 90 disease areas
  - FDA carefully considered these public comments and the perspectives of our drug review divisions at FDA

- **FDA selected a set of 16 diseases selected to be the focus of meetings for fiscal years 2013-2015; this set was published in the Federal Register in April 2013**
  - Another public process will be initiated in 2015 to determine the set for fiscal years 2016-2017

Disease Areas to be the focus of meetings for FY 2013-2015

FY 2013

- Chronic fatigue syndrome
- HIV
- Lung cancer
- Narcolepsy

FY 2014 – 2015

- **Sickle cell disease**
- Fibromyalgia

- Alpha-1 antitrypsin deficiency
- Breast cancer
- Chronic Chagas disease
- Female sexual dysfunction

FY 2014 – 2015 (continued)

- Hemophilia A, Hemophilia B, von Willebrand disease, and other heritable bleeding disorders
- Idiopathic pulmonary fibrosis
- Irritable bowel syndrome, gastroparesis, and gastroesophageal reflux disease with persistent regurgitation symptoms on proton-pump inhibitors
- Neurological manifestations of inborn errors of metabolism
- Parkinson's disease and Huntington's disease
- Pulmonary arterial hypertension

Tailoring Each Patient-Focused Meeting

- **In planning the format and questions we consider unique characteristics of the disease context**
  - E.g., current state of drug development, specific interests of the FDA review division, and the needs of the patient population
  - Each meeting focuses on a set of questions that aim to elicit patients' perspectives on their disease and on treatment approaches

- **We've been exploring different methods of gathering input:**
  - polling questions
  - interactive webcast and phone participation

- **Common to all of the meetings:**
  - Patient, caretaker, and patient advocate perspectives were powerful and insightful
  - Patient stakeholder involvement was key to the success of past meetings

Product of Patient-Focused Meetings

- **Each meeting results in a meeting report that faithfully reflects the input heard from patients**
  - The report will be shared with FDA reviewers and posted on the FDA website
  - The patient perspectives captured in the report will provide helpful insights for FDA reviewers conducting benefit-risk assessments for drugs to treat this disease

Background on Sickle Cell Disease and Treatment

Nicole Verdun, MD
Division of Hematology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

February 7, 2014

Overview

- Definition
- Genetics
- Complications
- Treatment

Sickle Cell Disease: A global health problem

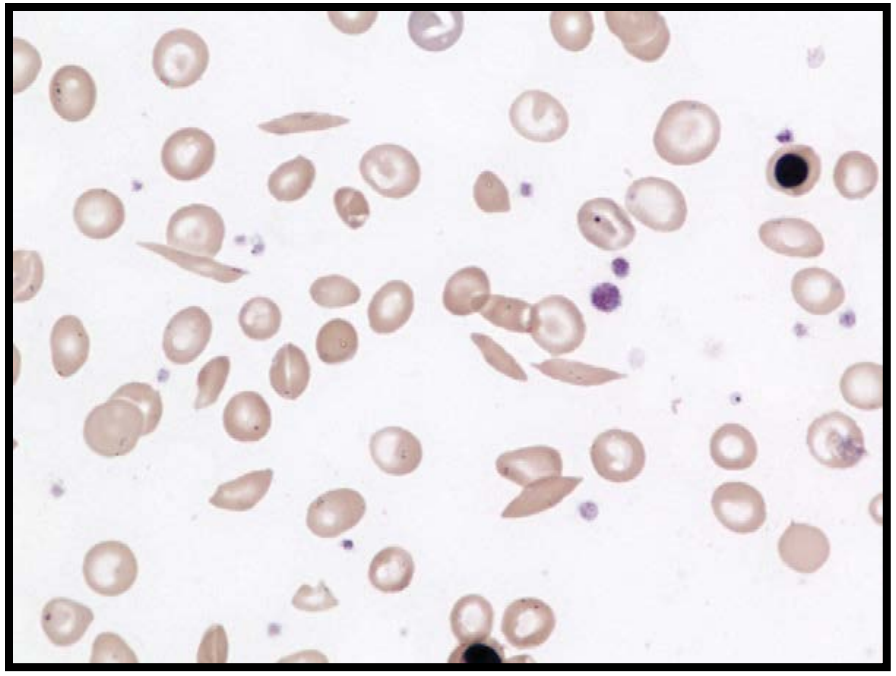
- 100,000 affected in the United States
- Millions affected globally
- 1 in 500 African-American Births
- 1 in 36000 Hispanic Births
- Sickle Cell Trait 1 in 12 African-Americans

Source: CDC.gov

Goal at FDA

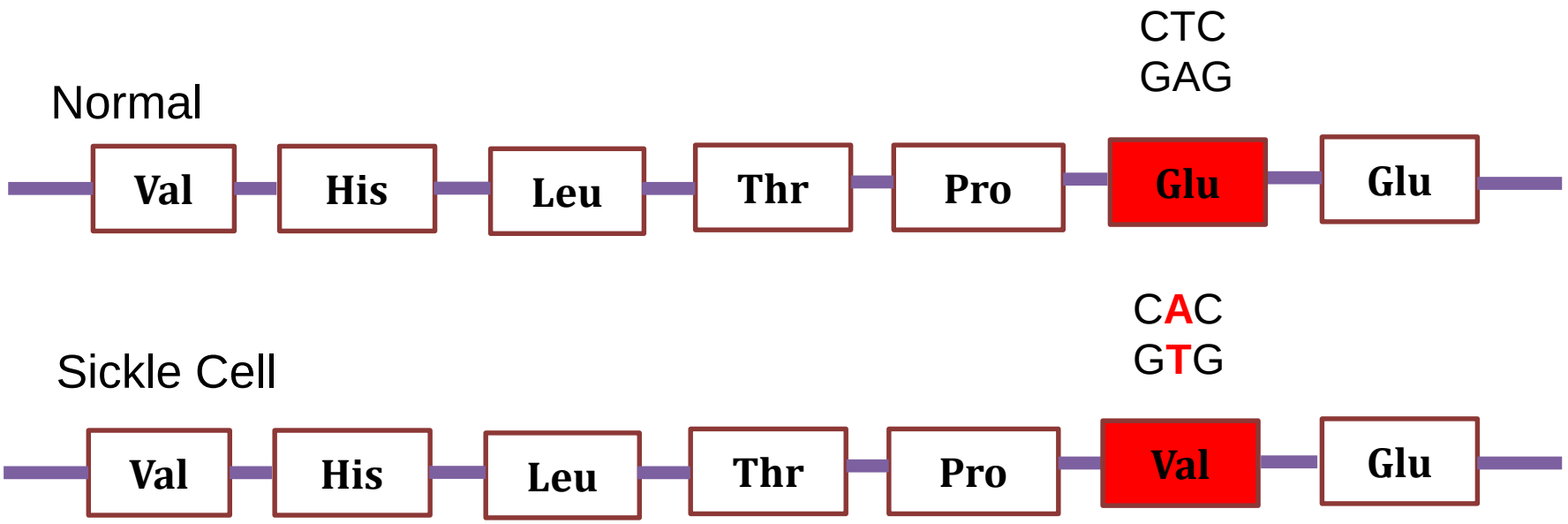
Development of safe and effective treatments for preventing and reducing the complications of sickle cell disease

Sickle Cell Disease



- Multisystem disease associated with episodes of acute illness and progressive organ damage
- Red blood cells change to a sickled shape in presence of decreased oxygen and inflammation
- Sickled red blood cells and white blood cells trapped in small blood vessels

