



Public Meeting on Patient-Focused Drug Development for Hemophilia A, Hemophilia B, von Willebrand Disease and other Heritable Bleeding Disorders

September 22, 2014



Welcome

Donna Lipscomb

Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

September 22, 2014

Agenda

- **Setting the context**
 - Opening Remarks
 - Overview of FDA's Patient-Focused Drug Development Initiative
 - Background on Heritable Bleeding Disorders
 - Overview of Discussion Format
- **Discussion Topic 1:** Disease symptoms and daily impacts that matter most to patients
- **Discussion Topic 2:** Patients' perspectives on current approaches to treating heritable bleeding disorders
- **Open Public Comment**
- **Closing Remarks**



Opening Remarks

Ginette Michaud, MD

Deputy Director, Office of Blood Research and Review
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

September 22, 2014



FDA's Patient-Focused Drug Development Initiative

Theresa Mullin, PhD

Director, Office of Strategic Program
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

September 22, 2014

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's oversight both during drug development and during our review of a marketing application
- **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
 - CDER will convene 17 meetings and CBER will convene 3 meetings
 - Meetings will help develop a systematic approach to gathering input

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. 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**
 - 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

- Sickle cell disease
- Fibromyalgia
- Pulmonary arterial hypertension
- Inborn errors of metabolism
- **Hemophilia A, Hemophilia B, von Willebrand disease, and other heritable bleeding disorders**

FY 2014 – 2015

- Alpha-1 antitrypsin deficiency
- Breast cancer
- Chronic Chagas disease
- Female sexual dysfunction
- Idiopathic pulmonary fibrosis
- Irritable bowel syndrome, gastroparesis, and gastroesophageal reflux disease
- Parkinson's disease and Huntington's disease

Tailoring Each Patient-Focused Meeting

- **Each meeting focuses on a set of questions that aim to elicit patients' perspectives on their disease and on treatment approaches**
 - We start with a set of questions that could apply to any disease area; these questions are taken from FDA's benefit-risk framework and represent important considerations in our decision-making
 - We then further tailor the questions to the disease topic of the meeting (e.g., current state of drug development, specific interests of the FDA review division, and the needs of the patient population)
- **Focus on relevant current topics in drug development for the disease at each meeting**
 - E.g., focus on HIV patient perspectives on potential “cure research”
- **We've learned that active patient involvement and participation is key to the success of these meetings.**

“Voice of the Patient” Reports

- Following each meeting, FDA publishes a Voice of the Patient report that summarizes the patient testimony at the meeting, perspectives shared in written docket comments, as well as any unique views provided by those who joined the meeting webcast.
- These reports serve an important function in communicating to both FDA review staff and the regulated industry what improvements patients would most like to see in their daily life.
- FDA believes that the long run impact of this program will be a better, more informed understanding of how we might find ways to develop new treatments for these diseases.



Background on Heritable Bleeding Disorders

Stephanie O. Omokaro, MD

Division of Hematology Clinical Review
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

September 22, 2014

Introduction: Normal Clotting Mechanism

- Platelets stick together and form a plug at the site of an injured blood vessel.
- Proteins in the blood called clotting factors then interact to form a fibrin clot.
- This interaction holds the platelets in place and allows healing to occur at the site of the injury while preventing blood from escaping the blood vessel.

Heritable Bleeding Disorders

- Diverse group of disorders
 - range from mild to severe life-threatening conditions
- Generally, defects in the clotting mechanism of the blood are present life-long
 - Problems with platelet plug (e.g. vWD)
 - Defect in fibrin clot (e.g. Hemophilia and other factor deficiencies)
- Excessive Fibrinolysis (e.g. α 2-antiplasmin deficiency)
- Fragile blood vessels (e. g. Hereditary Hemorrhagic Telangiectasia)

von Willebrand Disease

- Most common inherited bleeding disorder
 - 1 in 100 people affected
 - More than 65% of patients have no symptoms or have mild symptoms
- Occurs equally in men and women
- Due to a reduced or abnormal production of von Willebrand factor (vWF)
 - Results in abnormal platelet adhesion and function
- Bleeding may vary in severity from mild to severe

Hemophilia A

- Second most common inherited bleeding disorder
 - 1 in 5000 male births affected
- Almost all patients are male
- Due to reduced levels of factor VIII
 - Results in abnormal clot formation
- Bleeding severity is related to the Factor VIII levels in blood

Hemophilia B

- Also known as Christmas Disease
 - 1 in 30,000 male births affected
- Almost all patients are male
- Due to reduced levels of factor IX
 - Results in abnormal clot formation
- Bleeding severity is related to the levels of Factor IX in blood

Platelet Disorders

- Due to a reduced platelet count or abnormal function
 - Can result from abnormal platelet production, adhesion, aggregation, activation or secretion
- Rare in occurrence (few examples):
 - Glanzmann thrombasthenia: 1 in 1,000,000
 - Bernard-Soulier syndrome: < 1 in 1,000,000
 - Gray platelet syndrome: Very rare
- Prolonged bleeding time and abnormal clot formation
- Variable bleeding tendency ranging from mild to severe

Examples of Other Rare Disorders

Bleeding Disorder	Prevalence
Factor I (fibrinogen) deficiency	> 200 cases reported
Factor II (prothrombin) deficiency	< 100 cases reported
Factor V deficiency	< 1 in 1,000,000
Factor VII deficiency	1 in 500,000
Factor X deficiency	1 in 500,000
Factor XI deficiency	4% in Ashkenazi Jews, otherwise rare
α_2 -antiplasmin deficiency	> 10 families reported
Factor XIII deficiency	More than 200 cases reported

Adapted from Crookston et al at pathologyoutlines.com

Signs and Symptoms

- Bleeding that may vary in severity
 - Bleeding after circumcision or after having shots such as vaccinations
 - Skin (i.e. bruising) or muscle and soft tissue causing a build-up of blood in the area (called a hematoma)
 - Blood In the urine or stool
 - Frequent and hard-to-stop nosebleeds
 - Spontaneous bleeding as well as bleeding following injuries or surgery
 - Joints : can cause swelling and pain or tightness in the joints; often affects the knees, elbows, and ankles
 - Heavy and frequent menstrual bleeding or heavy bleeding after childbirth
 - Head bleeds

Treatment

- Avoidance of medication that can aggravate bleeding
- Current therapies depend on the type of bleeding disorder and the severity of bleeds:
 - Platelet transfusions
 - Fresh Frozen Plasma
 - Cryoprecipitate
 - Specific Factor Concentrates
 - DDAVP (desmopressin)
 - Supportive treatments such as hormone replacement therapies, pain medications and clot stabilizing medications (i.e. antifibrinolytics)
- Gene therapy is being studied as a possible treatment for hemophilia

Treatment Complications

- Inhibitor development (Antibodies) to Factor Concentrates
 - Bleeds are more difficult to treat
 - Treatment is less effective
- Severe allergic reactions
- Complications due to frequent intravenous infusions
 - Scarring of veins
 - Implanted catheter devices with risks
 - Risks for infections

Patient Focused Meeting

We encourage you to take this opportunity to provide FDA greater insight into your bleeding disorder.

THANK YOU



Overview of Discussion Format

Donna Lipscomb

Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

Discussion Overview

Topic 1: The effects of your bleeding disorder

- Of all of the symptoms that you experience because of your condition, which one to three symptoms (bleeding or non-bleeding) have the most significant impact on your life?
- Are there specific activities that are important to you, but that you cannot do at all, or as well as you would like, because of your condition?
- How have your condition and its symptoms changed over time?
- What worries you most about your condition?

Discussion Overview

Topic 2: Current approaches to treatment

- What are you currently doing to treat your condition or its symptoms?
 - How well do these treatments work for you?
 - What are the most significant disadvantages or complications of your current treatments, and how do they affect your daily life?
 - How has your treatment changed over time and why?
 - What aspects of your condition are not improved by your current treatment regimen?
 - What treatment has had the most positive impact on your life?
- If you could create your ideal treatment, what would it do for you (i.e., what specific things would you look for in an ideal treatment)?
- If you had the opportunity to consider participating in a clinical trial studying experimental treatments, what things would you consider when deciding whether or not to participate?

Discussion Format

- **We will first hear from a panel of patients**
 - The purpose is to set a good foundation for our discussion
 - They reflect a range of experiences with heritable bleeding disorders

- **We will then broaden the dialogue to include patients and 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

- **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 be incorporated into our summary report

Send us your comments!

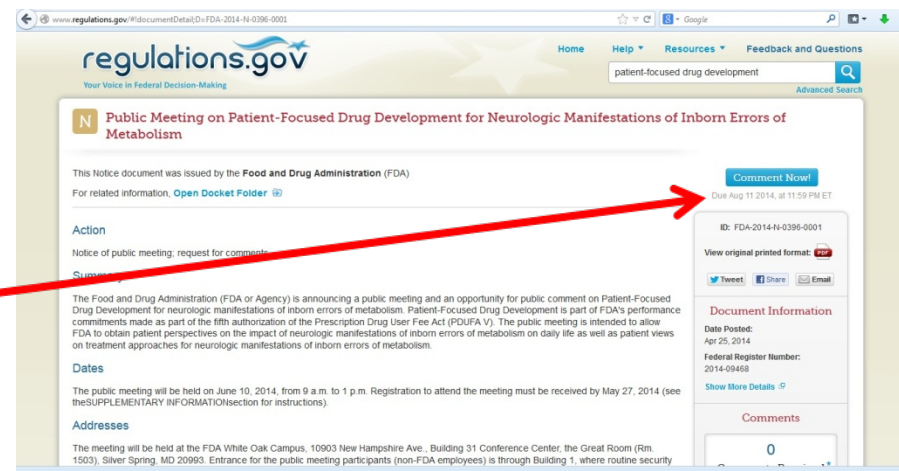
You can send us comments through the “public docket”.

