



DRAFT Working Group 3: Participant Education, Recruitment, and Informed Consent

Informed Consent in HIV Cure-Oriented Studies: Guidance and Recommendations for Future Research

A critical component of human subjects studies is the careful planning and implementation of processes to educate potential participants about the goals, risks, and benefits of the study and obtaining informed consent (IC). The process of obtaining informed consent can present major challenges, particularly in the context of early phase research with little or no prospect of direct medical benefit and the potential for coercion via false expectations from news media and language that may impart false hopes (e.g., using the word cure to inform participants). There is a plethora of both conceptual and empirical literature from bioethics and social sciences regarding optimal approaches to reduce potential coercion, and adequately inform participants about the study and study risks that may offer no direct benefits to participants. With the recent interest in human trials aimed at eliminating HIV-1 reservoirs or achieving antiretroviral (ART)-free remission, there is a growing need to apply lessons learned from previous work as well as consider unique circumstances raised in the IC process for HIV Cure-Oriented (HCO) research.

In order to approach cure-oriented issues, it is important to understand the type of research and clinical trials that fall under its relatively large umbrella of HCO strategies. For example several general approaches that are currently being implemented include:

- Reactivation of latent virus and clearing of activated cells ("kick and kill")
- Very early ART initiation in adults
- Post-partum ART initiation (e.g. the Mississippi Child)
- Therapeutic vaccine / immune-modulating therapies
- Antiviral antibody or novel ART studies
- Gene modification therapy (e.g. zinc finger CCR5 editing)
- Stem cell transplantation
- Cytoreductive/cytotoxic therapies
 - ART intensification or diversification studies

Combinations of the above strategies, which require substantial modifications to the existing standard of care for HIV treatment, will likely be necessary to achieve progress towards ART-free HIV remission. As a result, the IC process presents several unique challenges requiring the development of strategies that can address these challenges.

Project Background: The Forum for Collaborative HIV Research is a public-private partnership that is part of the University of California, Berkeley and based in Washington, DC. The Forum engages a cross-section of experts from academic, clinical, community, industry, and government settings to address emerging issues related to HIV/AIDS and Hepatitis C. This guidance document is an outcome of the HIV Cure Project working group convened on participant education, recruitment, and informed consent and draws upon expertise within the working group as well as systematic reviews of existing informed consent documentation from HCO studies.

Considerations for the Development of the Informed Consent Process in HCO studies

I. Introduction of the study to patients and framing risks and benefits

One particular challenge with approaching potential participants is that, for many of them the current standard of HIV-1 care involves one or only a few numbers of pills taken once daily with few side effects and that leads to long-term suppression of viremia and preservation of immune function. With the exception of largely unsuccessful ART intensification regimens, however, HCO strategies often involve agents or combinations of agents that have significant side effects, toxicities, and have the potential to have long-term impacts on health and/or fertility. (Tebas, P., D. Stein, W.W.Tang et al., 2014; Kent, S.J., J.C. Reece, J. Petravic, et al., 2013; Palpant NJ, Dudzinski D, 2013; Allers, K., G. Hutter, J. Hoffman, et al., 2011; Lewin, Rouzioux, 2011). As a result, HCO strategies differ from cancer or other studies in that the experimental agent may cause more harm than the current standard of care. On the other hand, novel chemotherapuetic trials for malignancy often involve participants with morbid disease refractory to other agents, and participants may directly benefit from the experimental agents (e.g. prolonged life expectancy, improved quality of life, and increase in disease free remission). A partial list of the potential risks and benefits of HCQ strategies is shown below:

Possible risks of HCO trial participation include, but are not limited to:

- Risks involved with ART treatment interruption (see below for details)
- Drug toxicities and adverse effects and potential for long-term toxicities
- Unknown drug toxicities in studies involving more than one experimental agent or strategy
- Long-term toxicities related to fertility
- Oncogenic potential of drug
- Development of drug resistance
- No clear way to predict the timing of viral rebound when off ART (see above)
- Risks associated with chemotherapy and stem cell transplantation
- Highly invasive procedures required (e.g. gut biopsy, lymph node biopsy, lumbar puncture)
- Burdens related to study visits
- Inadequate protection of confidential or identifiable information
- Possible exclusion from future trial participation

Possible benefits of HCO trial participation include, but are not limited to:

- Reduction in the size of the HIV reservoir (although long-term benefit of this is unknown)
- Control of viremia in the absence of ART (a.k.a "functional cure")
- Absence of rebound viremia during an extended period of time

- Preservation of immune function or reconstitution of immune function
- Favorable alteration of the viral set point
- Decreased viral evolution and limited viral diversity
- Reactivation of latent replication-competent proviruses (e.g. latency-reversing agents)followed by clearance of infected cells using combination agents/strategy

II. Use of language and the semantics of HIV "cure"

The word "cure" resonates strongly with both community and scientific communities. As a result, use of this terminology in the informed consent process may lead to false hope and therapeutic misconception or misestimation, where participants may incorrectly estimate the chances of benefits or risks. (Pentz, White, Harvey et al., 2012; King, N., G. Henderson, L. Churchill et al., 2005; Horng, Grady, 2003). It is also debatable whether the world "cure" should be used at all in the informed consent process, even though there may be circumstances when using this direct language is important to explain the long-term goals and potential value of the research (e.g., benefit to society).

Analogies can also be made with terminology used in cancer research in which chemotherapeutic agents may be used to slow or halt progression of disease, improve quality of life, lead to partial, full, transient or pro-longed disease remission, or in a smaller percentage of agents, lead to disease eradication (*a.k.a.* cure). Creating semantic parallels with known disease lexicons may prove useful to accurately describe goals of potential therapeutic strategies to patients and avoid leading participants to be confused about the potential for direct medical benefit. For example, phrases such as long-term ART-free remission, eradication or reduction of the viral reservoir, or HIV-1 remission without the use of ART may be less likely to lead to misplaced optimism than functional cure etc.

III. Communication between study investigators and interested parties

Understanding and communicating limitations of proposed HCO strategies and setting study team and participant expectations are likely to be key in creating a successful informed consent process. Early cross talk between members of institutional review boards during the design of clinical trials may also substantially streamline study design and facilitate handling of controversial or challenging issues. Issues that have arisen in previous or ongoing HIV-1 eradication and persistence studies include establishing how and when to communicate results from research tests, or how to conduct a stepped trial with antiretroviral treatment interruptions based on results from earlier phases of the study as discussed in more detail below.

IV. Justifying and communicating risks and the risks of studies incorporating more than one experimental agent

Combinations of experimental agents will likely be necessary to achieve sustainable activity against HIV-1 reservoir and/or lead to extended periods of ART-free remission. (Margolis and Hazuda, 2013). Furthermore, several agents currently in development or clinical trial phase involve chemotherapeutic agents that may have significant toxicities to patients and that may be amplified when used in combinations with other drugs. These agents have not been previously used together in humans, and adverse events may limit trial completion or the ultimate utility as HCO strategies (Chapman, 2011). Careful communication of the potential risks, the potential for unknown risks, and the potential benefits to participants, study teams within the scientific field, or review committees will likely establish realistic expectations of a trial and facilitate the overall

process.

V. Risks of ART treatment interruptions and implications for participants in studies with multiple phases

Treatment interruption remains the only definitive test for a long-term ART free remission, as there are no clear biomarkers to predict responses to novel treatment/eradication strategies. As a result, a growing number of studies involving analytical treatment interruptions (ATI) are being designed or implemented. Treatment interruption is inherently risky, but the potential risks of ATI vary depending on the duration and type of interruption planned as show below in **Table 1**.

VI. Return of research results to participants

A priority issue for informed consent processes is to ensure participants understand the extent to which they will be informed of their clinical status as a result of trial participation. However, there are significant differences in how HCO trials address information related to return of results to patients. Clinical trial policies on these issues must be clearly conveyed to participants, including restrictions on return of results due to institutional review board requirements. Additional considerations should be made for how to address return of results in investigations with tiered study designs as discussed below.

A review of thirteen HCO study informed consent forms was conducted to assess the current state of return of results to participants (Henderson,G., manuscript). Among these, three consent forms did not mention anything about possible return of research results. Of the 10 that did, three types of return were discussed:

- 1) Screening results: 5 consent forms mentioned results from screening tests, including for HBV and HCV.
- 2) Study results: Four consent forms mentioned returning results from the study itself, while 3 specifically stated that no results will be returned.
- 3) Future research results: Two consent forms state there will be no return of results from future research conducted on specimens/data; while three stated that return of results from future research is unlikely ("probably not," "cannot guarantee," "cannot ensure"). One consent form stated that return of results will only occur if needed for care and if requested. Five consent forms mentioned genetic results, including not returning them. One mentioned the possibility of incidental findings, produced from optional MRIs. Only one mentioned return of aggregate study data.

The question arises whether or not the participant has a right to know individual results of a curative therapy that may have had an impact on HIV-1 persistence or reservoir size. The principle behind return of results to participants is that if an investigator has information about a participant that is clinically relevant, it should be revealed. For example, patients in traditional ART-drug trials are often aware of their viral load measurements, which correlate strongly with clinical outcomes. The rationale for providing results to participants in HCO studies is more challenging as tests of viral reservoir size and function are often surrogate endpoints, experimental in nature (*e.g.* viral outgrowth assays) and are not FDA-approved or performed under Clinical Laboratory Improvement Amendments (CLIA) certification and Good Clinical Practice guidelines. Many institutional review boards will only allow participants to know results when approved or certified as above. Whether and under what conditions investigators are obligated to return research results is currently under debate. It is therefore strongly advised to

develop a plan regarding return of results and to discuss this plan with Institutional Review Boards in advance of conducing cure-oriented research.

Potential risks involved with returning results to patients are outlined in Table 2. water Not For Distribution

> enhancing and facilitating HIV research 1608 Rhode Island Avenue NW • Suite 212 • Washington DC 20036 202.833.4617 www.hivforum.org

Table 1: Type of Analytical Treatment Interruption and Potential Risk to Participant							
	Time to V	Time to Viral Rebound-		Set Point-	Recurrent Interruptions		
	Immediate ART Re-Initiation after Rebound		Delayed ART Re-Initiation after Rebound				
ART Re-	Restart immediately	Restart after viral rebound	Restart after specified	Restart ART after viral	Intermittent ART		
Initiation Criteria	after viral rebound	or at specified interval if no	interval regardless of viral	load reaches stable set-	Interruption		
Example	Start after confirmed VL	Start after confirmed VL	Restart ART after 16	Continue treatment	SMART study,		
-	>50 or 200 copies/ml	>200 or 16 weeks	weeks, VL may be <200 or	interruption until VL	"ART conservation"		
Detential	Development of	(whichever is first)	>200	decay slope plateaus	Development of		
Potential Major Risks	Development of resistance in the setting	Development of resistance;	Development of resistance: acute retrovital	Development of	Development of resistance: acute		
to	of ART during rapid		syndrome; marked	retroviral syndrome;	retroviral syndrome;		
Participant	expansion of viral load,		decrease in CD4 T cell	marked decrease in CD4	decreased CD4 T cell		
	especially in setting of		counts; opportunistic	T cell counts;	counts; Ols; extensive		
	suboptimal adherence;		Infections (OIS); extensive		cellular reservoir		
	acute retroviral		disease progression	reservoir seeding, faster	of death or AIDS		
	syndrome			disease progression			
Benefit to	None	None	None	None	None		
Participant	Taata potantial for	Tooto potontial for ourstive	Nlove inter patient	Allowa inter nationt	Should not be performed		
Benefit	curative strategy to	strategy to eradicate virus	comparisons of viral	comparisons of viral	Should not be performed		
	eradicate virus or lead to	or lead to prolonged ART-	rebound kinetics/evolution	rebound			
	prolonged ART-free	free remission	and immune dynamics;	kinetics/evolution and			
	remission		may inform on peak and	immune dynamics;			
			set-point VL during ATT	point VL during ATI			
Limitations	Requires frequent	Requires frequent	Potential need for	Potential need for	Should not be performed		
and	monitoring; does not	monitoring; does not inform	management of AEs and	management of AE			
Logistical	inform on differences in	on differences in immune	retroviral syndromes, OIS,	retroviral syndromes,			
135003	or VL peak/nadirs during	peak/nadirs during ATI; loss		013, 010.			
	ATI	of information when ART					
		restarted prior to rebound					
	$\langle \rangle$				6		
enhancing and facilitating HIV research							

enhancing and facilitating HIV research 1608 Rhode Island Avenue NW • Suite 212 • Washington DC 20036 202.833.4617 www.hivforum.org

Table 2. Theoretical Risks of Returning Results to Patient in HIV Cure Oriented Studies: Surrogate Endpoints								
Type of Result	Result	Potential Risks	Duration of Risk					
Quantitative	Significant decrease in reservoir measure	Patient independently stops ART leading to viral rebound; decreased medication adherence; Patient induced by result to participate in next step of tiered study (<i>e.g.</i> ATI)	Long-term					
reservoir (e.g. SCA, CA-DNA	Significant increase in reservoir measure	intensification when not otherwise indicated	Long-term					
or RNA, VOA)	Inaccurate, insensitive or unspecific results from experimental assays	Patient anxiety; ART change or intensification when not indicated; Patient induced by result to participate in next step of tiered study (<i>e.g.</i> ATI)	Long-term					
SCA = single copy RNA assay; CA = cell associated; VOA = viral outgrowth assay								

VII. Phased or tiered studies and those that incorporate ATI

There has also been discussion around the use of multi-phased or tiered studies in which participants that meet particular criteria, such as a significant reduction in HIV-1 proviral DNA in peripheral blood, qualify for a second therapeutic/diagnostic step and/or ATI. Because there are currently no reliable biomarkers for the duration of ART-free HIV remission or control, the decision to pursue the second tier of the study may be based on a number of laboratory values that have not been shown to predict viral response following ART cessation. Furthermore, ethical issues are raised as to when and how it is appropriate to inform a patient of their results or aggregate results from others in the study from the first stage so that the participant can make a decision to proceed with a second step or tier.

Several approaches may be taken:

- 1) Design the study so that the second step or tier is automatic and all participants proceed with this stage (such as ATI). Potential risks must be clearly stated and explained in the initial IC process.
- 2) Incorporate a protocol that automatically advances a participant to the next step or tier based on a single test or group of laboratory values in which the patients gives consent to proceed to a second step prior to knowing these results. For example, if a patient experiences a 1 log₁₀ reduction in cell-associated HIV-1 DNA, they are advanced to ATI. Of course, the participant would know that they achieved this step 1 "goal" by simply moving forward with ATI.
- 3) Initiate a second IC process that allows the participant to decide whether or not they should proceed based on results from the first step or tier. While this scenario introduces several logistical and ethical issues, it has been successfully applied in stem cell transplant studies to proceed with treatment interruption or further invasive tissue sampling once a patient experienced a lack of detectable HIV-1 DNA in peripheral blood. This approach may be more useful in prospective cohort studies than randomized trials of novel therapeutic agents.

Regardless of the approach taken in tiered studies, the question arises whether or not the participant has a right to know individual results of HCO therapies that may have had an impact on HIV-1 persistence or reservoir size. As described above, these strategies should be addressed in advance, and in consultation with relevant institutional review boards.

VIII. Engage participants via formative research and by other strategies and address participant-centered concerns

Decision-making processes for participants may vary for different target populations. This may include clinical and non-clinical implications for their current and future health, as well as how trial participation may affect quality of life. An example of this includes participant perceptions regarding the potential for trial participants to develop drug resistance (FDA public meeting, 2013). In fact, emerging evidences indicates a low but present risk of drug resistance formation with the re-initiation of antiretrovirals (Graham, S. M., Jalalian-Lechak, Z., Shafi, J., 2012; El-Sadr, W.M., J. D. Lundgren, J.D. Neaton et al., 2006).

As a part of the trial enrollment process, investigators should consider basic qualitative methods to identify patient-concerns within the target study population and ensure patient-driven concerns are addressed within the informed consent process. Early engagement with community advisory boards or using directed surveys may be useful tools to provide estimates as to potential participation rates or interests in participating in certain trials. (Please refer to the recommendations for survey research among potential HCO trial participants for more detail.)

IX. Address alternatives to study participation and eligibility for future HIV cure-oriented trials

While rapidly evolving, HCO research is still at a relatively nascent stage. Decisions to participate in a given trial may influence the participant's eligibility to enroll in subsequent trials, which may offer more direct benefits to participants. Informed consent processes should directly address consequences to trial participation that may influence future treatment and participation in HCO trials. In addition, standard practice should reflect potential participants informed of their option to opt out of the study and continue on normal treatment regimens. This should allow for individualized discussions between potential participants and investigators to assess the various options for participants and is particularly critical when HCO research is conducted within resource-limited settings, where standards of care for treatment may vary.

X. Reproductive risks

Novel HCO strategies may involve fertility or reproductive risks that are not well understood or defined in the literature. These reproductive risks should be communicated directly to potential participants. Where there is concern of significant risks of teratogenicity and/or fertility, investigators should consider strategies to ensure women of reproductive age are included in trial populations. An example of a strategy to address this includes administration of a separate test of understanding of reproductive risks while including a written agreement for participants not to participate in a conception process for a certain length of time.

XI. Specimen, data storage and sharing, and use of electronic medical records

Another priority issue for informed consent processes is to ensure participants understand how specimens/ data collected during their trial participation will be used. There is considerable

heterogeneity in whether and how consent forms address these issues. The following data were abstracted from a review of thirteen HCO informed consent forms (Henderson, manuscript). Among informed consent forms that addressed specimen/data storage & sharing, four consent forms did not mention sharing with others for future research; one study stated specimens/data would not be shared. One consent form stated that agreement to store specimens and/or data for future research use is part of joining the study. Seven included optional requests to store and share. If storage for future research is mentioned, it is usually described as HIV-related. Four studies prohibited commercial use; two mentioned profit as a possibility. One stated that specimens are owned by the university. Of those that described storage, 5 stated they would store "indefinitely," while 3 reported they would store for a set number of years (5, 10, or 15 yrs). With regard to electronic medical record, five consent forms mention a participant's electronic medical records. Two stated nothing will go in the electronic medical records; three described putting study data or the consent form in the electronic medical records.

XII. Privacy issues for HIV cure-oriented trials

Study administrators should consider media attention to HIV cure-oriented trials and implications for participant privacy.

Items of Consideration for the Development of Informed Consent Forms

Informed consent (IC) documents are critical components of research studies and the IC process. For example, they describe in lay language why the study is being performed, explain why a patient is a potential participant, introduce the risks and benefits of participation, and other options aside from participation, and serve as legal documentation of the communication to and understanding by the participant of the study's risks and benefits. Consent forms are often lengthy, difficult to read, and present a large amount of information in numerous sections. There is particular need to streamline IC forms to adequately address these issues in HCO studies because there are tangible risks of participation with little to no known direct medical benefits to patients. The use of visual cues within larger blocks of text and summarizing or presenting information in tabular or bullet format may substantially improve the accessibility of the document to the lay reader/patient. Below are potential suggestions for the drafting of IC documents to be used in HCO studies.

I. Introductory information in consent forms

The introduction and overview is a critical component of the IC form as this is the first, and in many cases, the only section potential participants will read in detail or remember. Key information that should be conveyed in introductory information includes: what the study is trying to learn, reason for the study, and how does the study differ from their normal treatment in the context of HCO research.

As a result, there is a need to use simple, straightforward language in a concise format that explains the reason for the study and what will be expected from patients. A brief introduction may also be used to frame the potential benefits and risks of the study while taking into account the type of HCO study.

Traditionally, IC forms either include a brief introductory paragraph or proceed directly to more detailed sections such as why is the study is being performed. It may be helpful to draft an introductory paragraph with eye-friendly formats such as bullets or numbered lists that are then followed by more in-depth sections. The use of the word "cure" also needs special attention as discussed above in the informed consent process in order to successfully contextualize the purpose of a study, but to minimize therapeutic misestimation by potential participants.

A hypothetical example of a brief introduction is as follows:

"You are being asked to participate in this study because you:

- 1) have HIV infection
- 2) are taking antiretroviral medication
- 3) do not have detectable virus in your blood during the past year

The study will test a new drug that will help doctors and scientists learn how to clear HIV from the body that you will take in addition to your regular HIV medications. The study drug is designed to make cells in your body that are infected with HIV to make more virus. There are potential risks with taking this experimental drug, such as 1) ----, 2) -----, and 3) -----. Since it is a study, the outcome might be that the drug does not work as expected or produces unexpected harms for participants. You are not expected to benefit directly from taking this drug. However, information learned from you and others in this study will contribute to scientific knowledge, and help in the development of new ways of reducing the amount of HIV in the body."

II. Risk/ Benefit language

The risk/benefits section of cure-oriented studies is perhaps the most important, but complex component of the IC document. As there is the potential for numerous risks involved in single agent or combinatorial HCO studies, presenting risk information in bullet or tabular format may draw attention to and/or increase participant understanding of these risks. This tabular format should contain frequency, severity, and/or duration of risks and benefits. One example of a bulleted list of risks from a consent form for ATI in participants that have undergone allogeneic HSCT is shown below:

Potential risks of stopping HIV treatment include:

- Return of detectable virus in your blood (Likely, >50%)
- Development of mild symptoms of viral infection, including fever, rash, feeling tired, body or joint aches, swollen lymph nodes, sore throat (**Occasionally**, **<25%**)

Increased risk to spread HIV to other persons while off medication (risk unknown)
Reduction in your peripheral CD4 T lymphocyte (helper T cells) counts (Rare as treatment will be restarted once virus returns in your blood, <10%)

- Development of resistance to HIV medications once treatment is restarted if virus returns in your blood (Rare – Serious, <10%)
- Development of an infection associated with poorly controlled HIV disease (Rare Serious, <5%)

- Return or progression of your previously treated cancer of the blood (Rare Serious, <5%)
- Inability for your prior HIV treatment to control virus in the blood once medications have been restarted (Rare – Serious, <5%)
- Development of severe symptoms of viral infection, such as inflammation of the brain or the covering around the brain and spinal cord (**Rare Serious**, <**5%**)
- Development or worsening of graft-versus-host disease (GVHD, which may involve organs such as skin, liver, eyes, gut) as acute or chronic infections can at times trigger GVHD. You may need to start or increase dosage of medications to treat GVHD if GVHD were to occur after stopping HIV treatment (risk unknown)

Similar information in tabular format:

Risks Associated with ATI Following Allogeneic HSCT								
Risk	Frequency	Severity	Duration of Risk					
Return of detectable virus in your blood	Likely, >50% of patients	Low to moderate	Days to months - until ART is restarted					
Development of symptoms of viral infection, including fever, rash, feeling tired, body or joint aches, swollen lymph nodes, sore throat	Occasionally, <50% of patients	Low to moderate	Days to weeks - until ART is restarted and virus becomes undetectable					
Increased risk to spread HIV to others while off medications	Unknown, likely rare	Serious	Days to months - until ART is restarted and virus becomes undetectable					
Development of resistance to HIV medications once treatment is restarted if virus returns in your blood	Rare, <10% of patients	Serious	Weeks to years - new medications may need to be started in order to suppress virus					
etc.								

The Cancer Therapy Evaluation Program CTEP) of the National Cancer Institute developed guidelines on how to build risk tables for informed consent that may be applied to novel HCO agents or combinations of agents:

(http://ctep.cancer.gov/protocolDevelopment/sideeffects/drugs.htm).

An example of one CTEP table of potential side effects of cyclophosphamide is shown below:

Possible Side Effects of Cyclophosphamide (Table Version Date: May 28, 2013)

(Taken from: http://ctep.cancer.gov/protocolDevelopment/sideeffects/regimes/regimes.htm accessed 5/10/14)

COMMON, SOME MAY BE SERIOUS

In 100 people receiving Cyclophosphamide, more than 20 and up to 100 may have:

- Hair loss
- Nausea, vomiting, loss of appetite
- · Sores in mouth
- · Infection, especially when white blood cell count is low
- Absence of menstrual period which may decrease the ability to have children
- Blood in urine

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving Cyclophosphamide, from 4 to 20 may have:

- Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions
- · Loss or absence of sperm which may lead to an inability to father children
- Stuffy nose
- Fluid around the heart

RARE, AND SERIOUS

In 100 people receiving Cyclophosphamide, 3 or fewer may have:

- Severe skin rash with blisters and peeling which can involve mouth and other parts of the body
- Damage to the heart or heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness
- A new cancer including cancer of bone marrow (leukemia) caused by chemotherapy
- Swelling of the body including the brain which may cause dizziness, confusion
- Scarring of the lungs

Language describing the nature, likelihood, duration, and magnitude of direct medical benefits should also be described clearly and concisely. All consent forms are required to describe benefit in a separate section, and here language is often vague, especially in early phase trials. A key concern arises when optimistic messages about the nature of possible direct benefit are described as the surrogate or clinical endpoints in a trial but are contradicted by cautious statements about the likelihood of these benefits in the 'benefit' section.

III. Return of results to participants

Consent forms should indicate whether or not results from screening or research participation will be routinely returned to participants, returned only upon request, or never returned. This should be treated separately from the question of <u>future</u> research results. Consent forms should

describe the nature of those results, who is conducting the future research (the original research team or other researchers with whom specimens/data are shared), and whether results are anticipated to be returned, returned upon request, or not returned. Genetic results may or may not be described separately.

IV. Reproductive Risks

Language related to teratogenic effects are relatively well established and defined in the literature but language related to changes in hormones and fertility patterns are not. Below is an example of consent form language in the AIDS Clinical Trials Group A5337 study of sirolimus and HIV-1 reservoirs.

Potential Impact on Fertility

Sirolimus may decrease sperm counts while you are taking the drug. However, sperm counts have been shown to increase to normal levels several months after sirolimus is stopped.

Sirolimus has also been associated with the absence of menstruation (monthly period) that develops in some women while they are taking the drug, and there has been at least one report of a female patient who had permanent loss of menstruation after she stopped taking sirolimus. Fertility problems are usually identified 5 to 12 months after patients start taking the drug, and you will not be asked to take sirolimus for more than 5 months duration. The long-term effects of sirolimus on fertility and the ability to become pregnant are not well understood, and you may be at risk for temporary or long-term infertility if you enroll in this study and take study medication.

V. Specimen/ data sharing, & electronic medical records

Consent forms should describe plans for research with stored specimens/data and whether there are plans to share with other researchers. Separate consent forms should be included, when appropriate.

In addition, it is important that participants understand what study results will or will not be placed in their electronic medical records, including the implications, and whether participants have any control over the process. All studies should describe potential risks when results are placed in the EMR, and protections afforded by Genetic Information Nondiscrimination Act (GINA). This should also apply to future research results.

VI. Next Steps

The working group has collectively highlighted key areas for consideration in devising informed consent processes for future HCO studies. We conjecture that HCO trials will continue to raise new sets of ethical questions and challenges. This will require collaboration of a broad range of expertise to ensure HIV "cure" oriented scientific advancements remain participant centered and are adapted to address the unique characteristics posed by HCO studies. As such, this guidance document is considered to be a living document to be modified as HCO research continues to rapidly evolve globally.

References:

Allers, K., Hütter, G., Hofmann, J., Loddenkemper, C., Rieger, K., Thiel, E., & Schneider, T. (2011). Evidence for the cure of HIV infection by CCR5 Δ 32/ Δ 32 stem cell transplantation. *Blood*, *117*(10), 2791-2799.

Chapman, Audrey R. (2011). Addressing the Ethical Challenges of First-in-Human Trials, *Journal of Clinical Research and Bioethics*, 2:113.

El-Sadr, W. M., Lundgren, J. D., Neaton, J. D., Gordin, F., Abrams, D., Arduino, R. C., ... & Rappoport, C. (2006). CD4+ count-guided interruption of antiretroviral treatment. *New Engl J Med*, *355*(22), 2283-2296.

Graham, S. M., Jalalian-Lechak, Z., Shafi, J., Chohan, V., Deya, R. W., Jaoko, W., Kishor, N., Mandaliya, N.M.P, Overbaugh, J. & McClelland, R. S. (2012). Antiretroviral treatment interruptions predict female genital shedding of genotypically resistant HIV-1 RNA. *Journal of acquired immune deficiency syndromes (1999)*, *60*(5), 511.

Henderson, G.(2014). "Is new ethical guidance needed for clinical HIV cure research? A consent form analysis", unpublished manuscript.

Horng S., Grady C. (2003). Misunderstanding in clinical research: distinguishing therapeutic misconception, therapeutic misestimation, and therapeutic optimism. *IRB* 2003, 25 (1): 11-6.

Kent, S. J., Reece, J. C., Petravic, J., Martyushev, A., Kramski, M., De Rose, R., D. Cooper & Davenport, M. P. (2013). The search for an HIV cure: tackling latent infection. *The Lancet infectious diseases*, *13*(7), 614-621.

King, N., G. Henderson, L. Churchill, A. Davis, S. C. Hull, D. K. Nelson, P. Parham-Vetter, B. Rothschild, M. Easter, and B. Wilford (2005). Consent forms and the therapeutic misconception. *IRB*,27, 1-7.

Lewin, S. R., & Rouzioux, C. (2011). HIV cure and eradication: how will we get from the laboratory to effective clinical trials?. *Aids*, *25*(7), 885-897.

Margolis, D. M., & Hazuda, D. J. (2013). Combined approaches for HIV cure.*Current Opinion in HIV and AIDS*, ⁽⁸(3), 230-235.

Palpant NJ, Dudzinski D. (2013). Zinc finger nucleases: looking toward translation. *Gene Therapy*, 20(2): 121-7.

Pentz, R.D., White, M., Harvey, R.D., Farmer, Z. L., Liu, Y., Lewis, C., Dashevskaya, O. Owonikoko, T., and Khuri, F. R. (2012). "Therapeutic misconception, misestimation, and optimism in participants enrolled in phase 1 trials." *Cancer* 118, no. 18 (2012): 4571-4578.

Tebas, P., Stein, D., Tang, W. W., Frank, I., Wang, S. Q., Lee, G., Spratt, S.K. & June, C. H. (2014). Gene editing of CCR5 in autologous CD4 T cells of persons infected with HIV. New England Journal of Medicine, 370(10), 901-910.

Wolf, S. M., Crock, B. N., Van Ness, B., Lawrenz, F., Kahn, J. P., Beskow, L. M., Cho, M.K. & Wolf, W. A. (2012). Managing incidental findings and research results in genomic research involving biobanks and archived data sets. Genetics in Medicine, 14(4), 361-384.

Appendix 1

Informed Consent Working Group Members:

attendet David Evans (Project Inform) Sam Garner (NIH/ NAIDS) Sara Goldkind (FDA) Cynthia Grossman (NIH/NIMH) Gail Henderson (UNC) Timothy Henrich (Harvard) Richard Klein (FDA) Diane Lawrence (NIH) Bernard Lo (Greenwall Foundation) Debbie Persaud (JHU) Seema Shah (NIH) Jeremy Sugarman (JHU) Jeff Taylor (CAB) Mark Wainberg (McGill)