Genetics of Sickle Cell Disease



- **Normal Hemoglobin** - Two alpha globin chains and two beta globin chains
- **Hemoglobin S** - Point mutation changing sixth amino acid in the β hemoglobin chain from glutamic acid to valine

Genetics

- Sickle cell anemia (Homozygous SS)
- Other forms sickle cell disease, Hb S with other abnormal β chains
  - Ex. SC, $S\beta^0$, $S\beta^+$, SO-Arab, SD
- Differences in severity, complications
  - *Somewhat* attributable to genes and type of sickle cell disease
  - *But* even within same family or mutation, differences exist
  - Inherit other genetic factors

    Ex. α-thalassemia, Hereditary Persistence of Fetal Hemoglobin

Sickle Cell Disease Complications

- Dactylitis
- Infection (*splenic dysfunction*)
- Splenic sequestration
- Aplastic Crisis
- Vaso-occlusive pain episodes
- Acute chest syndrome
- Stroke
- Silent Cerebral Infarcts
- Cerebral hemorrhage
- Moyamoya disease
- Hepatopathy
- Priapism
- Leg ulcers
- Pulmonary hypertension
- Cholelithiasis
- Avascular necrosis
- Kidney disease
- Restrictive lung disease
- Retinopathy
- Cardiomyopathy
- Delayed growth and sexual maturation
- Iron overload

Sickle Cell Disease

- Recurrent episodes of blood vessel occlusion and tissues not getting enough oxygen result in progressive damage involving most organs (bones, lungs, liver, kidneys, brain, eyes, cardiovascular system)

- Chronic hemolysis results in varying degrees of anemia, jaundice, fatigue, gallstones, delayed growth and sexual maturation, progressive damage to blood vessels

- Increased rates of hemolysis can predispose to pulmonary hypertension, priapism, leg ulcerations

Neurologic Complications

- One of the most common causes of stroke in children
- Damage to blood vessels in brain can start in infancy
- Some with progressive vasculopathy, recurrent strokes despite transfusion program
- Silent brain infarcts
  - Neurocognitive deficits
- Intracranial bleeds in adolescents, young adults
  - Moyamoya, Cerebral aneurysms
  - Treatment largely neurosurgical, limited

Complications of Sickle Cell Disease

- Acute chest syndrome
  - Form of acute lung injury
  - Significant morbidity and mortality associated
  - 2nd most common cause of hospitalizations

- Renal complications
  - Chronic damage to blood vessels in kidney
  - Starts at an early age
  - Adults can develop chronic renal failure

Sickle Cell Disease and Pregnancy

- Manifestations vary
- Increase in acute painful episodes
- Increased risk for thrombosis
- Infectious complications
- Cardiac complications
- Low birth weight

Current Treatment for Sickle Cell Disease

Specific Treatments Commonly Used- Prevention

- Hydroxyurea
  - FDA Approved in 1998
  - **Indication**- *To reduce the frequency of painful crises and to reduce the need for blood transfusions in adult patients with sickle cell anemia with recurrent moderate to severe painful crises*
  - Uses continue to grow, and are much broader than the indication
  - Works very well for some to decrease complications, increase survival
  - Mechanism of action not completely understood
    - Increase in hemoglobin
    - Reduction in hemolysis
    - Hb F production, RBC lives longer
    - Decreasing inflammation
    - Dilation of blood vessels

Other Preventive Treatments

- Penicillin prophylaxis
- Timely immunizations, pneumococcal, influenza vaccine
- Folic Acid (*due to increased RBC turnover*)
- Chronic RBC transfusion therapy
- Although not a "treatment"…
  - Ongoing education of caregivers, patients essential
  - A lot of surveillance (*TCD, Echos, Eye screening, U/A etc*.)
  - Monitoring growth and development

Stem Cell Transplantation

- Can be curative
- Significant risks during and after transplant have traditionally limited its use to those with significant complications
- Problems with finding matched donors
- Continued improvements in immunosuppression, management of transplant-related complications are ongoing
- Criteria for consideration of a transplant changing

Limitations of some of the preventive treatments used

- Chronic transfusion therapy
  - Iron overload
  - Antibodies
  - Transfusion reactions
  - Infections
- Hydroxyurea
  - Not universally effective
  - Laboratory monitoring required
  - Can be harmful during pregnancy to unborn baby
- ***Need further development of safe and effective treatments for sickle cell disease…***

Treatment of Complications

- Antibiotics
- Blood transfusion at the time of an event
- Surgery
- Pain crisis management is supportive
  - Hydration management, oxygen, anti-inflammatory agents, pain medication
- Acute chest syndrome management also supportive
  - Broad spectrum antibiotics, oxygen, pain management, transfusions, bronchodilators, mechanical ventilation

Interested in continuing to switch the treatment paradigm from supportive to preventive or curative

Future of Sickle Cell Disease Treatment

- Several clinical trials in the planning stages or in process

- ***But***…we need more development to have the global impact on sickle cell disease we need and that is overdue

Overview of Discussion Format

Sara Eggers, PhD
Office of Strategic Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Discussion Overview

Topic 1: The health effects that matter most to you

- We'll discuss pediatric /young adults first, then adults
- What are the specific ways that sickle cell disease affects your health?
- We want to hear about your "average" days (with no acute pain crisis) and your "worst" days (when a pain crisis hits)

Topic 2: Your perspectives on treatments

- What are you doing to treat your sickle cell disease?
- How well do your treatments work for you?
- What would you look for in an "ideal" treatment?
- What might you think about if you had the chance to participate in a study for an experimental new treatment?

Discussion Format

- **We will first hear from a panel of patients and caregivers**
  - The purpose is to set a good foundation for our discussion
  - They reflect a range of experiences with sickle cell disease
  - Some also represent sickle cell disease organizations

- **We will then broaden the dialogue to include patients and other patient representatives in the audience**
  - The purpose is to build on the experiences shared by the panel
  - We will ask questions and invite you to raise your hand to respond
  - Please state your name before answering

Discussion Format, continued

- **You'll have a chance to answer "polling" questions**
  - Their purpose is to aid our discussion
  - In-person participants: use the "clickers" to respond
  - Web participants: answer the questions through the webcast
  - Patients and patient representatives only, please

- **Web participants can add comments through the webcast**
  - Although they may not all be read or summarized today, your comments will incorporated into our summary report
  - We'll occasionally go to the phones to give you another opportunity to contribute

Send us your comments!

- **Your comments can be sent to the "public docket"**
  - The docket will be open until April 8, 2014
  - Share your experience, or expand upon something discussed today
  - Comments will be incorporated into our summary report
  - Anyone is welcome to comment

Visit:
http://www.regulations.gov/#!documentDetail;D=FDA-2013-N-1328-0001

Click Comment Now!