- The docket will be open until November 28, 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/#!/docketDetail;D=FDA-2014-N-0851>

Click Comment Now!



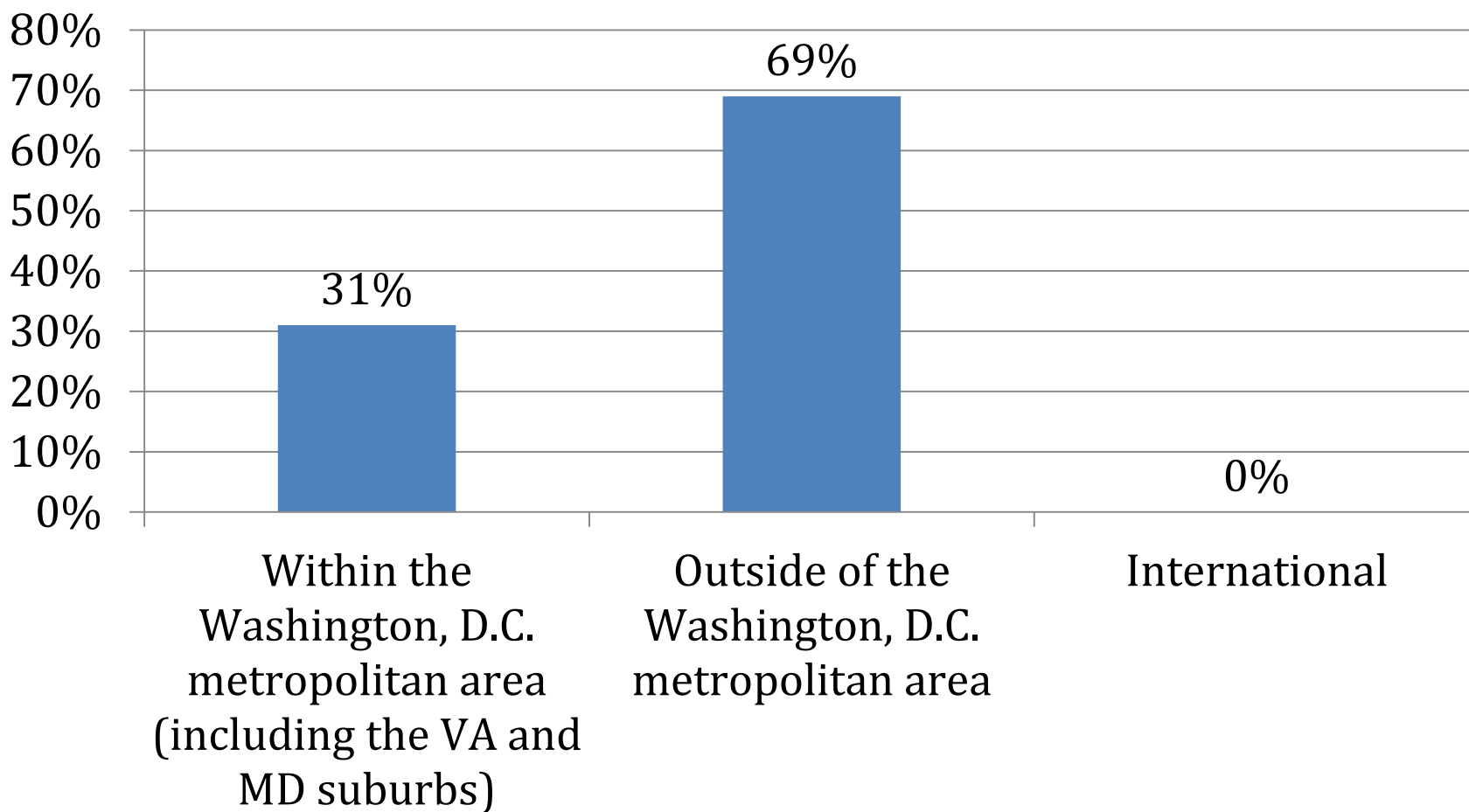
Discussion Ground Rules

- We encourage patients, caregivers and advocates to contribute to the dialogue
- FDA is here to listen
- Discussion will focus on symptoms 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 the meeting went today; evaluations at registration desk

Where do you live?

- A. Within the Washington, D.C. metropolitan area
(including the VA and MD suburbs)
- B. Outside of the Washington, D.C. metropolitan area
- C. International

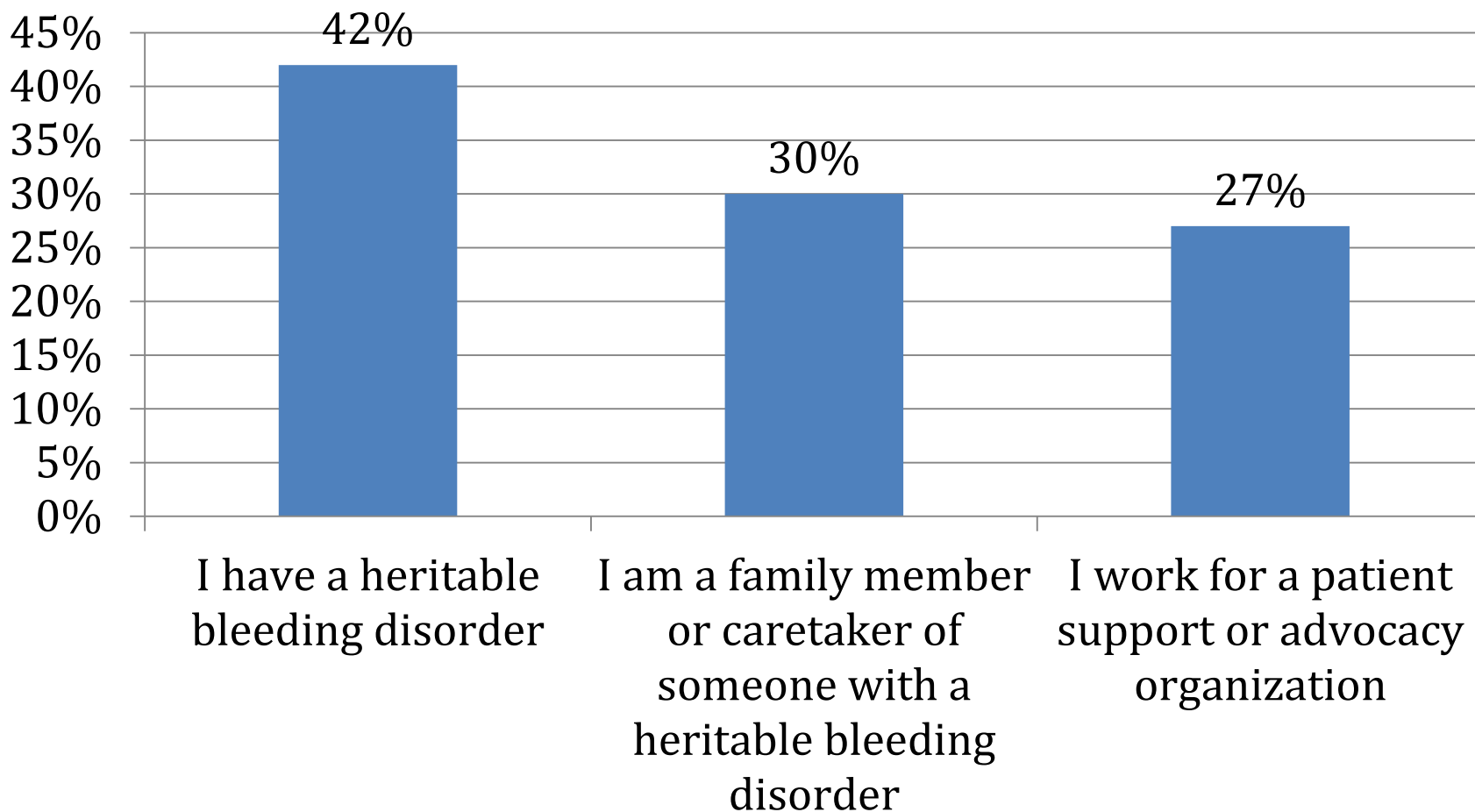
Where do you live?



Which of the following best describes you?

- A. I have a heritable bleeding disorder
- B. I am a family member or caretaker of someone with a heritable bleeding disorder
- C. I work for a patient support or advocacy organization

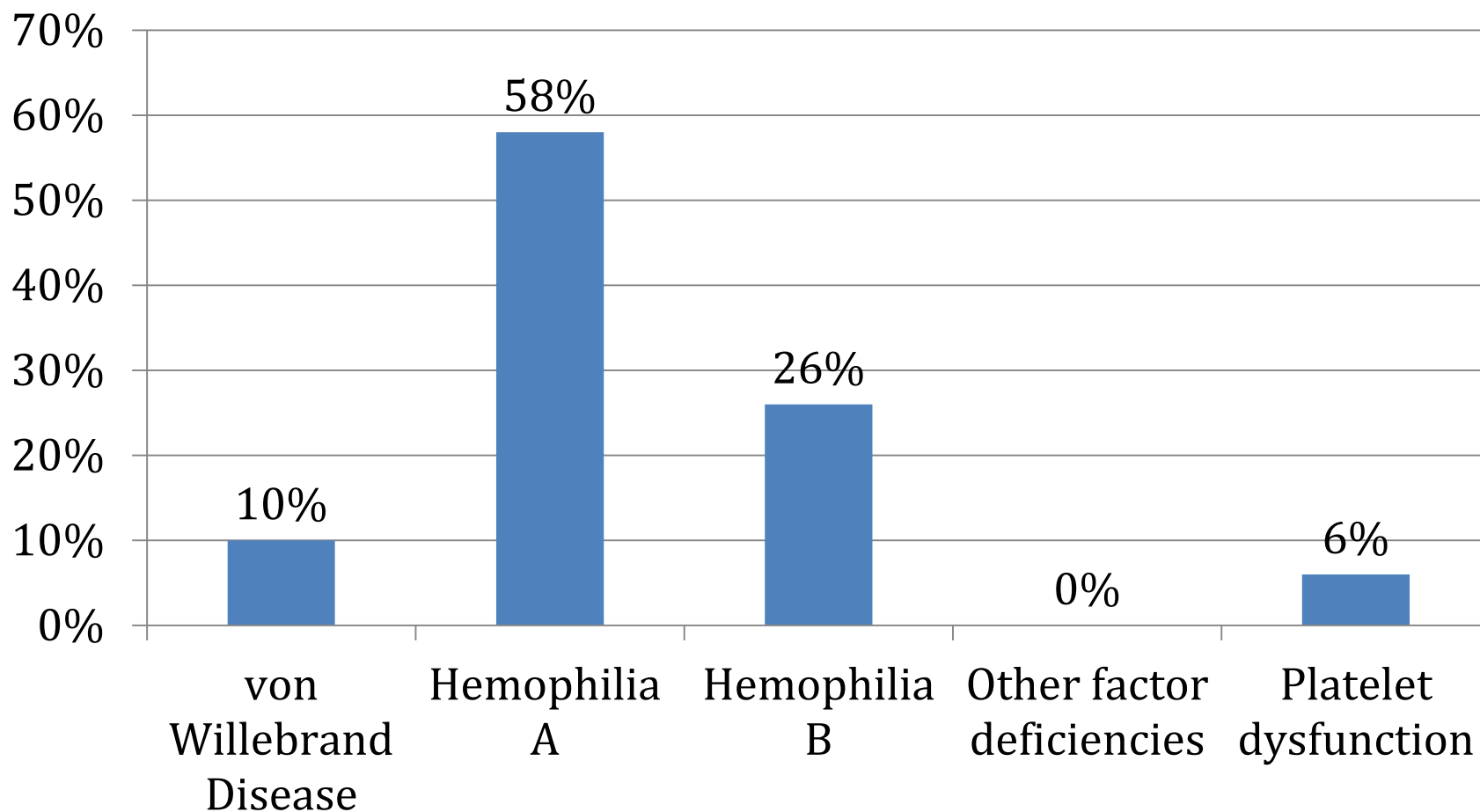
Which of the following best describes you?



Have you/your loved one been diagnosed with any of the following heritable bleeding disorders?

- A. von Willebrand Disease
- B. Hemophilia A
- C. Hemophilia B
- D. Other factor deficiencies
- E. Platelet dysfunction

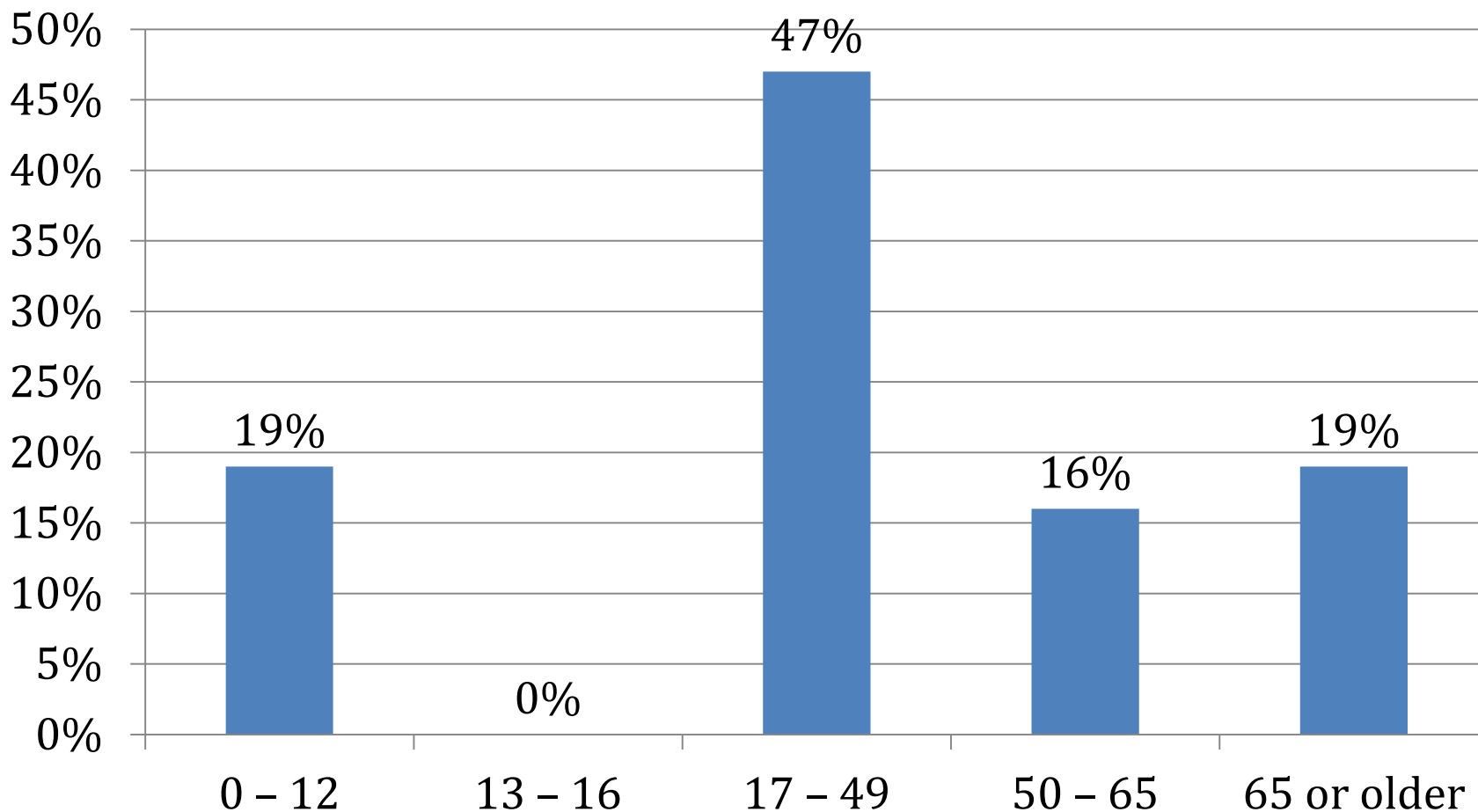
Have you/your loved one been diagnosed with any of the following heritable bleeding disorders?



What is your/your loved one's age?

- A. 0 – 12
- B. 13 – 16
- C. 17 – 49
- D. 50 – 65
- E. 65 or older

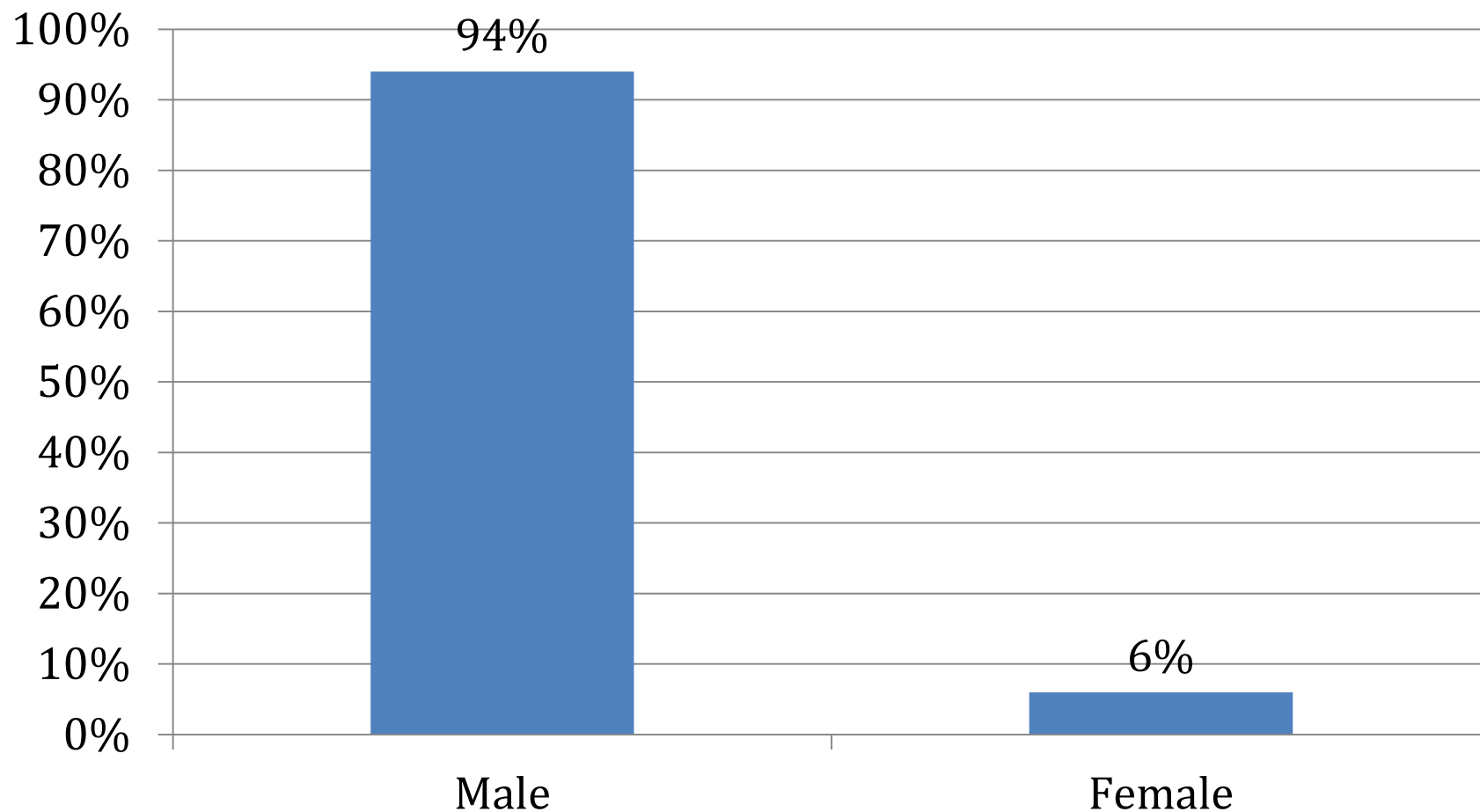
What is your/your loved one's age?



Are you/Is your loved one:

- A. Male
- B. Female

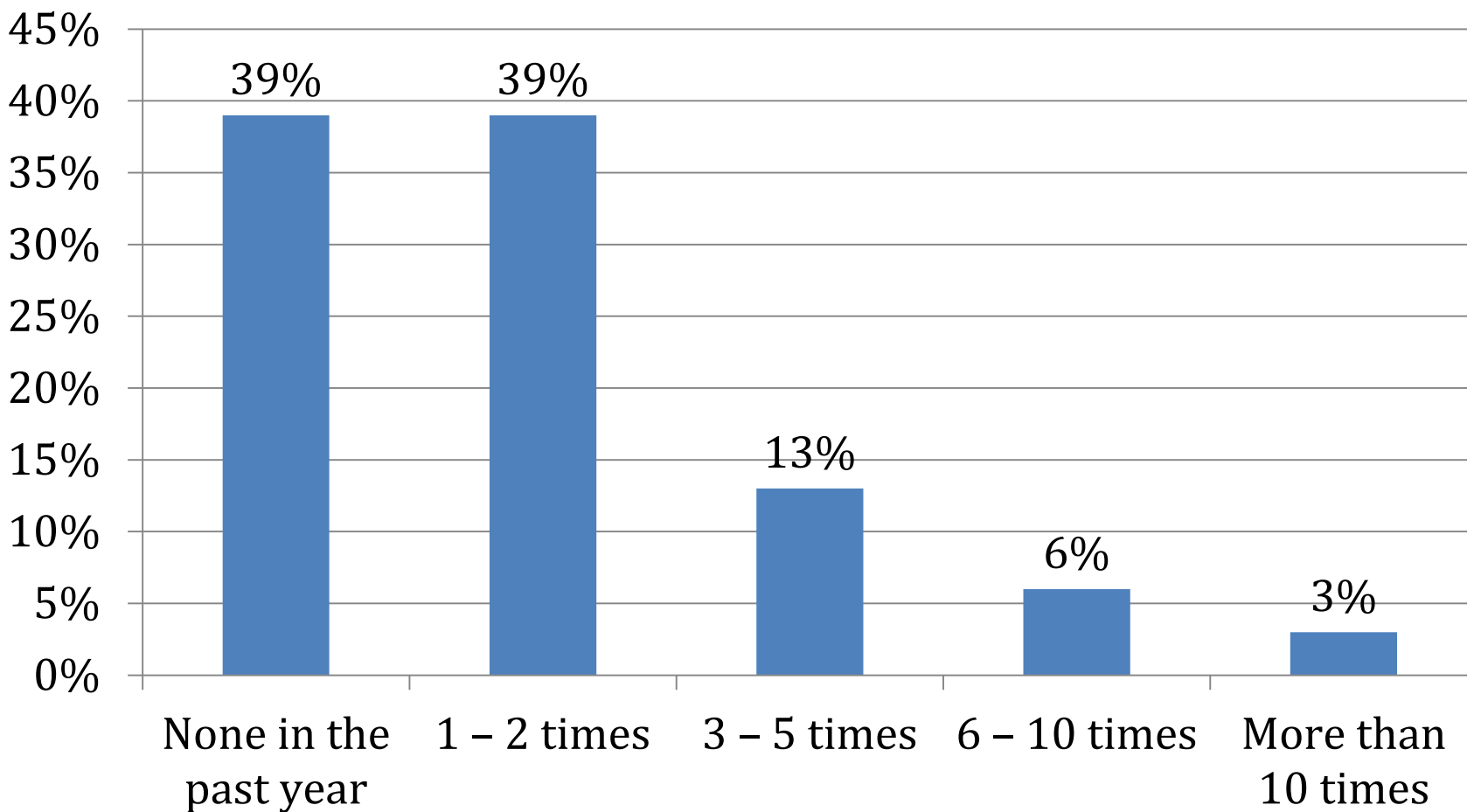
Are you/Is your loved one:



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

- A. None in the past year
- B. 1 – 2 times
- C. 3 – 5 times
- D. 6 – 10 times
- E. More than 10 times

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





Discussion Topic 1

Disease symptoms and daily impacts that matter most to patients

Donna Lipscomb

Facilitator

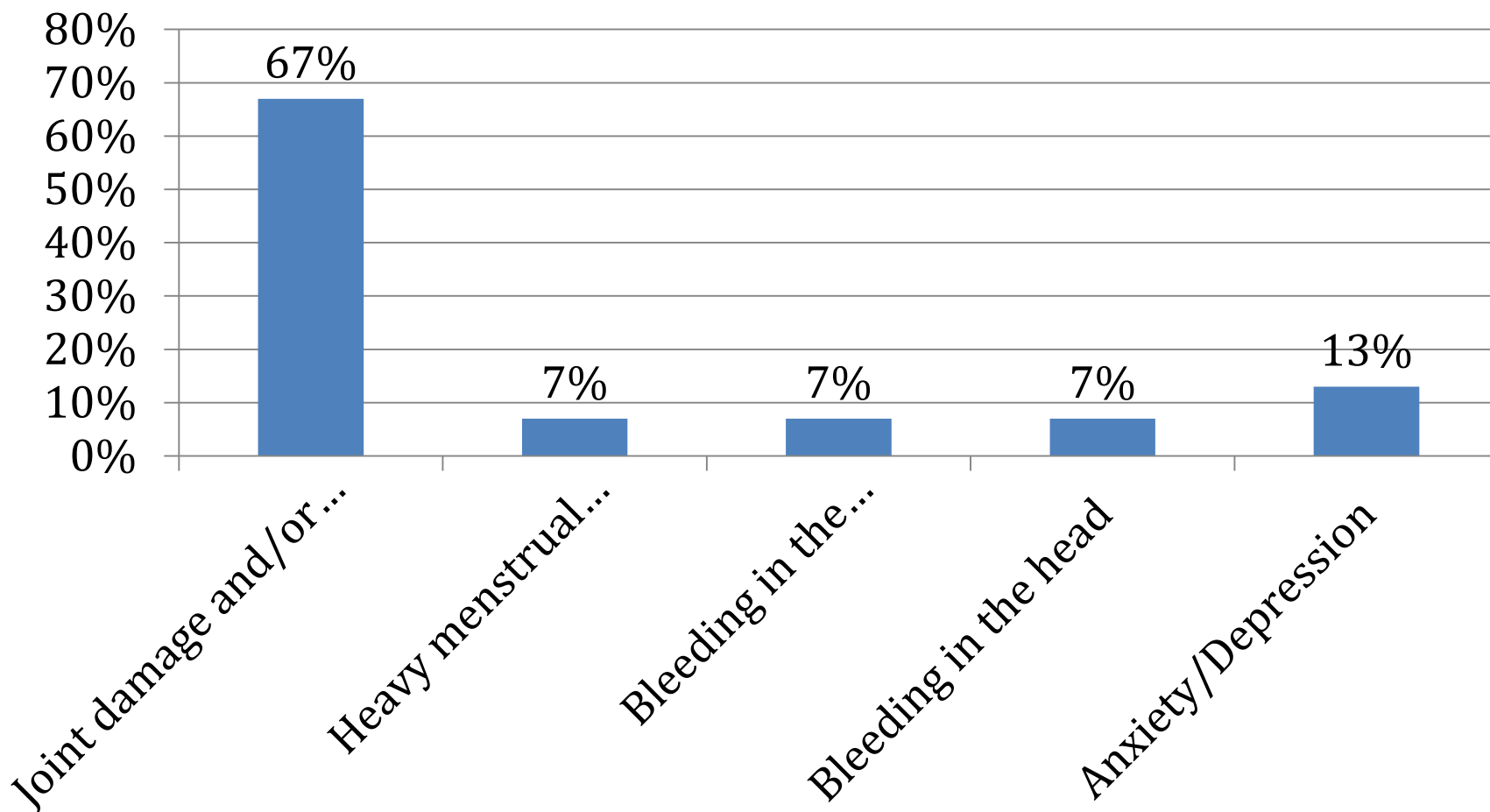
Topic 1 Discussion: Disease symptoms and daily impacts that matter most to patients

- Of all of the symptoms that you experience because of your condition, which symptoms (bleeding or non-bleeding) have the most significant impact on your life?
- Are there specific activities that are important to you but you cannot do at all or as well as you would like because of your condition?
- How has your condition and its symptoms changed over time?
- What worries you most about your condition?

Which of the following symptoms currently has the most significant impact on you/your loved one's life?

- A. Joint damage and/or pain
- B. Heavy menstrual bleeding
- C. Bleeding in the muscles and soft tissues
- D. Bleeding in the head
- E. Anxiety/Depression

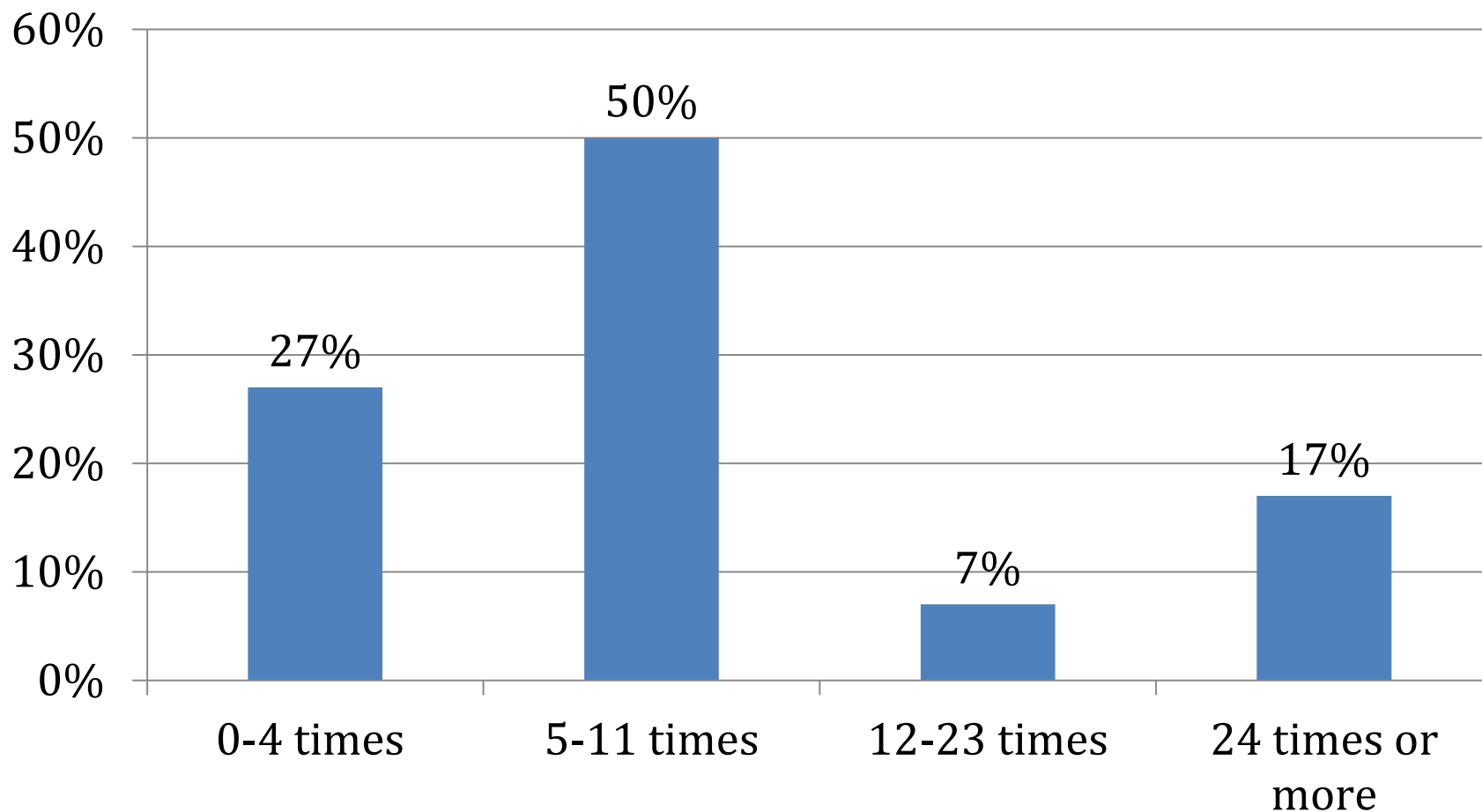
Which of the following symptoms currently has the most significant impact on you/your loved one's life?



How many times in the past year did you/your loved one experience a bleed?

- A. 0-4 times
- B. 5-11 times
- C. 12-23 times
- D. 24 times or more

How many times in the past year did you/your loved one experience a bleed?



Topic 1 Discussion: Disease symptoms and daily impacts that matter most to patients

- Of all of the symptoms that you experience because of your condition, which symptoms (bleeding or non-bleeding) have the most significant impact on your life?
- Are there specific activities that are important to you but you cannot do at all or as well as you would like because of your condition?
- How has your condition and its symptoms changed over time?
- What worries you most about your condition?



LUNCH



Discussion Topic 2

Patients' perspectives on current approaches to treating heritable bleeding disorders

Donna Lipscomb

Facilitator

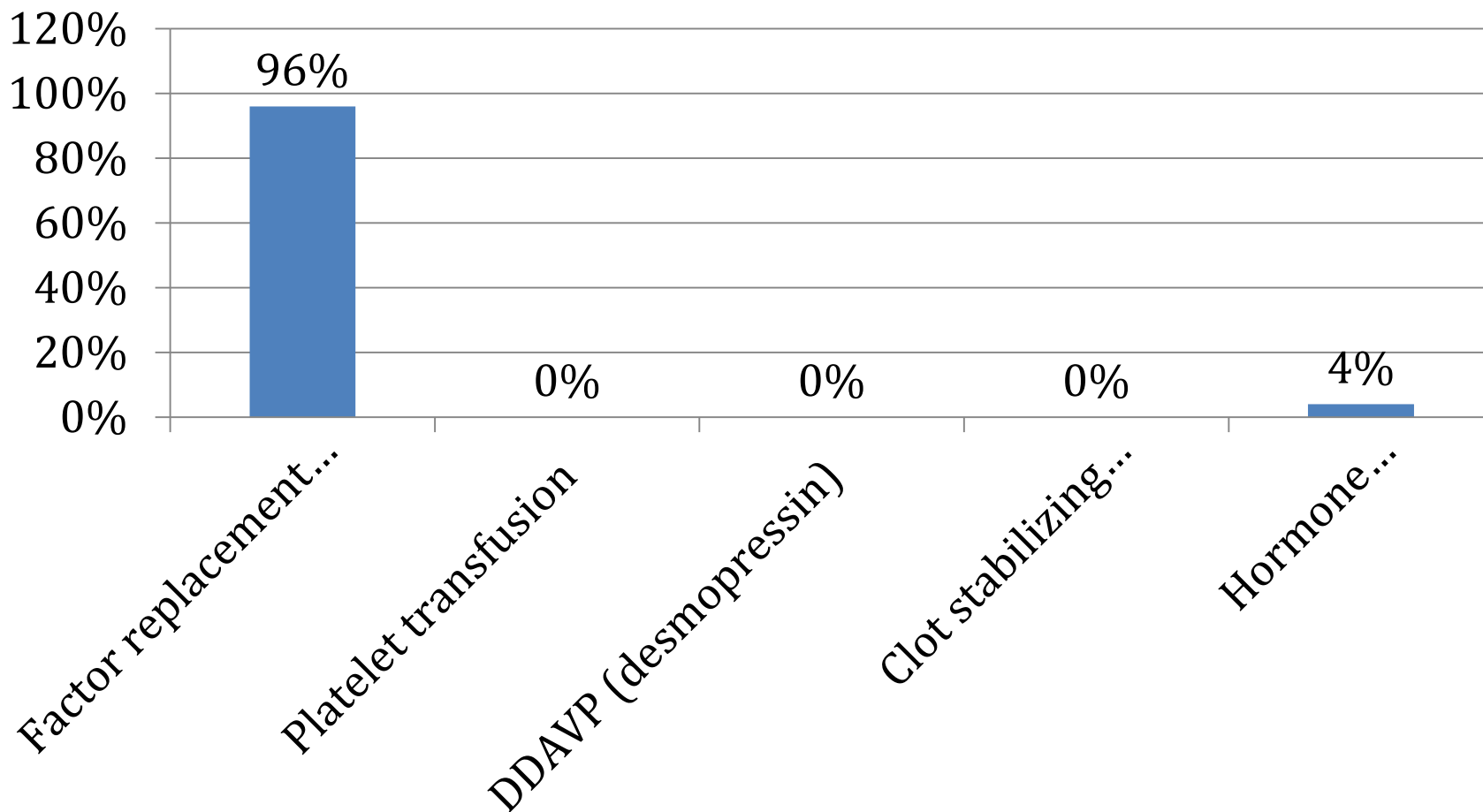
Topic 2 Discussion: Patients' perspectives on current approaches to treating heritable bleeding disorders

- What are you currently doing to treat your condition or its symptoms?
 - How well do these treatments work for you?
 - What are the most significant disadvantages or complications of your current treatments, and how do they affect your daily life?
 - How has your treatment changed over time and why?
 - What aspects of your condition are not improved by your current treatment regimen?
 - What treatment has had the most positive impact on your life?
- If you could create your ideal treatment, what would it do for you (i.e., what specific things would you look for in an ideal treatment)?
- If you had the opportunity to consider participating in a clinical trial studying experimental treatments, what things would you consider when deciding whether or not to participate?

Name one therapy used to manage your/your loved one's bleeding disorder, in the past year?

- A. Factor replacement therapies
- B. Platelet transfusion
- C. DDAVP (desmopressin)
- D. Clot stabilizing medications
- E. Hormone replacement therapy

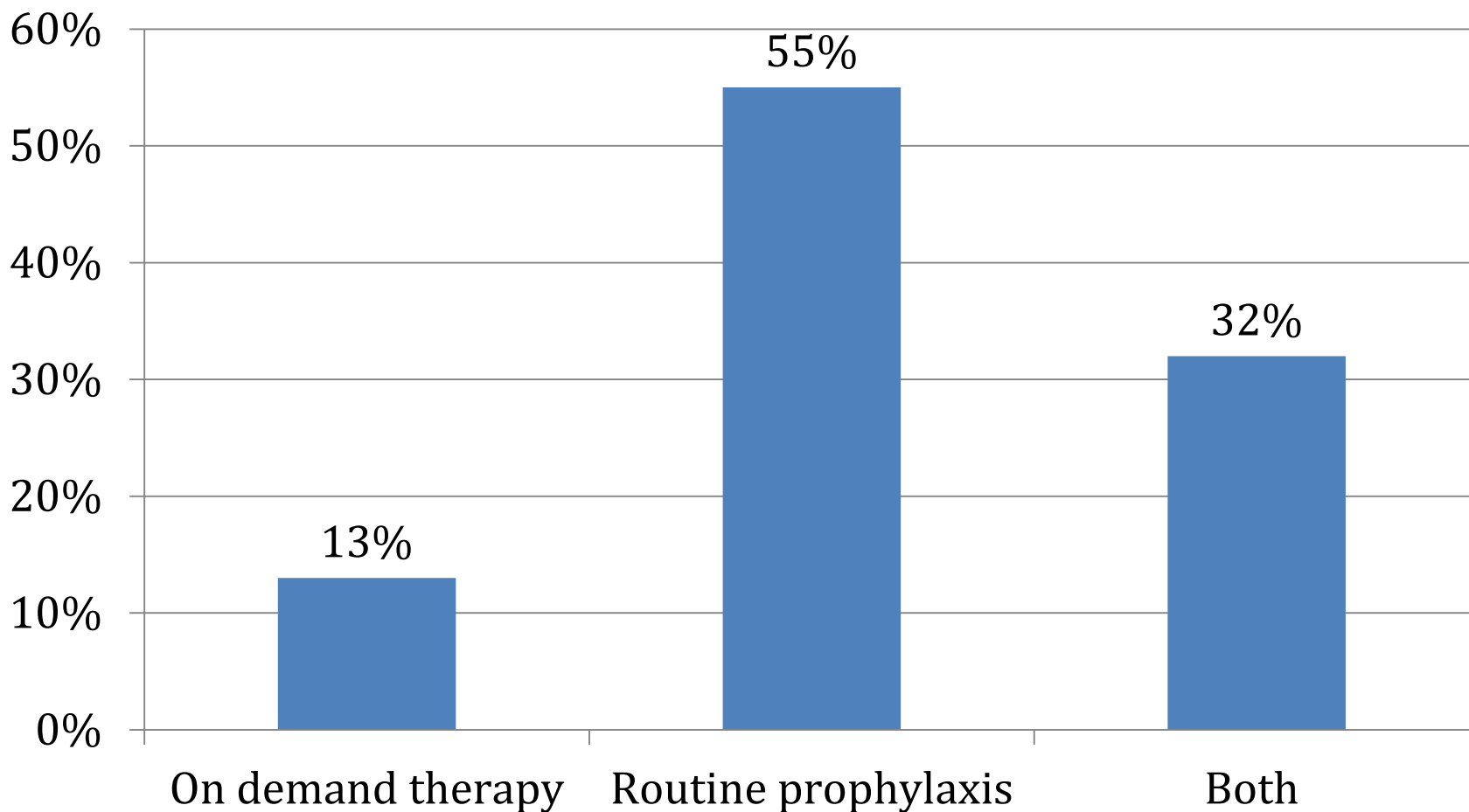
Name one therapy used to manage your/your loved one's bleeding disorder, in the past year?



If you/your loved one are being treated with factor replacement therapy, what is the current treatment regimen?

- A. On demand therapy
- B. Routine prophylaxis
- C. Both

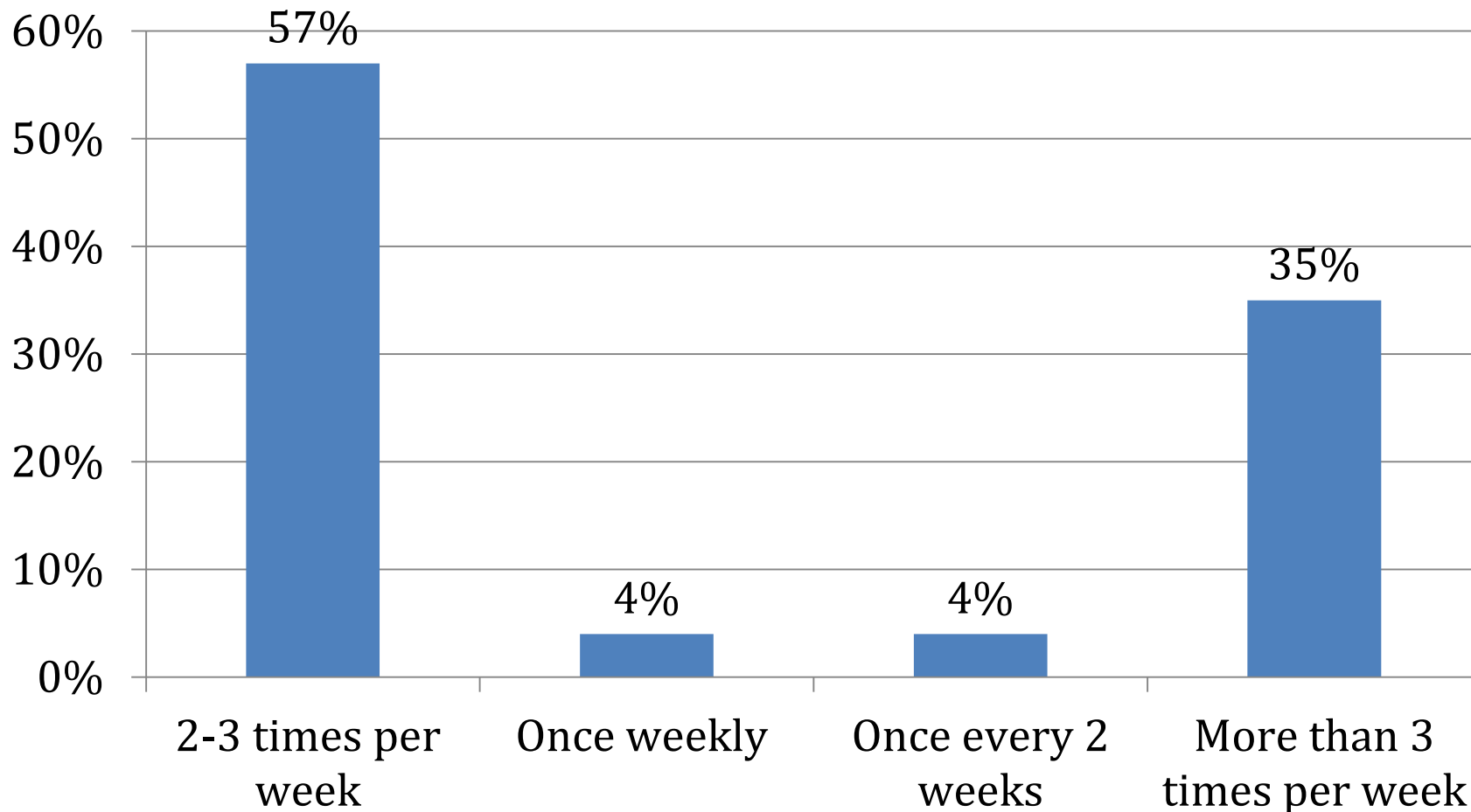
If you/your loved one are being treated with factor replacement therapy, what is the current treatment regimen?



If you/your loved one are being treated with routine prophylaxis, how often do you receive replacement therapy?

- A. 2-3 times per week
- B. Once weekly
- C. Once every 2 weeks
- D. More than 3 times per week

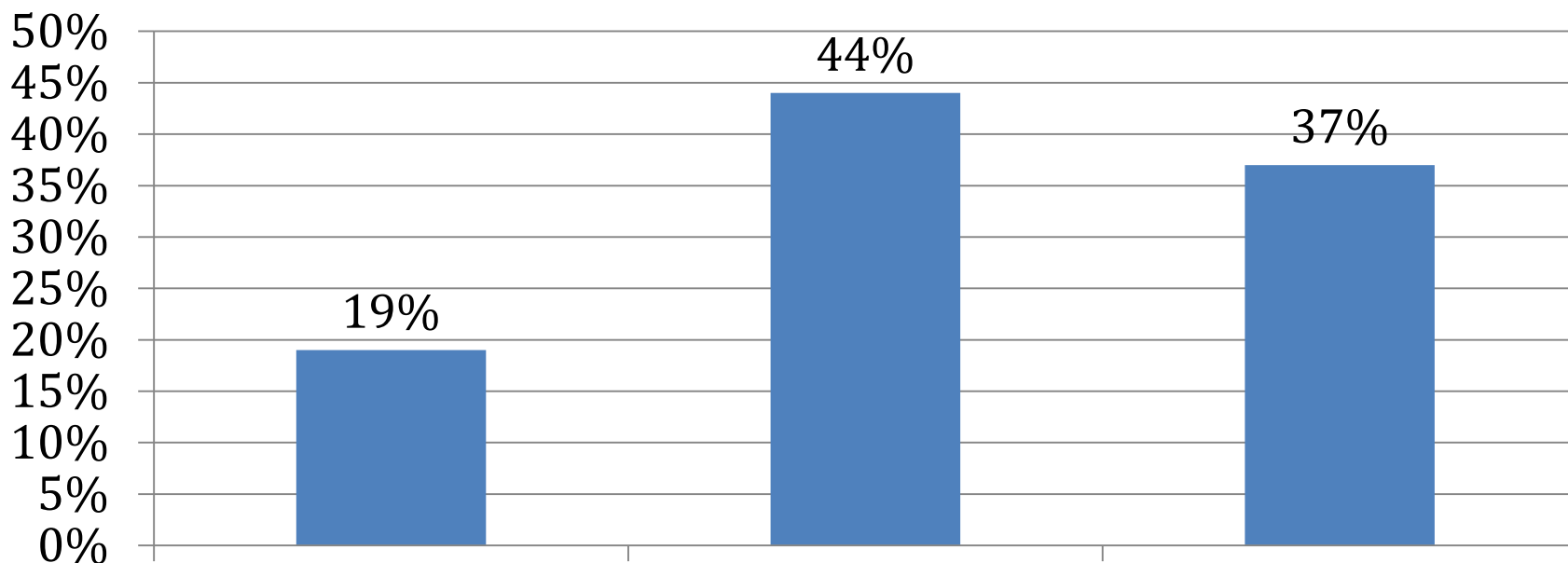
If you/your loved one are being treated with routine prophylaxis, how often do you receive replacement therapy?



Which of the following best describes how you/your loved one feel about your current treatment regimen?

- A. I am satisfied with my current treatment regimen and do not want to change it.
- B. I am satisfied with my current treatment regimen, but am willing to consider new options.
- C. I am not satisfied with my current regimen

Which of the following best describes how you/your loved one feel about your current treatment regimen?



I am satisfied with my current treatment regimen and do not want to change it.

I am satisfied with my current treatment regimen, but am willing to consider new options.

I am not satisfied with my current regimen

Topic 2 Discussion: Patients' perspectives on current approaches to treating heritable bleeding disorders

- What are you currently doing to treat your condition or its symptoms?
 - How well do these treatments work for you?
 - What are the most significant disadvantages or complications of your current treatments, and how do they affect your daily life?
 - How has your treatment changed over time and why?
 - What aspects of your condition are not improved by your current treatment regimen?
 - What treatment has had the most positive impact on your life?
- If you could create your ideal treatment, what would it do for you (i.e., what specific things would you look for in an ideal treatment)?
- If you had the opportunity to consider participating in a clinical trial studying experimental treatments, what things would you consider when deciding whether or not to participate?

Topic 2 Discussion: Patients' perspectives on experimental treatments for heritable bleeding disorders

- What specific things would you look for in an ideal treatment?
- If you had the opportunity to consider participating in a clinical trial studying experimental treatments, what things would you consider when deciding whether or not to participate?

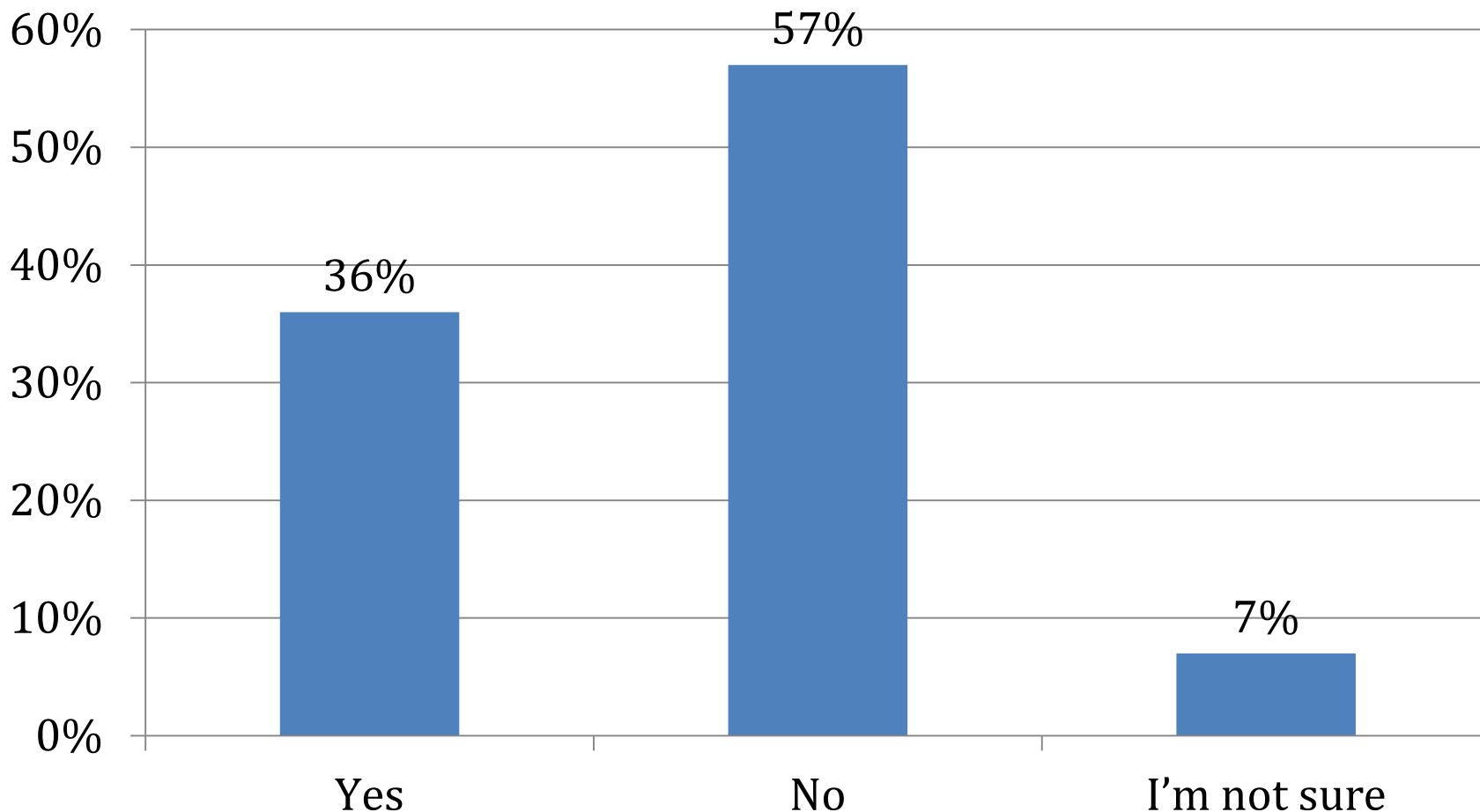
Have you /your loved one ever participated in any type of clinical trial studying experimental treatments for heritable bleeding disorders?

A. Yes

B. No

C. I'm not sure

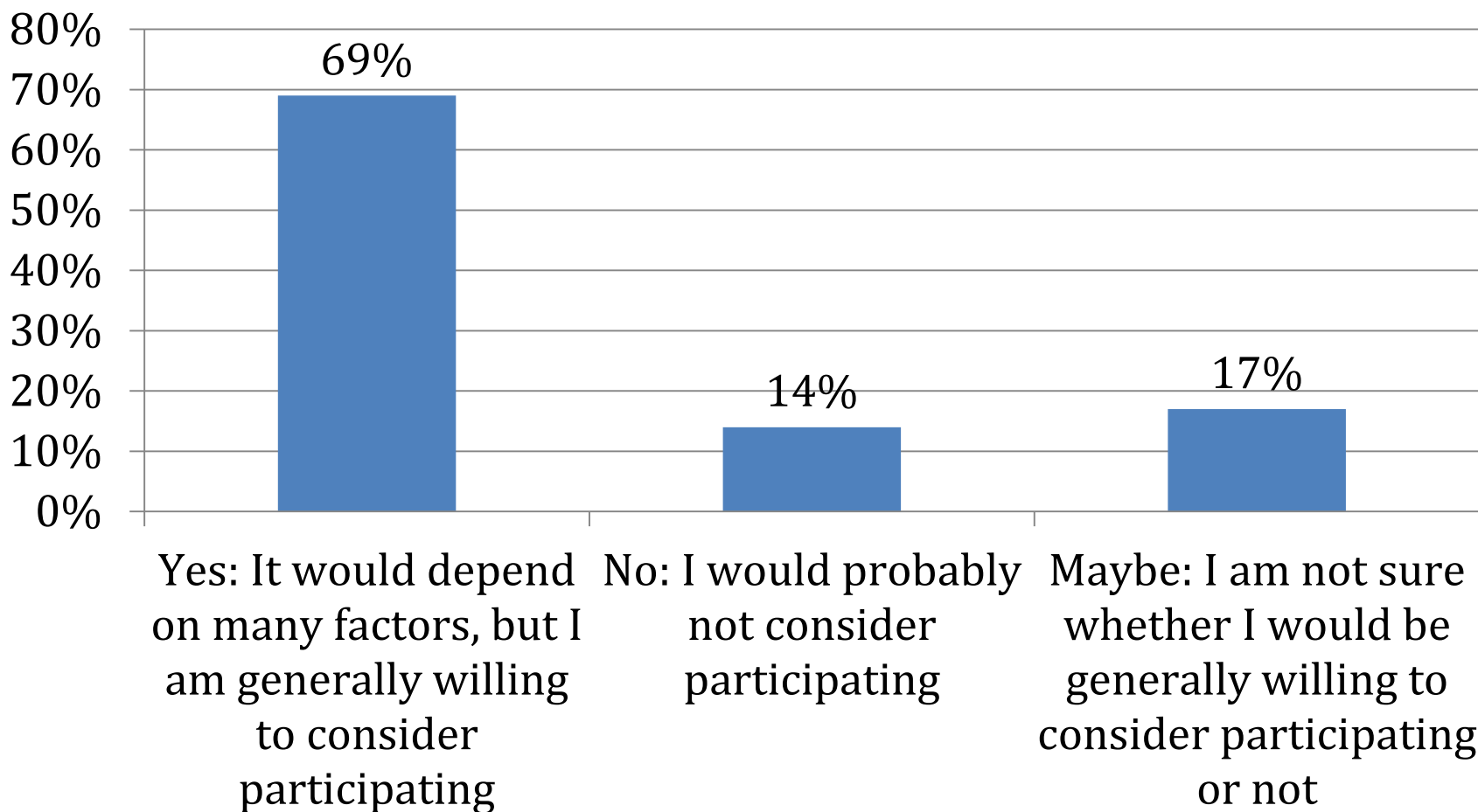
Have you /your loved one ever participated in any type of clinical trial studying experimental treatments for heritable bleeding disorders?



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:** It would depend on many factors, 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 generally willing to consider participating or not

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?



Scenario for Discussion

- Imagine that you/your child had the opportunity to consider participating in a clinical trial for an experimental oral replacement therapy.
- The study will enroll 50 participants. This clinical study lasts one year, and involves six clinic visits, occurring once every 2 months.
- More common side effects of this therapy may include nausea, diarrhea, fatigue, headache, or rash. Rarer but more serious side effects may include bleeding, blood clots, or life-threatening allergic reactions.

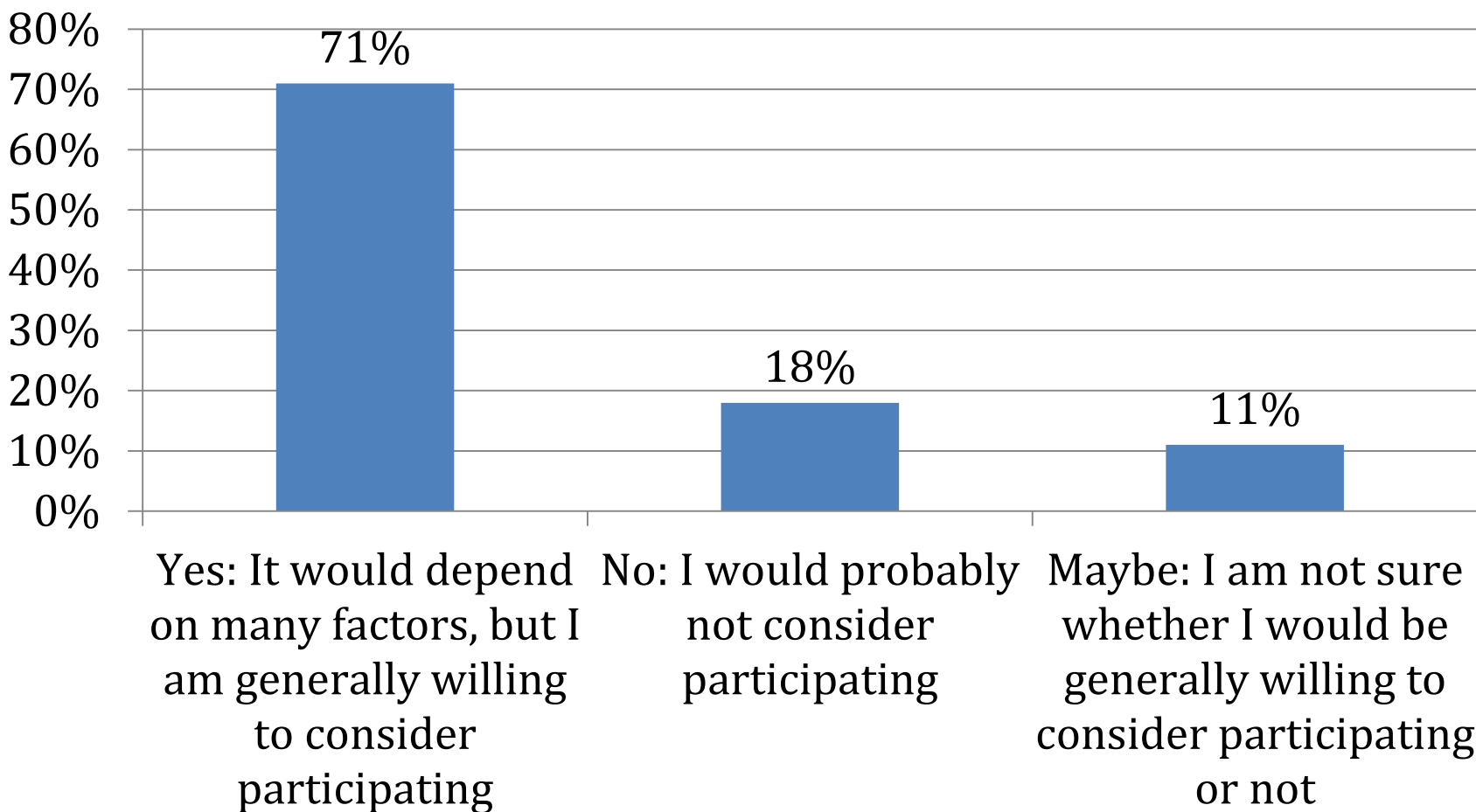
What thoughts come to mind?

What questions would you have?

Would you/your loved one participate in the hypothetical clinical trial described today?

- A. **Yes:** It would depend on many factors, 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 generally willing to consider participating or not

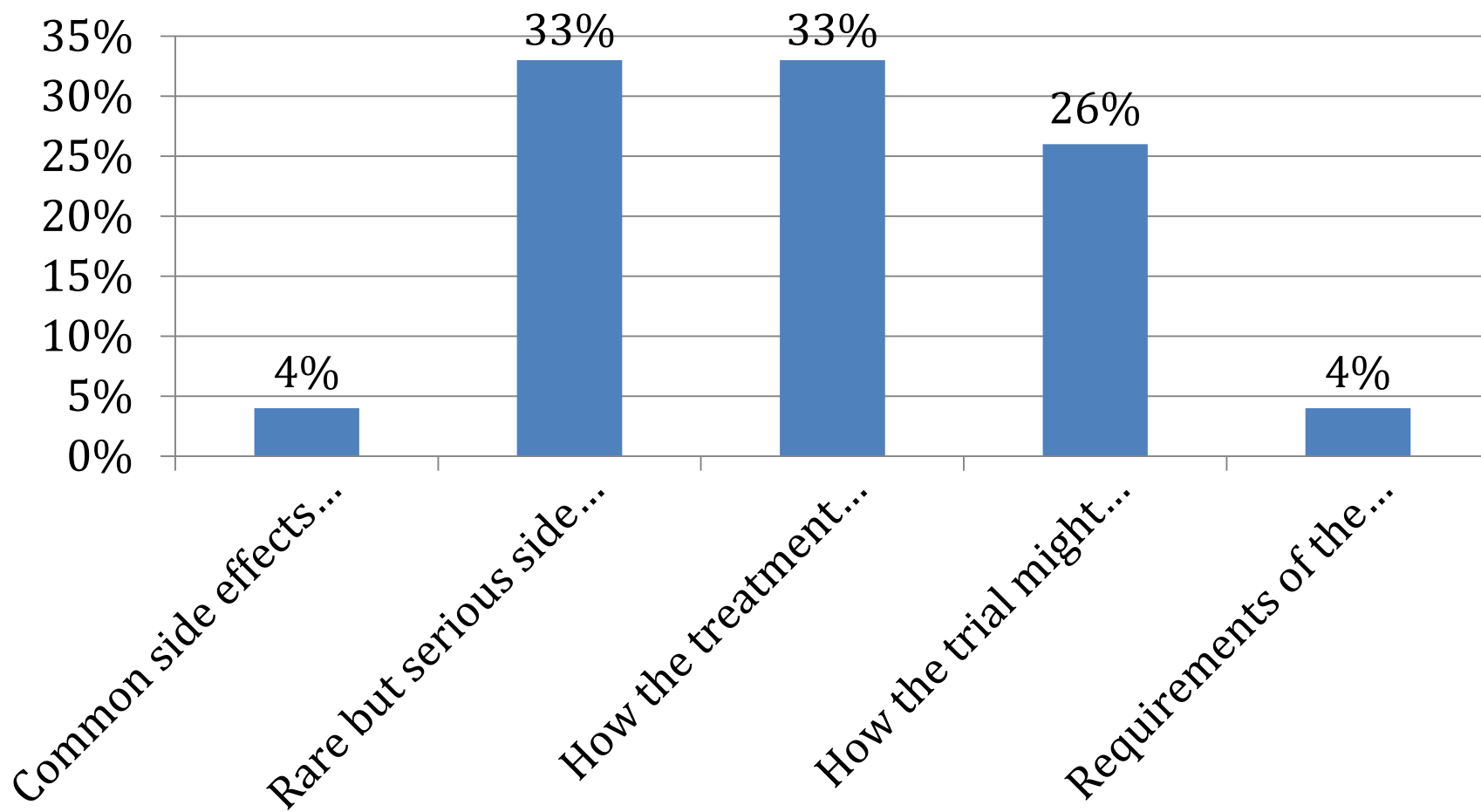
Would you/your loved one participate in the hypothetical clinical trial described today?



Which of the following factors 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 life-threatening allergic reaction)
- 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 blood tests or hospital stays) or length of trial

Which of the following factors would you rank as most important to your decision about whether to participate in a clinical trial to study an experimental treatment?





Open Public Comment Period



Closing Remarks

Ginette Michaud, MD

Deputy Director, Office of Blood Research and Review
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration