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## HIV Patient-Focused Drug Development and Cure Research

June 14, 2013



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## Welcome

**Edward Cox, MD, MPH**  
Director, Office of Antimicrobial Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration

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## Agenda Overview

### Morning

- **Setting the Context:**
  - Patient-Focused Drug Development (Theresa Mullin)
  - Current HIV Treatment (Kimberly Struble)
  - Discussion Format (Sara Eggers)
- **Discussion Topic 1:** Patient perspective on current HIV treatment and most significant symptoms

### Afternoon

- **Setting the Context:**
  - HIV Cure Research (Ilan Irony)
  - Informed Consent in HIV Cure Research (Sara Goldkind)
- **Discussion Topic 2:** Patient perspective on HIV cure research
- **Open Public Comment Period**

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## Patient-Focused Drug Development

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

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## Patient-Focused Drug Development Overview

- **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
  - This perspective could contribute more broadly to drug development efforts, for example, supporting FDA's guidance on clinical trial design
- **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
  - FDA expects that patients, patient advocates, drug developers, and other interested parties will attend these meetings

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## Initiating the Process

- **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
- **The disease areas that will be the focus of meetings for fiscal years 2013-2015 have been announced in the Federal Register**
  - Another public process will be initiated in 2015 to determine the set for fiscal years 2016-2017

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## Considerations on Identifying Disease Areas

- **FDA sought a diverse set of disease areas that represent the range of diseases the Agency encounters in its regulatory decision-making**
- **We took into account the following overarching considerations:**
  - Disease areas that are chronic, symptomatic, or affect functioning and activities of daily living
  - Disease areas for which aspects of the 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 affect how a patient feels or functions
  - Disease areas that reflect a range of severity, from diseases that are life-threatening to those that are mild and symptomatic
  - Disease areas that have a severe impact on identifiable subpopulations, such as children or the elderly
  - Disease areas that represent a broad range in terms of size of the affected population, including common conditions experienced by large numbers of patients and rare diseases that affect much smaller patient populations

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## Meeting Design Considerations

- **In planning the format and questions for each meeting, we consider the unique characteristics of the disease context**
  - This context includes the current state of drug development, the specific interests of the FDA review division, and the specific 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
  - Meeting formats are tailored based on a general design to most effectively engage patients in dialogue
- **Patients and other stakeholders can contribute their perspectives in multiple ways**
  - Patients and patient representatives are invited to contribute to the meeting discussion
  - Anyone is invited to submit comments to the docket
- **A meeting report will be posted on our website, capturing the input we obtain in response to these key questions**
- **More information can be found on our website:**  
<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>

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## Background on Current HIV Treatment

Kimberly Struble, PharmD  
Medical Team Lead, Division of Antiviral Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration



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## Background

- HIV identified in 1983
  - After 30 years still no vaccine or cure, although research is ongoing
- More than 1.1 million people in US are living with HIV
  - About 50,000 new infections per year
- FDA recognizes
  - HIV/AIDS is a serious and life-threatening disease
  - Each antiretroviral therapy (ART) has benefits and risks
  - YOUR input is important to ART drug development process

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## Background

- FDA works with many groups (industry, academia, patient groups) to foster:
  - Improvements to existing therapy approaches
  - Continual development of novel therapy approaches



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## ART Benefits

- Today's treatments are highly successful
  - Recommended treatment is 3 or more ARTs
- People living near-normal life spans
- Significant improvements in treatment regimens



**Simplified Dosing: One Pill / Once a Day**

Atripla		Complera		Stribild	
					
Drug	Class	Drug	Class	Drug	Class
Tenofovir	NRTI	Tenofovir	NRTI	Tenofovir	NRTI
Emtricitabine	NRTI	Emtricitabine	NRTI	Emtricitabine	NRTI
Efavirenz	NNRTI	Rilpivirine	NNRTI	tenofovir disoproxil fumarate	NRTI
				cobicistat	CYP3A4 inhibitor

Image Source: AIDS Info.org      Image Source: AIDS Info.org      Image Source: Photos.com

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## ART Side Effects

- ARTs can come with:
  - Short-term effects
    - Diarrhea, nausea, headache, sleep disturbances
  - Long-term effects
    - Body changes, kidney, liver, heart or bone effects
- ARTs can affect quality of life or side effects of ARTs can worsen over time

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## Downsides

- It takes energy and commitment to adhere to life long ART treatment
- “Fatigue” from:
  - having to take medications
  - living with a long-term condition
- Recent studies show taking “pill holidays” or stopping/restarting meds can result in serious health risks
- Therefore, it is important to find ways to take medications daily
  - Suboptimal adherence can lead to loss of virologic response and resistance

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FDA wants YOUR perspectives:



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## Topic 1: Current HIV Treatments and Most Significant Symptoms

- FDA is interested in your input on:
  - What are you currently doing to help manage your HIV and symptoms?
  - How well does your current treatment treat your significant symptoms?
  - What are the most significant downsides to your treatments and how do they affect your daily life?
  - What specific things would you look for in an ideal treatment to manage your condition?

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## Overview of Discussion Format

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



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## Discussion Format

- **We will first hear from a panel of patients and representatives**
  - The purpose is to set a good foundation for our discussion
  - Panel members include patients and advocates
  - They reflect a range of experiences with HIV and HIV advocacy
- **We will then broaden the discussion to include other patients and patient representatives in the audience**
  - The purpose is to build on the experiences shared by the panel
  - The facilitator will ask follow up questions, inviting participants to raise hands to comment

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## Discussion Format, continued

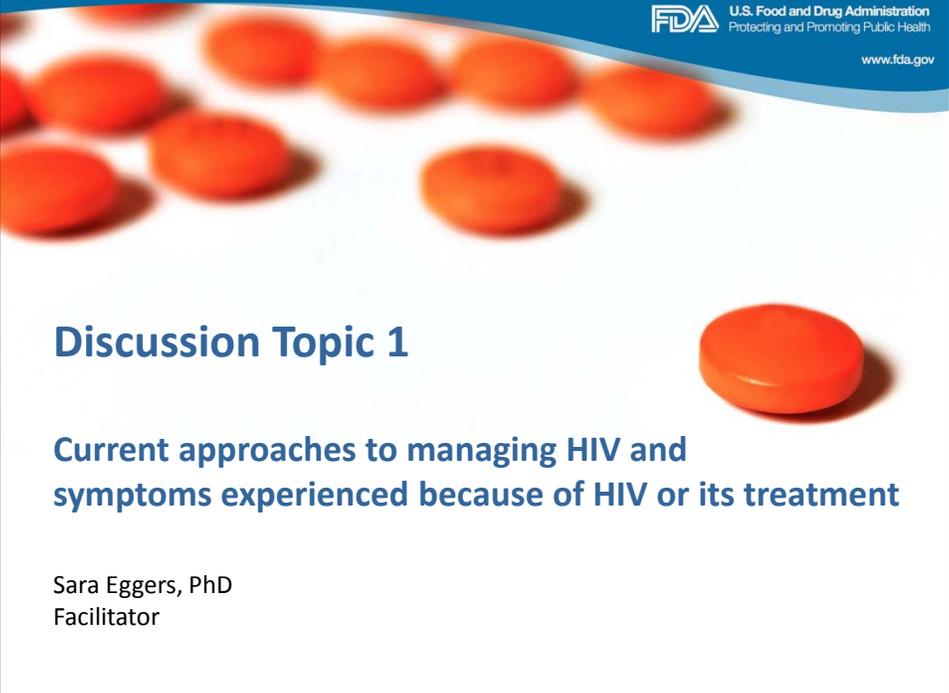
- **Periodically, we will invite in-person and web participants to respond to specific questions**
  - The purpose is to aid discussion by seeing how many participants share a particular perspective
  - In-person participants can use the “clickers” to respond to a question
  - Web participants can respond to the poll through the webcast
  - Patients and patient representatives only, please
- **Those participating by live webcast can add additional comments through the webcast comment box**
  - Although they may not be read or summarized today, they will be considered part of the public record

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## Discussion Ground Rules

- We encourage patients, caregivers and other patient representatives to contribute to the dialogue
- FDA staff is here to listen
- Our discussion will focus on understanding the common ground regarding HIV treatment, symptoms and their impacts on daily life
- Participant feedback on the meeting is important
- Respect for one another is paramount

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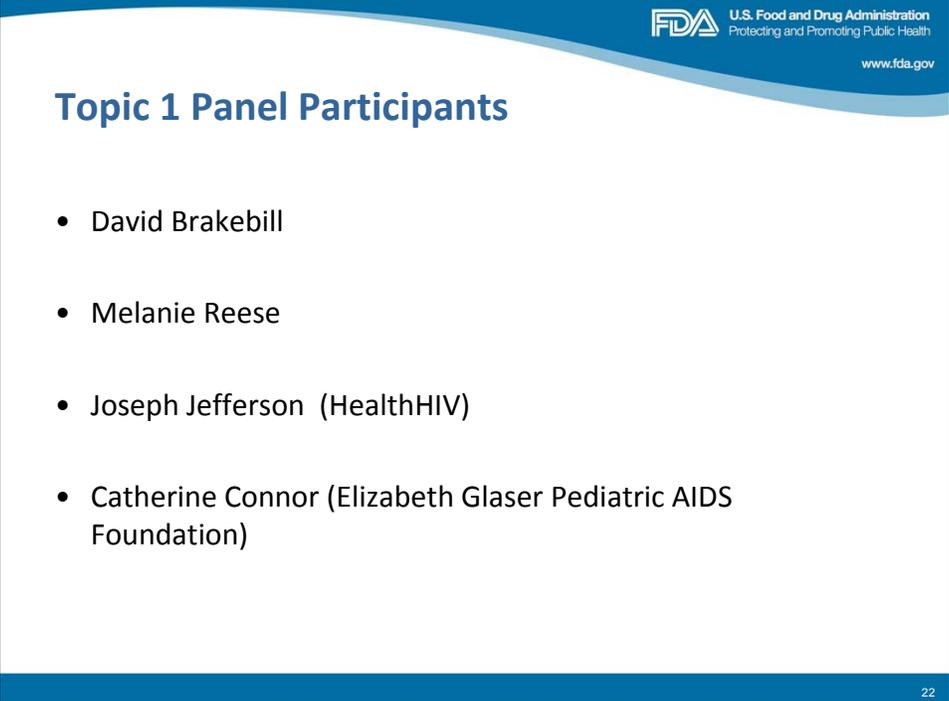


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## Discussion Topic 1

**Current approaches to managing HIV and symptoms experienced because of HIV or its treatment**

Sara Eggers, PhD  
Facilitator



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## Topic 1 Panel Participants

- David Brakebill
- Melanie Reese
- Joseph Jefferson (HealthHIV)
- Catherine Connor (Elizabeth Glaser Pediatric AIDS Foundation)

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## Discussion on HIV Treatments

- **What are you currently doing to help manage your HIV?**
  - How long have you been on treatment and how has your treatment regimen changed over time?
- **What are the greatest benefits of current HIV Treatments?**
- **What are the most significant downsides to current HIV treatments, and how do they affect your daily life?**

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# BREAK

## Discussion: Most Significant Symptoms

- **Of all the symptoms that you experience because of your condition or because of your treatment, which have the most significant impact on your life?**
- **What are you currently doing to help manage the symptoms you experience because of your condition or its treatment?**
- **How well do your current treatments treat your significant symptoms?**
- **Assuming there is currently no complete cure for your condition, what specific things would you look for in an ideal treatment to manage your condition?**

# LUNCH



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## Summary of Morning Discussion

**Richard Klein**  
Director, Patient Liaison Program  
Office of Health and Constituent Affairs  
Office of the Commissioner  
U.S. Food and Drug Administration



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## Background on HIV Cure Research

**Ilan Irony, MD**  
Chief, General Medicine Branch/DCEPT/OCTGT  
Center of Biologics Evaluation and Research  
U.S. Food and Drug Administration

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## Outline

- FDA organization
- Research strategies towards a cure
- A word about gene therapies
- Combination strategies in Cure Research

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## FDA Organization

- **Office of the Commissioner**
  - Center for Veterinary Medicine
  - Center for Food Safety and Applied Nutrition
  - Center for Tobacco Products
  - National Center for Toxicological Research
  - **Center for Devices and Radiological Health**
  - **Center for Drug Evaluation and Research**
  - **Center for Biologics Evaluation and Research**

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## CBER Organization

- Immediate Office of Director
- Office of Management
- Office of Communication, Training and Manufacturers Assistance
- Office of Compliance and Biological Quality
- Office of Biostatistics and Epidemiology
- **Office of Blood Research and Review**
- **Office of Vaccines Research and Review**
- **Office of Cellular, Tissue, and Gene Therapies**

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## Why Cure Research?

- HIV infection: manageable chronic condition
- But... life-long requirement for ART, with the short- and long-term side effects of ART
- Even with very low viral load, viral replication persists and latent viral reservoir is present
- Recent, isolated examples point to the possibility of a cure
- Cure = elimination or control of HIV infection without further medical intervention to maintain health

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## Research Strategies

- “Shock and kill”: “Shock” = activate virus from reservoir and “kill” = clear virus from the body using boosters of immune system + ART
- Induce resistance to HIV infection: through transplantation of immune cells from donors resistant to HIV or through gene therapies
- Experimental drugs and therapeutic vaccines to stimulate the patient’s immune system to recognize and eliminate HIV.

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## Challenges in Cure Research

- In each development step, safety is important (good balance of risks / benefits)
- How to define and establish cure:
  - Sterilizing (no detectable virus)?
  - Functional (no evidence of disease and no transmission of HIV infection)?
  - Validated measures for each type of cure
- Assessment of balance of risks and benefits of research interventions changes over the course of each product development, and as we learn about parallel development of other therapies.

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## Important features of gene products

- Manufacturing issues: production is relatively slow
- Use of retro- / lentiviral gene carrier allows prolonged gene activity
- Usually the product activity, if present, is from gene-modified cells that survive and function in the patient: raise resistance to HIV infection
- Using busulfan and other chemotherapy, drugs that “make room” for the new, gene-modified cells, improve the odds that more of such cells will survive and function
- Long presence or duration of activity (perhaps lifetime)
  - Inability to withdraw/discontinue product when adverse events occur
  - May have late-onset risks (e.g., malignancy)

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## Important features of gene products (continued)

- Risks of cancer with vectors that integrate into human DNA
- Risks of busulfan / other chemotherapy and other study procedures
- To show the product activity, need to interrupt ART
- Even early-phase studies have a longer period of safety follow-up than for most drugs (patients treated with lentivirus gene carrier must be followed for 15 years or longer)
- Levels of oversight: in addition to FDA and IRB, gene therapies are usually reviewed by the NIH Recombinant DNA Advisory Committee (RAC)

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## Combinations of strategies

- To attack different mechanisms of HIV persistence (low level replication, HIV reservoirs), combinations of different approaches may be needed
- Scientific issues with combined products, including novel products
  - Information on the safety and effectiveness of each component needed
  - Patient may be at risk, but unlikely to benefit, from research of each component alone: consent issues

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## Topic 2: Patients' perspectives on HIV Cure Research

- What do you believe are the benefits of participation in HIV cure research studies?
- What factors would you consider in your decision to participate or not?
- What study risks would make participation unacceptable to you?
- If stopping use of your HIV medications was part of a research study, how would this affect your decision to participate?
- What else do you want FDA to know about HIV cure research from your perspective?

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## OCTGT Contact Information

[Ilan.Irony@fda.hhs.gov](mailto:Ilan.Irony@fda.hhs.gov)

Regulatory Questions:  
Contact the Regulatory Management Staff in OCTGT at  
[CBEROCTGTRMS@fda.hhs.gov](mailto:CBEROCTGTRMS@fda.hhs.gov)  
or [Lori.Tull@fda.hhs.gov](mailto:Lori.Tull@fda.hhs.gov)  
or by calling (301) 827-6536

OCTGT Learn Webinar Series:  
<http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm>

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## Public Access to CBER

CBER website:  
<http://www.fda.gov/BiologicsBloodVaccines/default.htm>

Phone: 1-800-835-4709 or 301-827-1800

Consumer Affairs Branch (CAB)  
Email: [ocod@fda.hhs.gov](mailto:ocod@fda.hhs.gov)  
Phone: 301-827-3821

Manufacturers Assistance and Technical Training Branch (MATTB)  
Email: [industry.biologics@fda.gov](mailto:industry.biologics@fda.gov)  
Phone: 301-827-4081

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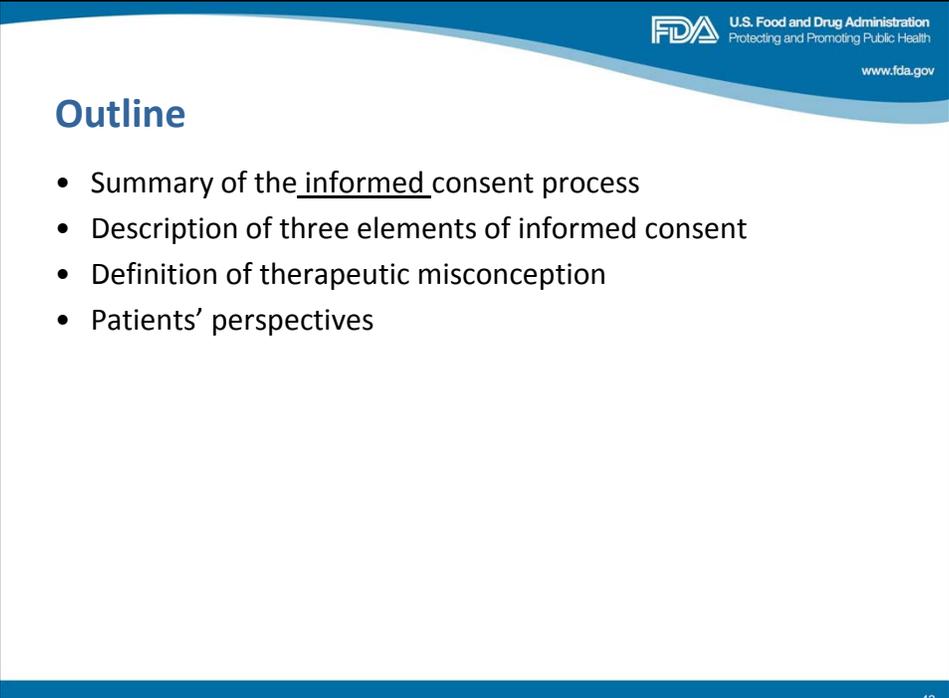
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## Background on Informed Consent Issues in HIV Cure Research

Sara F. Goldkind, MD, MA  
Senior Bioethicist  
Office of Good Clinical Practice/OSMP/OMPT  
U.S. Food and Drug Administration



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## Outline

- Summary of the informed consent process
- Description of three elements of informed consent
- Definition of therapeutic misconception
- Patients' perspectives

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## What is the informed consent process?

- It is an ongoing educational process between the investigator (or designee) and the participant.

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## Summary of the informed consent process

- Adequate disclosure of information to allow for an informed decision about participation in the research
- Adequate comprehension of the information
- Adequate opportunity to consider whether or not to participate
- Voluntary agreement to participate

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## Summary of the informed consent process

- Continued disclosure of information as the clinical trial progresses or as the participant or the situation requires (for example new information about risks)
- Participant's signature on the consent form is only part of the consent process

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## FDA informed consent requirements

- FDA has many requirements for informed consent, including:
  - Description of any reasonably foreseeable risks or discomforts to the participant
  - Description of any benefits to the participant or to others which may reasonably be expected from the research
  - Disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant

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## Description of reasonably foreseeable risks or discomforts

- Should describe:
  - Risks or discomforts of tests, interventions and procedures required by the protocol, especially those that carry significant risk of morbidity or mortality
  - Possible risks or discomforts due to changes to a participant's medical care
  - Potential risks of the study drug itself
  - Common and serious risks and what might be done to lessen risks or discomforts
- Should not understate the likelihood, severity or duration of the reasonably foreseeable risks and discomforts
- May need to include information on foreseeable risks to others

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## Description of benefits

- Should be clear, balanced, and not overly optimistic or overstated
- Should describe the benefits not only to the participants in the research but to others, if any
- Should state if there is no anticipated benefit to the participants from the research

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## Therapeutic misconception

- “The assumption that decisions about a participant’s care in the clinical trial are being made solely with that person’s benefit in mind [as opposed to being protocol-driven].”\*
- Research-designed to address specific scientific questions
- Treatment-what an individual physician determines is the best medical care for a given patient

\* Applebaum, Roth and Lidz, Int’l Journal of Law and Psychiatry, vol. 5, p. 319-29, 1982.

## Description of alternatives

- Participants should be made aware of alternatives to entering research, if any, that might be advantageous to them.
- Should include, if any:
  - Current medically recognized standard of care
  - Approved therapies or other forms of therapy (for example, surgical care, supportive care)
- Should describe if participation in other research would be possible or prohibited, if applicable

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## Patients' perspectives on HIV Cure Research

- For HIV cure research that may be designed only to gather scientific information that could guide future research and development of treatments, how should the informed consent clearly communicate to you:
  - The purpose?
  - The potential benefits? Particularly if there are no direct health benefits to the participants in the research?
  - The potential risks? Particularly if there is very limited understanding about the potential risks?
- Is there any other information that you would find helpful when deciding whether to enter an HIV cure research study?

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## OGCP Contact Information

Sara.Goldkind@fda.hhs.gov

For questions regarding the protection of participants in clinical trials and/or the general conduct of clinical trials:  
[gcp.questions@fda.hhs.gov](mailto:gcp.questions@fda.hhs.gov)

301-796-8340

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## Public access to OGCP webpage

Includes information about clinical trials and Good Clinical Practice:

<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm>

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## Overview of Discussion Format

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

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## Discussion Format, continued

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## Discussion Ground Rules

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- FDA staff is here to listen
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- Participant feedback on the meeting is important
- Respect for one another is paramount

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## Discussion Topic 2

### Patients' perspectives on HIV Cure Research

Sara Eggers, PhD  
Facilitator

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## Topic 2 Panel Participants

- David Evans (Project Inform)
- Murray Penner (National Alliance of State and Territorial AIDS Directors)
- Jeff Taylor
- Lynda Dee
- Matt Sharp

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## Topic 2 Discussion

1. What do you believe are the benefits of participating in an HIV cure research study?
2. What would motivate you to participate or to not participate in an HIV cure research study?
3. What risks would you find unacceptable for participating in an HIV cure research study, and why?
4. In certain HIV cure research studies, you would be asked to stop any other HIV medications that you are currently taking. How would this affect your decision whether to participate in an HIV cure research study?

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# BREAK

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## Topic 2 Discussion, continued

5. Perspectives on Informed Consent:
  - a) How should the informed consent clearly communicate to you the purpose of an HIV cure research study?
  - b) How should the informed consent clearly communicate to you the potential benefits of an HIV cure research study?
  - c) How should informed consent communicate clearly to you that there are potential risks of participating in an HIV cure research study, including unknown risks?
  - d) Is there any other information that you would find helpful when deciding whether to enter an HIV cure research study?
6. What else do you want FDA to know about HIV cure research from your perspective?

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## Closing Remarks

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