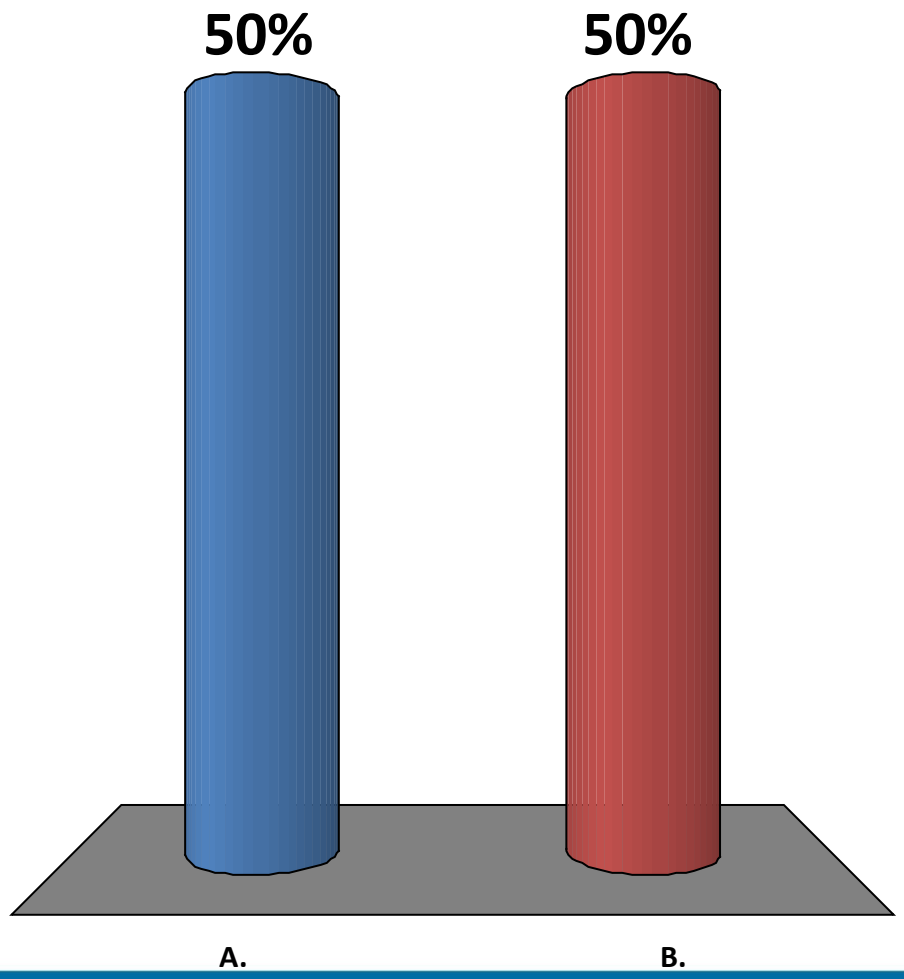
Discussion Ground Rules

- **We encourage patients to contribute to the dialogue--caregivers and advocates are welcome too**
- **FDA is here to listen**
- **Discussion will focus on health effects and treatments**
  - Open Public Comment Period is available to comment on other topics
- **The views expressed today are personal opinions**
- **Respect for one another is paramount**
- **Let us know how we're doing; evaluations at registration desk**

Where do you live?

A. Within Washington, D.C. metropolitan area (including the Virginia and Maryland suburbs)

B. Outside of the Washington, D.C. metropolitan area



Which of the following best describes you? Choose all that apply.

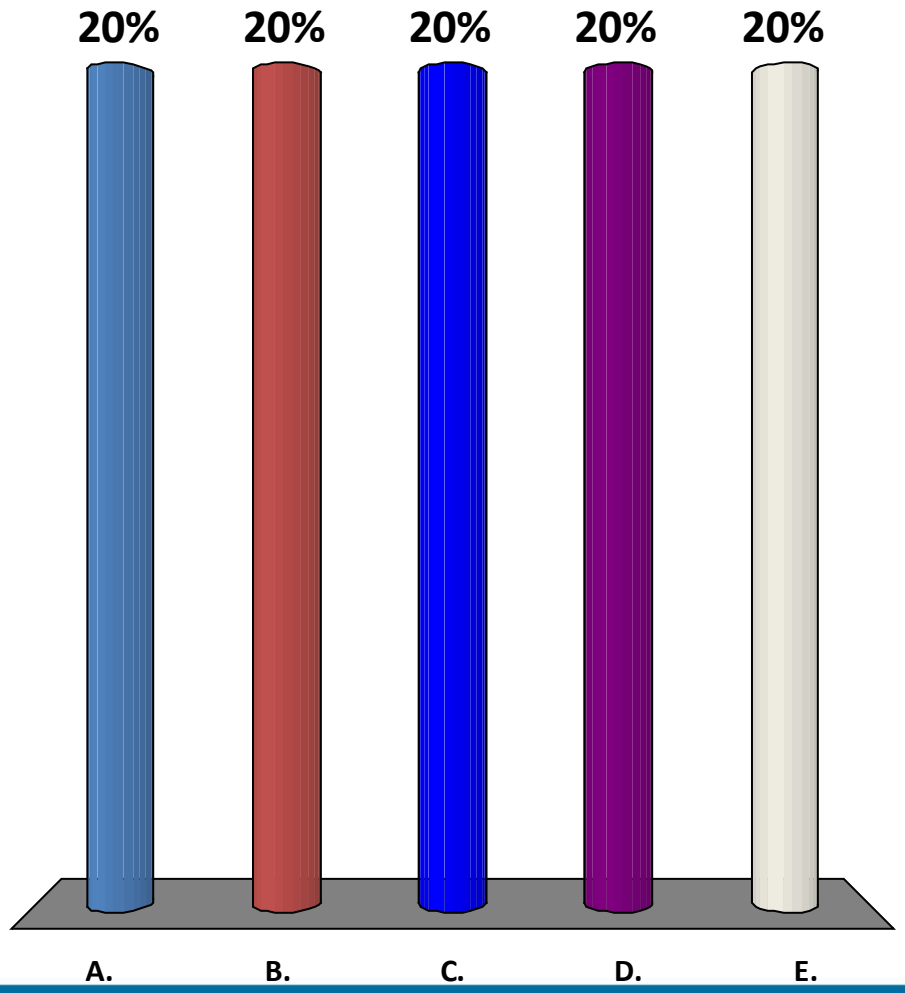
A. I have sickle cell disease

B. I am a family member or caretaker of someone with sickle cell disease

C. I work for a sickle cell disease patient support or advocacy organization

D. I am a healthcare professional who works with sickle cell disease patients

E. Other



What is your / your loved one's age?

A. 0 - 5

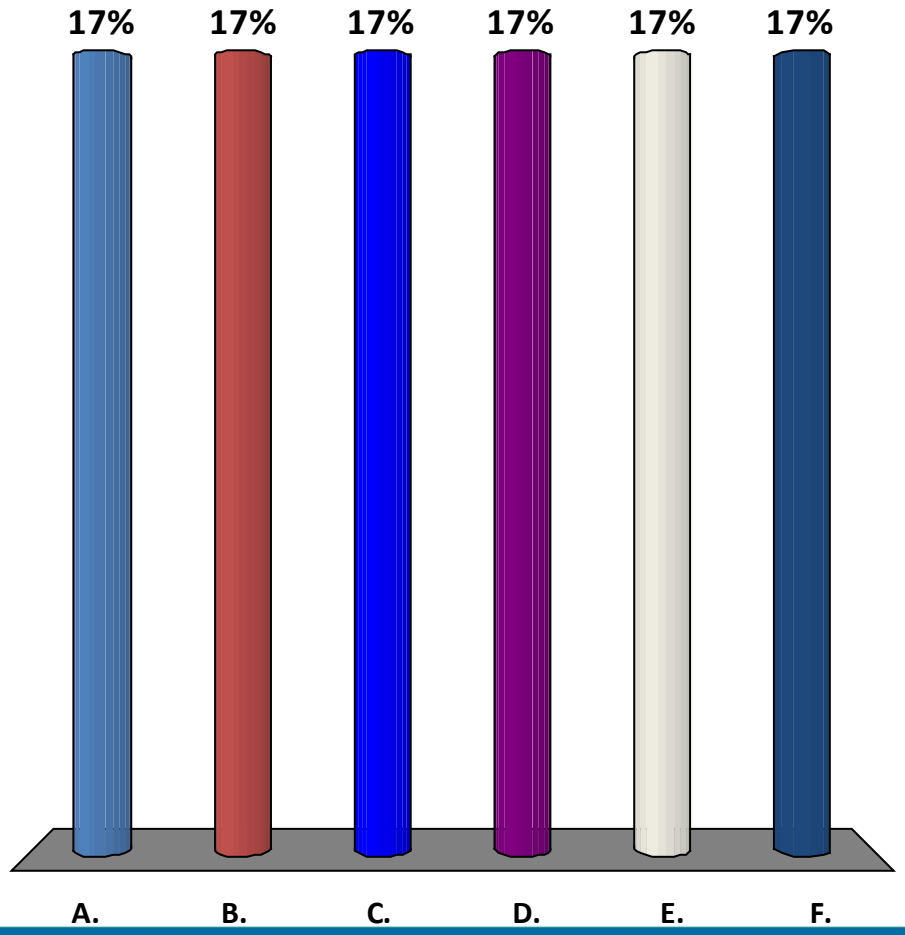
B. 6 - 12

C. 13 - 17

D. 18 - 22

E. 23 - 49

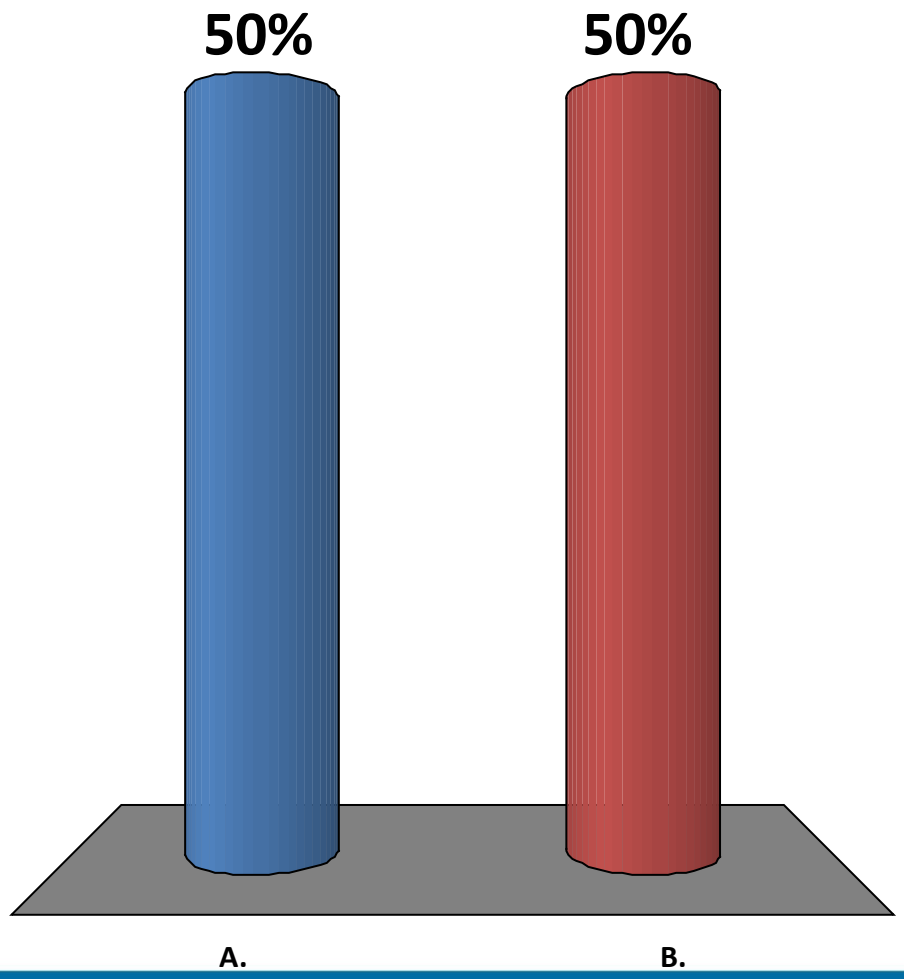
F. 50 or greater



Are you / Is your loved one:

A. Male

B. Female



Where do you / your loved one receive **most of your sickle cell care?**

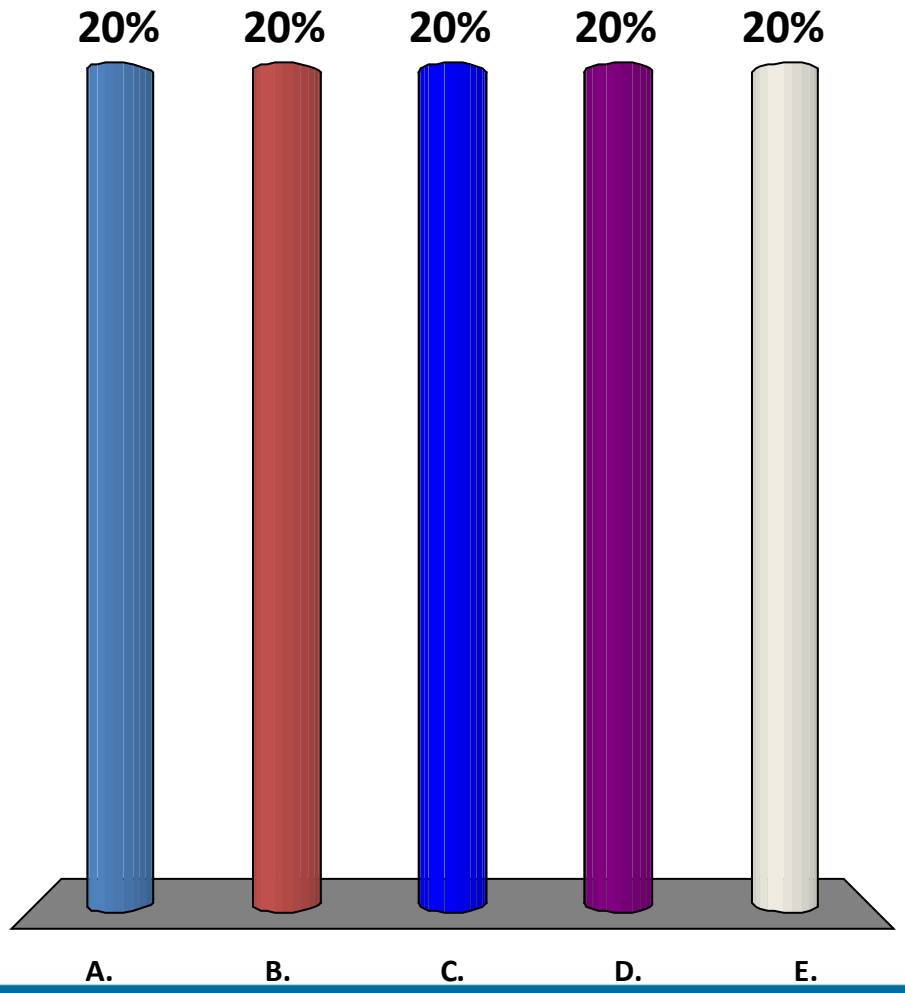
A. At a sickle-cell treatment center with a hematologist

B. Not at a sickle cell treatment center but with a hematologist

C. A primary care center (family medicine, internal medicine, pediatrician)

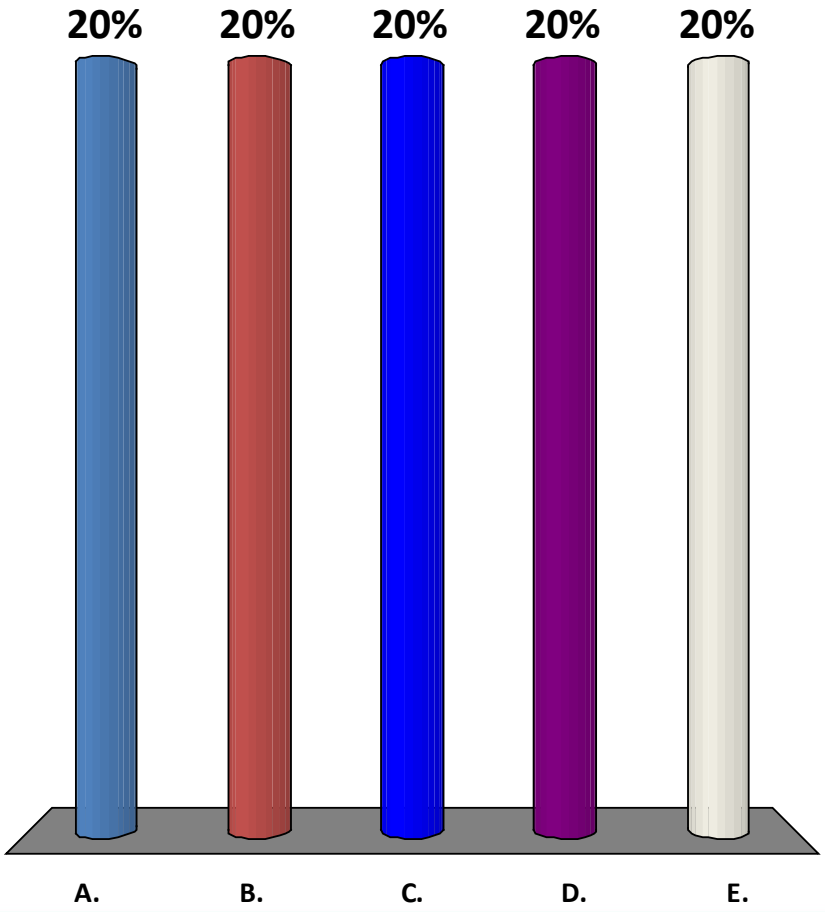
D. Only emergency rooms and hospitals as needed

E. Not sure



In the past year, how often have you / your loved one had to go to the hospital or the emergency room because of sickle cell disease?

A. No times in the past year
B. 1-2 times
C. 3-5 times
D. 5-10 times
E. More than 10 times



Discussion Topic 1

The effects of sickle cell disease that matter most to you

Sara Eggers
Facilitator

Topic 1: Health Effects
Pediatric and Young Adult Panelists

- Nancy Rene
- Andrea Williams
- Dawn Nelson
- Alana McClinton

Topic 1: Health Effects
Pediatric and Young Adult Perspective

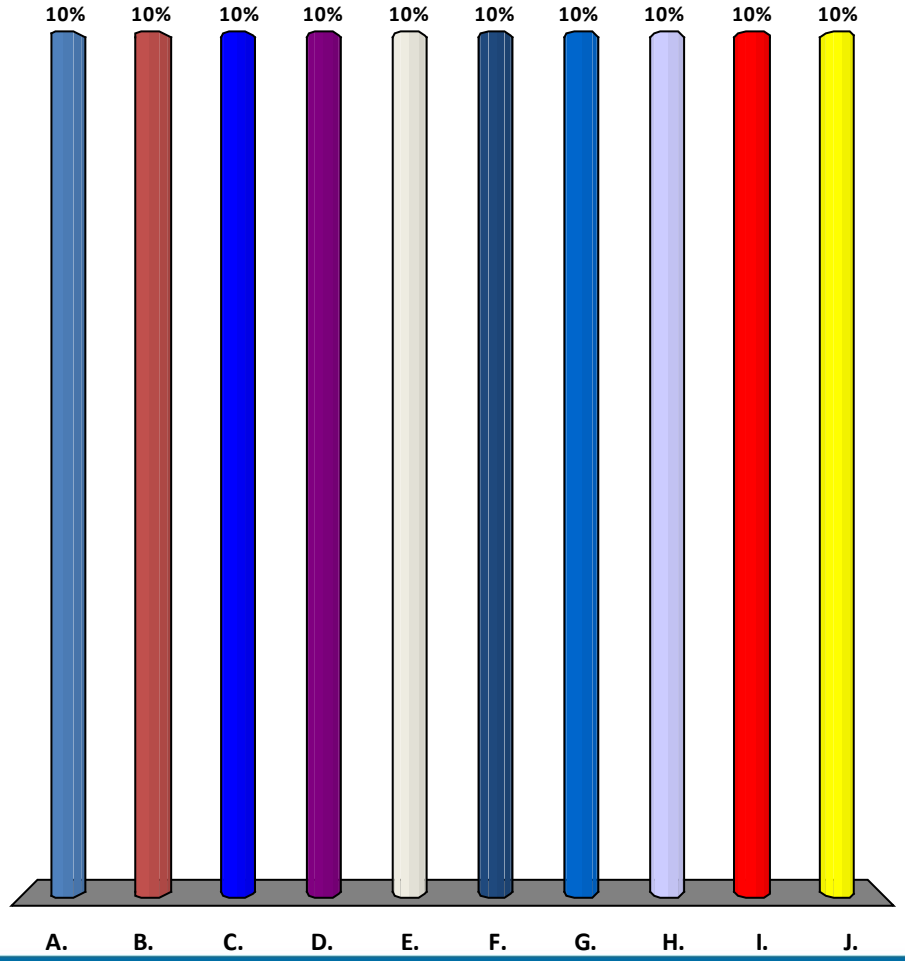
- Of all of the ways that sickle cell disease affects your health, which 1-3 effects have the greatest impact on your life?
- How does sickle cell disease affect your life on an “average” day? Are there activities that you cannot do at all or as well as you would like?
- How does sickle cell disease affect your life on the “worst” days, such as days when you have a pain crisis or have to be hospitalized for some reason?
- What worries you most about how sickle cell disease could affect your health in the future?

Pediatric and Young Adult

Other than acute pain crises, what health effects of sickle cell disease currently have the greatest impact on your / your loved one's life? **Please choose up to 3 effects.**

A. Chronic daily pain
B. Multiple infections
C. Strokes
D. Acute chest syndrome
E. Growth problems or delay in reaching puberty
F. Priapism
G. Problems with spleen

H. Difficulty concentrating
I. Other effects not listed above



Topic 1: Health Effects
Pediatric and Young Adult Perspective

- Of all of the ways that sickle cell disease affects your health, which 1-3 effects have the greatest impact on your life?
- How does sickle cell disease affect your life on an “average” day? Are there activities that you cannot do at all or as well as you would like?
- How does sickle cell disease affect your life on the “worst” days, such as days when you have a pain crisis or have to be hospitalized for some reason?
- What worries you most about how sickle cell disease could affect your health in the future?

Adult (Age 23+) Perspective on Topic 1: Panel Participants

- George Carter
- Terri Booker
- Helen Sarpong
- Marqus Valentine

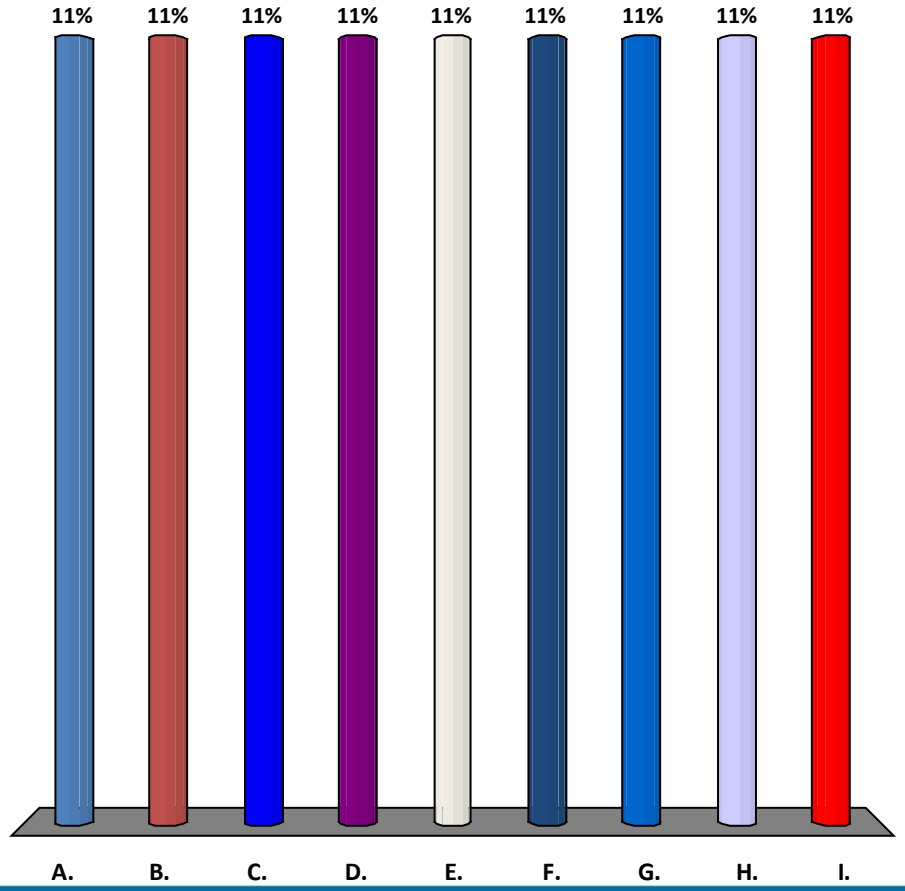
Topic 1: Health Effects
Adult (Age 23+) Perspectives

- Of all of the ways that sickle cell disease affects your health, which 1-3 effects have the greatest impact on your life?
- How does sickle cell disease affect your life on an "average" day? Are there activities that you cannot do at all or as well as you would like?
- How does sickle cell disease affect your life on the "worst" days, such as days when you have a pain crisis or have to be hospitalized for some reason?
- What worries you most about how sickle cell disease could affect your health in the future?

Adults

Other than acute pain crises, what health effects of sickle cell disease currently have the greatest impact on your / your loved one's life? **Please choose up to 3 effects.**

A. Chronic daily pain
B. Strokes
C. Acute chest syndrome
D. Fatigue
E. Priapism
F. Problems with eyesight (from sickle cell disease)
G. Damage to heart or pulmonary hypertension
H. Kidney disease or gallstones
I. Other effects not listed above



Topic 1: Health Effects
Adult (Age 23+) Perspectives

- Of all of the ways that sickle cell disease affects your health, which 1-3 effects have the greatest impact on your life?
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- How does sickle cell disease affect your life on the "worst" days, such as days when you have a pain crisis or have to be hospitalized for some reason?
- What worries you most about how sickle cell disease could affect your health in the future?

Lunch Break

Discussion Topic 2

Patients' perspectives on treatments for sickle cell disease

Sara Eggers
Facilitator

Topic 2: Panel Participants

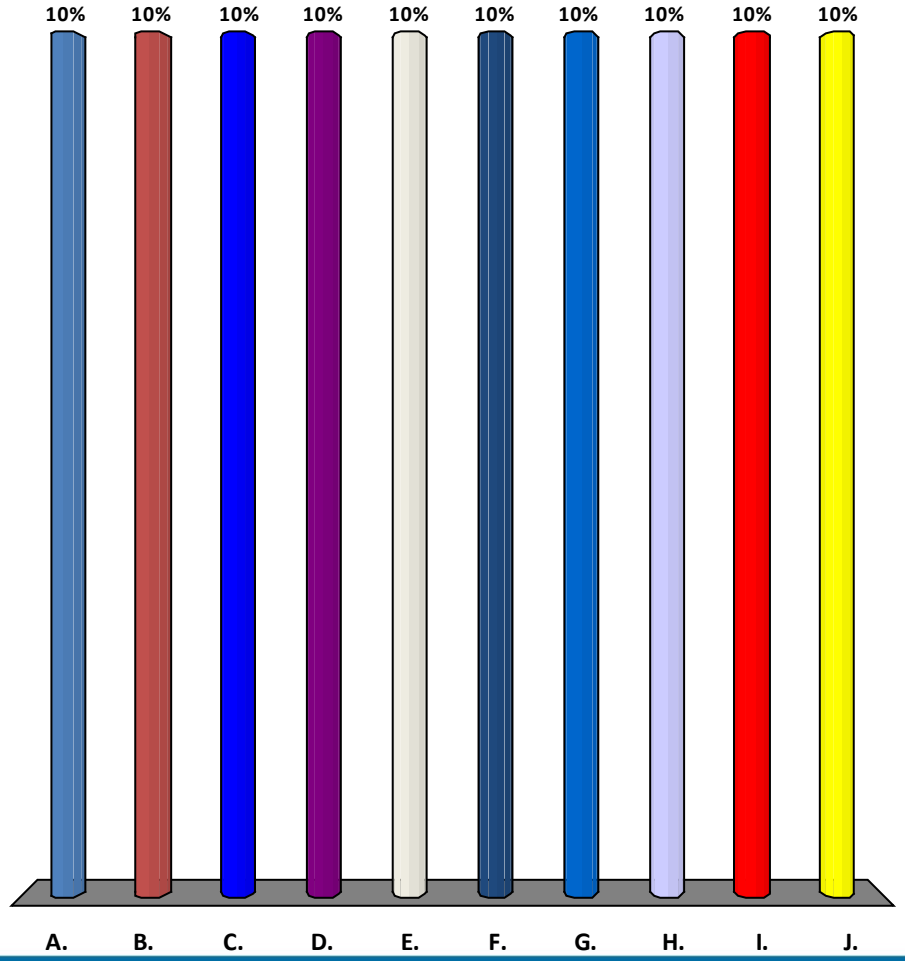
- John Moore
- Tina Kay Hughes
- Lakiea Bailey
- Olga Barnwell
- Anthony Braxton
- Adam BunduKarma

Topic 2 Discussion: Patients' perspectives on treatments for sickle cell disease

- Are you currently using any prescription medicines or medical treatments to prevent or treat any negative effects of your sickle cell disease?
- Besides prescription medications, what else do you do to prevent or treat any negative effects of your sickle cell disease?
- What parts of your sickle cell disease do your current treatments not treat at all or not as well as you would like?
- Assuming that there is no cure for sickle cell disease, what specific things would you look for in an ideal treatment?

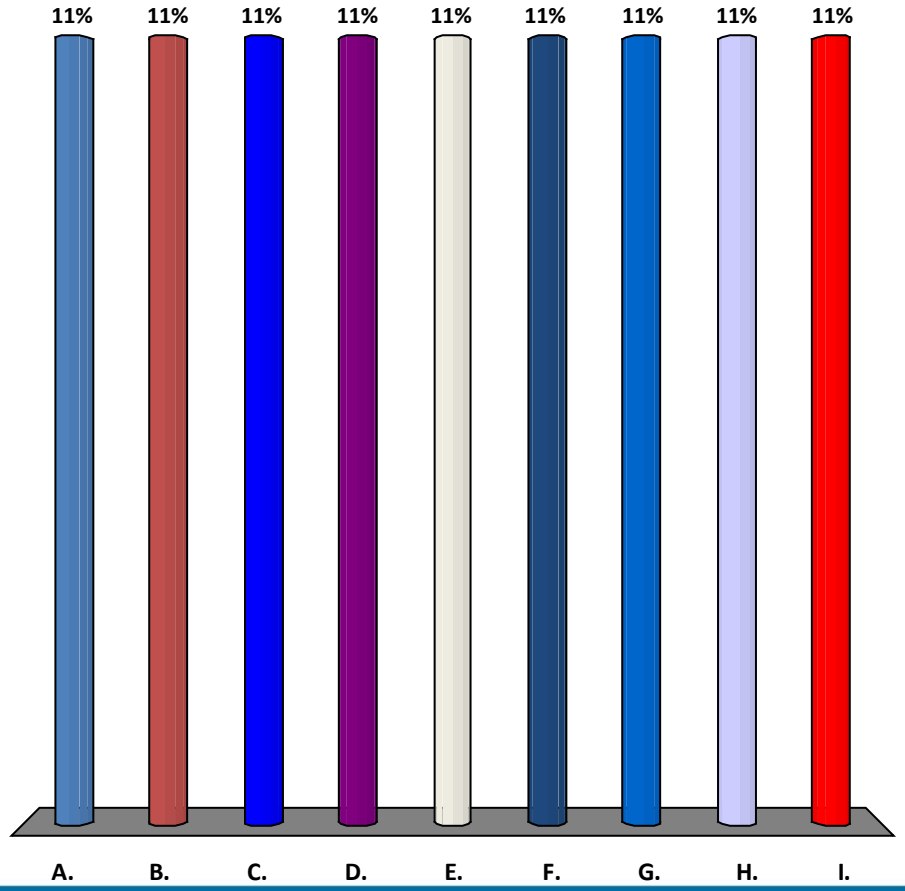
In the past year, have you / your loved one used prescription medicines or medical treatments to treat sickle cell disease? **Check all that apply.**

A. Folic acid
B. Prescription pain medications
C. Hydroxyurea
D. Blood transfusions
E. Oxygen therapy
F. Antibiotics
G. Transplants (such as bone marrow transplants)
H. Other prescription medicines or medical treatments
I. No prescription medicines or medical treatments
J. I'm not sure



In the past year, have you / your loved one done anything else to treat sickle cell disease? **Check all that apply.**

A. Taken over-the-counter pain medicines
B. Had a massage or acupuncture
C. Taken vitamins, dietary supplements, or herbal remedies
D. Take in extra fluids
E. Followed a special diet, such as avoiding certain foods
F. Attended pain programs or support groups
G. Used some other therapy
H. No other therapies
I. I'm not sure



Topic 2 Discussion: Patients' perspectives on treatments for sickle cell disease

- Are you currently using any prescription medicines or medical treatments to prevent or treat any negative effects of your sickle cell disease?
- Besides prescription medications, what else do you do to prevent or treat any negative effects of your sickle cell disease?
- What parts of your sickle cell disease do your current treatments not treat at all or not as well as you would like?
- Assuming that there is no cure for sickle cell disease, what specific things would you look for in an ideal treatment?

Hypothetical Scenario for Discussion on: Clinical Trial Participation

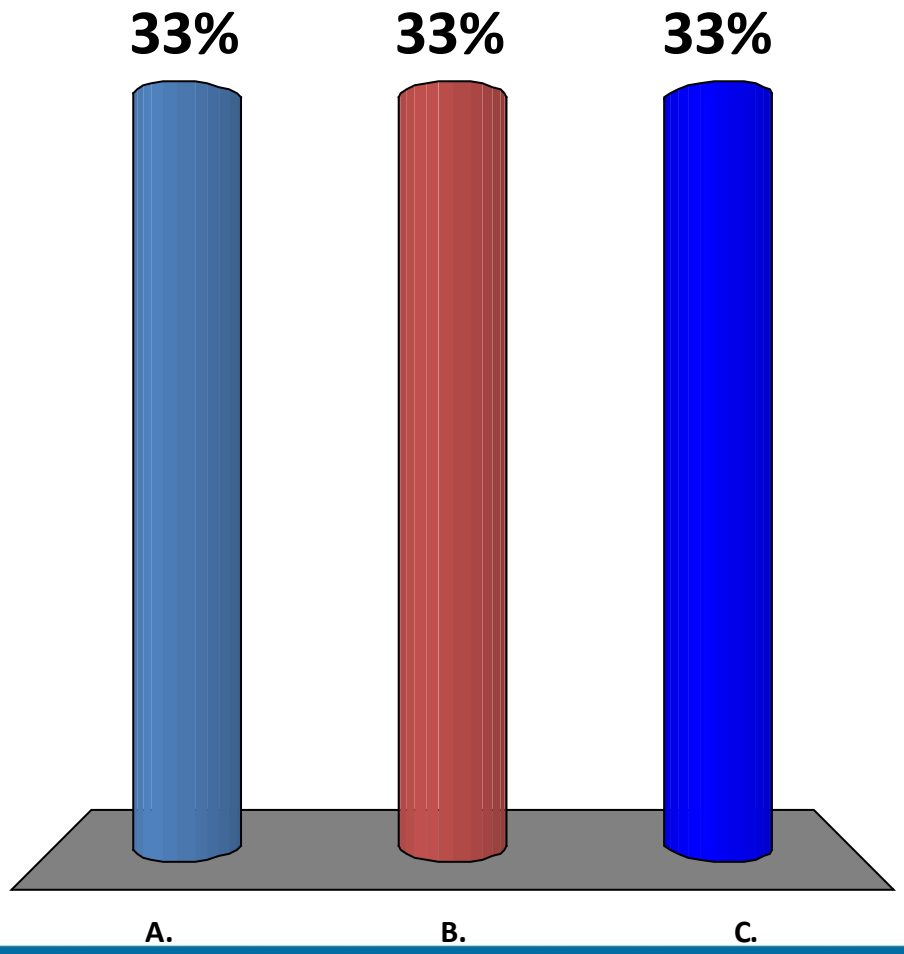
February 7, 2014

Have you /your loved one ever participated in a clinical trial studying experimental treatments for sickle cell disease?

A. Yes

B. No

C. I'm not sure



Hypothetical scenario

Imagine that…

- You have been invited to participate in a clinical trial to study an experimental treatment for sickle cell disease
- Early research in animals and people shows that this treatment may decrease the number of pain crises or hospitalizations in some people with sickle cell disease
- The purpose of the study is to better understand how well this treatment works and its safety
- The study will enroll 1000 participants with sickle cell disease

Hypothetical scenario

Imagine that…

- This clinical study lasts one year, and involves four clinic visits, occurring once every 3 months

- More common side effects of this therapy may include nausea, diarrhea, fatigue, headache, and rash

- Rarer but more serious side effects may include infection, bleeding and life-threatening allergic reaction

What thoughts and questions

come to mind as you hear this scenario?

Of the following factors, which **two** would you rank as most important to your decision about whether to participate in a clinical trial to study an experimental treatment?

A. Common side effects (such as nausea or diarrhea)

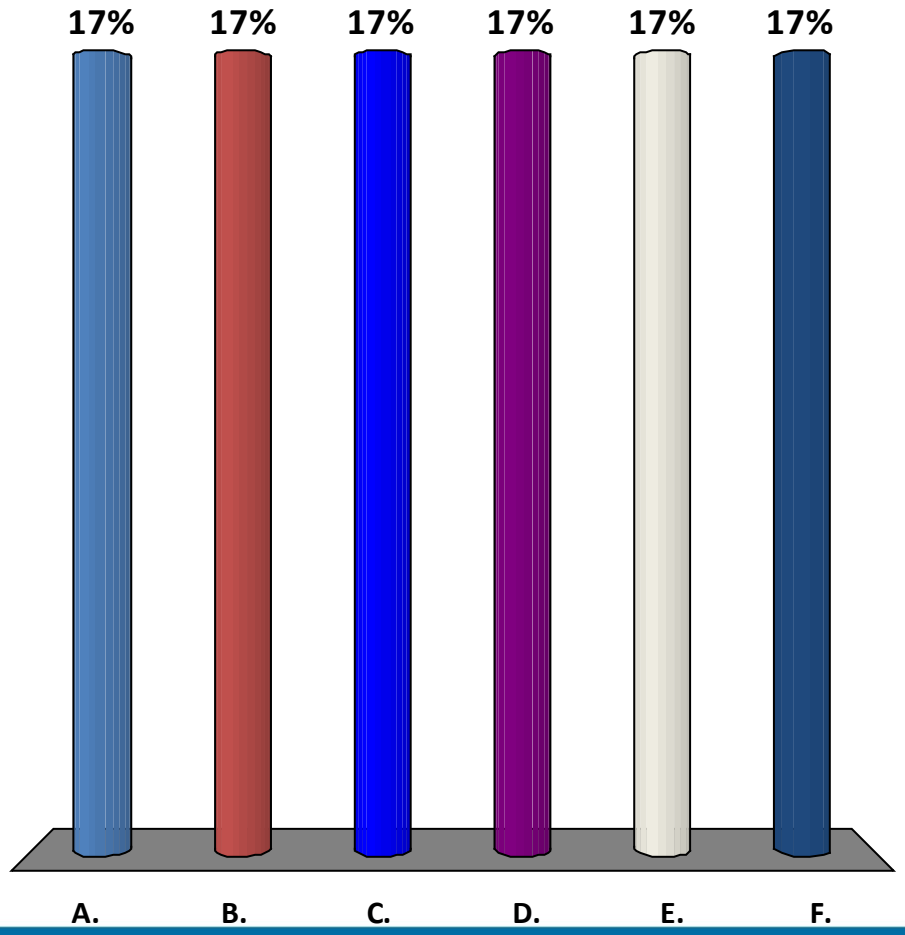
B. Rare but serious side effects (such as bleeding or infection)

C. How the treatment might improve my health

D. How the trial might affect my current treatment plan

E. Requirements of the trial (such as regular blood tests or hospital stays)

F. Length of the trial

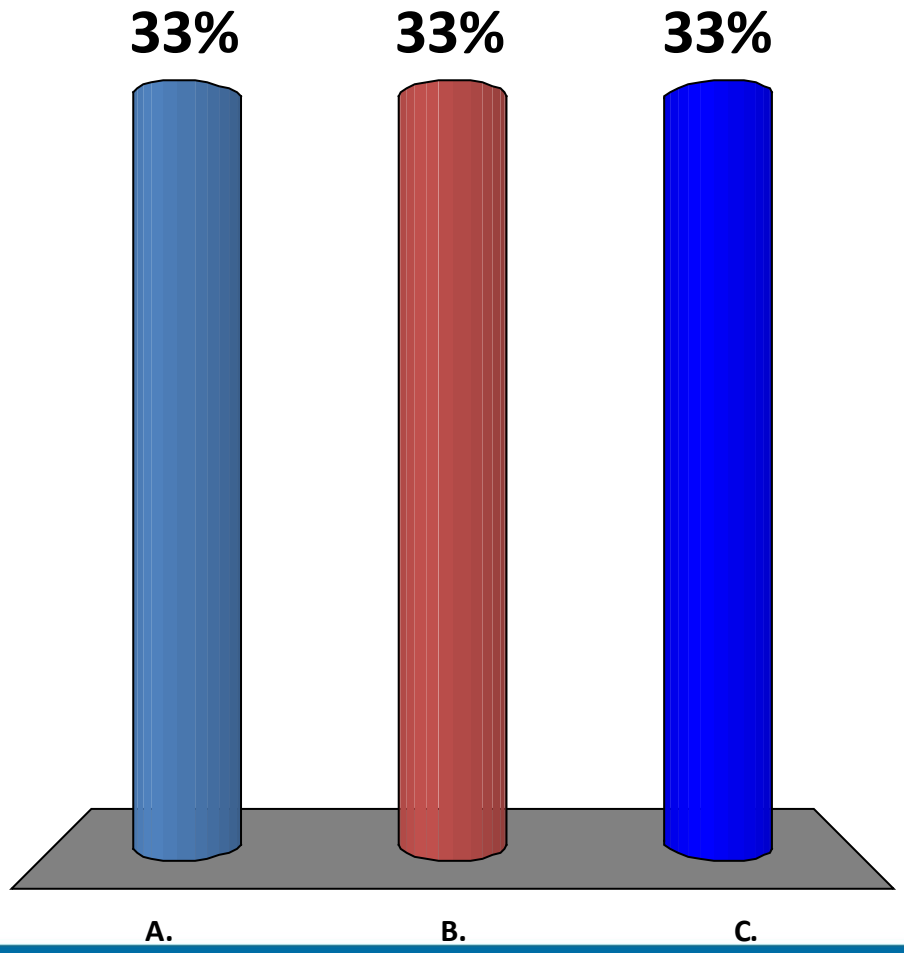


If you / your loved one had the opportunity to participate in a clinical trial to study an experimental treatment, which of the following best describes your thoughts?

A. **Yes:** I would want to know more, but I am generally willing to consider participating

B. **No:** I would probably not consider participating

C. **Maybe:** I am not sure whether I would be willing to consider participating or not



Open Public Comment Period

Closing Remarks

Kathy Robie-Suh, MD, PhD
Division of Hematology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration