SCHARP
Statistical Center for HIV/AIDS Research and Prevention

STATISTICAL ANALYSIS PLAN FOR SAFETY

Protocol HVTN *305* v1.0

A phase-1 open-label clinical trial to evaluate the safety and immunogenicity of synthetic DNAs encoding NP-GT8 and IL-12, with or without a TLR-agonist–adjuvanted HIV Env Trimer 4571 boost, in adults without HIV

Date finalized for signature: 14 November 2022

Document will become effective on date of last signature. **SAP version:** 1.0

Statistical Analysis Plan for Safety

Protocol: HVTN 305 v1.0

Document will become effective on date of last signature.

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SAP Modification History

The version history of, and modifications to, this statistical analysis plan are described below.

SAP Version	Date	Modification
1.0	Last Day of Signature	Initial

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1 INTRODUCTION

The following describes the Statistical Analysis Plan (SAP) for the analysis of safety and tolerability data from HVTN 305 for Safety Monitoring Board (SMB) reports and the Final Study Report (FSR) for Safety. As detailed in SCHARP SOP-0013, Version 8.0 (effective date: March 1, 2021), this SAP is required prior to the first analysis and must be approved by the protocol team chair and the lead protocol statistician. The plan will be reviewed and updated prior to the first SMB report and before the final analysis with all major revisions of the plan archived.

2 PROTOCOL SUMMARY

2.1 Title

A phase-1 open-label clinical trial to evaluate the safety and immunogenicity of synthetic DNAs encoding NP-GT8 and IL-12, with or without a TLR-agonist–adjuvanted HIV Env Trimer 4571 boost, in adults without HIV.

2.2 Design

This is a randomized trial to examine safety and immunogenicity of INO-6172 (synthetic DNAs encoding the GT8 nanoparticle and Interleukin-12), alone and with HIV envelope protein (Env) Trimer 4571 adjuvanted with 3M-052-AF + Alum. The primary hypothesis is that INO-6172 will elicit VRC01-class B-cell responses as well as antigen-specific T-cell responses.

2.3 Study products and route of administration

- **INO-6172 (sD-NP-GT8 coformulated with IL-12 DNA (pGX6001)):** Synthetic-DNA–encoded nanoparticle GT8 (sD-NP-GT8) was developed by the Wistar Institute and consists of a single plasmid, pGX1072 (in pGX0001 vector backbone), encoding the soluble self-assembling nanoparticle vaccine, which is decorated with a germline-targeting, B-cell precursor activating immunogen GT8. pGX6001, developed by Inovio Pharmaceuticals, consists of a single plasmid, pGX6001 (pGX0003 vector backbone), containing a dual promoter system for expression of both the IL-12 p35 and p40 genes necessary for production of the active heterodimeric IL-12 protein. The plasmid ratio is 4:1 (0.8 mg pGX1072/0.2 mg pGX6001 or 0.2 mg pGX1072/0.05 mg pGX6001) per 0.1-mL injection.

- **Trimer 4571:** HIV-1 Env Trimer 4571 (VRC-HIVRG096-00-VP) is a soluble protein that consists of BG505 DS-SOSIP.664 gp140 Env and is supplied as a sterile, aqueous, buffered solution filled into single-dose vials at a concentration of 500 mcg/mL and a volume of 1.2 ± 0.10 mL in 3-mL glass vials. Trimer 4571 is provided by the Dale and Betty Bumpers Vaccine Research Center (VRC) and will be used at a dose of 100 mcg.

- **3M-052-AF:** This adjuvant is an aqueous formulation (AF) of the small molecule imidazoquinoline, which works as a toll-like receptor (TLR) 7/8 agonist. To be administered at 5 mcg admixed with 100 mcg Trimer 4571 and 500 mcg Alum.

- **Aluminum Hydroxide Suspension (Alum) adjuvant:** Alhydrogel at 500 mcg will be admixed with 5 mcg 3M-052-AF along with 100 mcg Trimer 4571.

- **Phosphate Buffered Saline (PBS) (diluent VRC-PBSPLA043-00-VP):** The diluent is composed of phosphate-buffered saline (PBS) aseptically filled into single-dose vials at a volume of 1.5 mL.

2.4 Study devices

Electroporation device: The Inovio CELLECTRA Adaptive Constant Current Electroporation (EP) Device is a portable, battery-powered medical device designed to facilitate the introduction of DNA into skin through EP. The Inovio CELLECTRA 2000 will be used for intradermal (ID) delivery following Mantoux injection of the DNA vaccine, which is provided by Inovio Pharmaceuticals.

2.5 Study population

Forty-five healthy volunteers without HIV-1 aged 18 to 55 years, inclusive.

2.6 Study plan and schema table

Participants will receive INO-6172 (sD-NP-GT8 + IL-12 DNA) vaccinations at months 0, 1, 3, and 6 with a total dose of 0.5 mg (Group 1) or 2 mg (Groups 2 and 3). For Group 1, sD-NP-GT8 DNA will be administered at a dose of 0.4 mg along with IL-12 DNA at a dose of 0.1 mg (0.5 mg total). For Groups 2 and 3, sD-NP-GT8 DNA will be administered at a dose of 1.6 mg along with 0.4 mg of IL-12 DNA (2 mg total) . These will be administered intradermally via EP of the skin. Due to volume limitations of the device, the dose of the DNA will be administered as 2 separate intradermal (ID) injections. Each of 2 sites will receive 0.1 mL of study product (either the 1.0-mg/0.1-mL concentration or the 0.25-mg/0.1-mL concentration) via ID injection (Mantoux injection) bilaterally 1 on each upper arm. Following ID injections, EP will be performed with the Inovio CELLECTRA 2000 EP device.

A total of 18 out of 45 participants (Group 3) will also be administered Trimer 4571 at a total dose of 100 mcg at months 3 and 6. The Trimer dose is split over 2 injection sites. The injections are delivered intramuscularly (IM) via needle and syringe, 1 in each deltoid muscle. Participants will be evaluated for safety and immune responses through blood collection, lymph node fine-needle aspiration (FNA), and leukapheresis at specified timepoints throughout the study. The study schema is presented below in Table 2-1 :

Table 2-1 Schema

				Injection schedule in months (days)			
Group	**N**	**Product/Dose**	**Route**	**Month 0 (Day 1)**	**Month 1 (Day 29)**	**Month 3 (Day 85)**	**Month 6 (Day 169)**
1**	9	INO-6172 (0.5 mg)	ID EP (2 injections; 1 into skin of each upper arm)	**X**	**X**	**X**	--
2§	18	INO-6172 (2 mg)	ID EP (2 injections; 1 into skin of each upper arm)	**X**	**X**	**X**	--
3§	18	INO-6172 (2 mg)	ID EP (2 injections; 1 into skin of each upper arm)	**X**	**X**	**X**†	--
		Trimer 4571 (100 mcg) + 3M-052 AF (5 mcg) / Alum (500 mcg)	IM (2 injections; 1 into each deltoid)	--	--	**X**†	**X**
Total	**45***						

Notes:

*Up to 9 additional participants may be enrolled (for a total of up to 54), if needed, to have approximately 45 participants contribute to immunogenicity analyses. Specific scenarios that could necessitate enrollment of additional participants in order to prevent loss of statistical power of the study include, but are not limited to, the following: loss of participants due to moving, withdrawal of consent, missing vaccine visits, inability to complete FNA, or variations in the clinical care due to unpredictable events. Participants will not be replaced after completion of visit 6, the first FNA visit.

** Initial enrollment will be restricted to 1 participant per day for the first 5 participants in Group 1, and enrollment will pause after the first 5 participants are enrolled in Group 1. The Protocol Safety Review Team (PSRT) will review cumulative safety information for these first 5 participants recorded through the visit scheduled 2 weeks post–first vaccination and will determine whether it is safe to proceed with full enrollment in all groups.

†For the first five participants in Group 3, the Month 3 vaccination will be limited to 1 participant per day.

§FNA for Groups 2 and 3 is optional. A minimum target of 50% of participants in these groups will be asked to participate.

2.7 Duration per participant

The total duration per participant is 18 months, including 12 months of scheduled clinic visits (main study) followed by an adverse event of special interest (AESI) health contact at month 18

2.8 Estimated total study duration

At least 22 months (includes enrollment, planned safety holds, follow-up, and AESI health contact).

2.9 Study sites

HIV Vaccine Trials Network (HVTN) clinical research sites (CRSs) in the US and South Africa, to be specified in the Site Announcement Memo.

3 SAFETY OBJECTIVES AND ENDPOINTS

3.1 Primary objectives and endpoints

Objectives	Endpoints
1) To evaluate the safety and tolerability of 3 doses of sD-NP-GT8 + IL-12 DNA adjuvant with or without 2 doses of Trimer 4571 + 3M-052-AF/Alum adjuvant	a) Local and systemic reactogenicity signs and symptoms will be collected for a minimum of 2 weeks following receipt of any study vaccine b) SAEs, medically attended adverse events (MAAEs), AESIs, and AEs leading to early participant withdrawal or permanent discontinuation will be collected throughout the study and for 12 months following any receipt of study products. Additionally, all AEs will be collected for 30 days after any receipt of study vaccination.
2) To evaluate the immunogenicity of 3 doses of sD-NP-GT8 + IL-12 DNA adjuvant with or without 2 doses of Trimer 4571 + 3M-052-AF/Alum adjuvant	a) Response rate and magnitude of HIV-1–specific binding Ab responses to eOD-GT8-60mer, eOD-GT8 monomer, or Trimer 4571 as assessed by multiplex assay 2 weeks following the third (Groups 1 and 2) and fourth (Group 3) vaccinations b) Response rate and magnitude of CD4+ and CD8+ T-cell responses, measured by flow cytometry, to HIV-1–specific Env peptide pools 2 weeks following the third (Groups 1 and 2) and fourth (Group 3) vaccinations
3) To evaluate the induction of VRC01-class B cells	a) Frequency of VRC01-class B cells from lymph nodes and periphery following the second and third vaccinations

3.2 Secondary objectives and endpoints

Objectives	Endpoints
1) To further evaluate the immunogenicity of 3 doses of sD-NP-GT8 + IL-12 DNA adjuvant with or without 2 doses of Trimer 4571 + 3M-052-AF/Alum adjuvant	a) eOD-GT8-60mer and monomer Ab response rate and magnitude measured by multiplex assay at 2 weeks following the first, second, and third immunizations between Group 1 and Group 2 to assess dose-sparing effects of self-assembling nanoparticle vaccines b) Quantify and compare antigen-specific germinal center Tfh and B-cell responses across groups at 3 weeks after the second and third vaccinations c) Evaluate nAb magnitude and breadth against tier-2 HIV-1 isolates after third and fourth vaccinations

3.3 Exploratory objectives

1. To clinically evaluate EP-injection–related skin changes for 6 months after the last study product administration and subjective assessment by participant of tolerability at 12 months after the last study product administration

2. Evaluate ADCC and antibody-dependent cellular phagocytosis (ADCP) after the last vaccination

3. Describe the binding specificities of sera using electron microscopy-polyclonal epitope mapping (EMPEM) at 2 weeks post–third and fourth vaccinations, if Env binding is observed

4. Evaluate Abs for cross-reactive binding to eOD-GT8 and Trimer 4571 6 weeks after the fourth vaccination and after 6 months post–fourth vaccination for Group 3

5. To conduct analyses related to furthering the understanding of HIV, immunology, vaccines, and clinical trial conduct, including but not exclusive to B-cell repertoire analysis (including analysis of rare B-cell lineages associated with bnAb precursors), and assessment of lymph node aspirate for germinal center activity, including cellular phenotyping and mutational frequency analysis suggestive of somatic hypermutation and affinity maturation following immunization.

4 COHORT DEFINITION

This phase-1 study will target recruiting a total of 45 adult participants without HIV aged 18 to 55 years.

5 POTENTIAL CONFOUNDERS

Primary and secondary objectives will seek to characterize and compare immunogenicity endpoints between treatment groups. Since allocation ratios used to enroll participants may vary between groups during enrollment (eg, participants will be preferentially assigned to Groups 2 and 3 relative to Group 1 after Group 1 has enrolled its first 5 participants), group comparisons will be cautiously interpreted. Moreover, in order to mitigate potential biases, statistical analyses may adjust for potential confounders (eg, age) when comparing endpoints between groups.

6 RANDOMIZATION

A participant's randomization assignment will be computer generated and provided to the HVTN CRS pharmacist through a Web-based randomization system. Pause rules discussed in Section 9.6 of the protocol will be accounted for in this process. At each institution, the pharmacist with primary responsibility for dispensing study products is charged with maintaining security of the treatment assignments (except in emergency situations as specified in the HVTN MOP).

Enrollment will be restricted to 1 participant per day for the first 5 participants in Group 1 and pause once the first 5 participants are enrolled in Group 1. If the PSRT determines that it is safe to complete enrollment in all three groups, the remaining participants (approximately 40: n=4 in Group 1, n=18 in Group 2, and n=18 in Group 3) will be block randomized. Block size and allocation ratio will be determined based on group sizes.

The study will aim to ensure balanced representation with respect to sex assigned at birth. Sites will therefore be encouraged to enroll at least approximately 40% of each sex assigned at birth in the study.

7 BLINDING

This is an open-label study. Participants and site staff will be unblinded to participants' group assignments. Laboratory program staff will be blinded to participants' group assignments during assay analysis, whenever feasible.

8 SAMPLE SIZE

The goal of the safety evaluation for this study is to identify safety concerns associated with vaccine administration. The ability of the study to detect SAEs (see Section 9.2 of protocol) can be expressed by the true event rate above which at least 1 SAE would likely be observed and the true event rate below which no events would likely be observed. Specifically, for each treatment group of size n = 18 (Groups 2 or 3), there is at least a 90% chance of observing at least 1 event if the true rate of such an event is 12.5% or more, and there is at least a 90% chance of observing no events if the true rate is 0.53% or less. When pooling Groups 2 and 3 together (n = 36), there is at least a 90% chance of observing at least 1 event if the true rate of such an event is 6.5% or more, and there is at least a 90% chance of observing no events if the true rate is 0.29% or less. Safety data will be summarized as described in Section 6.4.3 of the protocol and evaluated using historical controls. As a reference, in HVTN vaccine trials conducted in the US from April 2008 through March 2018, about 1% of participants who received placebos experienced an SAE.

Binomial probabilities of observing 0 events, 1 or more events, and 2 or more events among 9 (or 18 or 36 or 45) participants receiving the study vaccine are presented in Table 8-1 for a range of possible true AE rates. These calculations provide a more complete picture of the sensitivity of this study design to identify potential safety problems with the vaccine.

Table 8-1 Probability of observing 0 events, 1 or more events, and 2 or more events among a group of 9, 18, 36, or 45 study participants for different true event rates

True event rate (%)	Arm size	0 events	1+ events	2+ events
1	9	0.91	0.09	0.00
4	9	0.69	0.31	0.05
10	9	0.39	0.61	0.23
20	9	0.13	0.87	0.56
30	9	0.04	0.96	0.80
1	18	0.83	0.17	0.01
4	18	0.48	0.52	0.16
10	18	0.15	0.85	0.55
20	18	0.02	0.98	0.90
30	18	0.00	1.00	0.99
1	36	0.70	0.30	0.05
4	36	0.23	0.77	0.42
10	36	0.02	0.98	0.89
20	36	0.00	1.00	1.00
30	36	0.00	1.00	1.00
1	45	0.64	0.36	0.07
4	45	0.16	0.84	0.54
10	45	0.01	0.99	0.95
20	45	0.00	1.00	1.00
30	45	0.00	1.00	1.00

An alternative way of describing the statistical properties of the study design is in terms of the 95% CI for the true rate of an AE based on the observed data. Table 8-2 shows the two-sided 95% CIs for the probability of an event based on a particular observed rate. Calculations are done using the score test method for CIs described in Agresti and Coull formula 2 (53). If none of the 18 participants receiving the study vaccine in Groups 2 or 3 experience a safety event, the 95% two-sided upper confidence bound for the true rate of such events in the total vaccinated population is 17.6%. Table 8-2 also includes CIs for groups of size n = 9 (Group 1 alone), n = 36 (Groups 2 and 3 pooled together), and n = 45 (all 3 treatment groups combined).

Table 8-2 Two-sided 95% CIs for the probability of observing a safety event based on observing a particular rate of safety endpoints in a group of 18, 36, or 54 study participants

Observed event rate	95% CI (%)
0/9	[0 ; 29.9]
1/9	[2.0 ; 43.5]
2/9	[6.3 ; 54.7]
0/18	[0 ; 17.6]
1/18	[1.0 ; 25.8]
2/18	[3.1 ; 32.8]
0/36	[0 ; 9.6]
1/36	[0.5 ; 14.2]
2/36	[1.5 ; 18.1]
0/45	[0 ; 6.6]
1/45	[0.3 ; 9.8]
2/45	[1.0 ; 12.5]

9 STATISTICAL ANALYSIS

This section describes the final study analysis, unblinded as to treatment arm assignment. All data from enrolled participants will be analyzed regardless of how many vaccinations they received. All analyses will be performed using SAS and/or R.

9.1 Baseline demographics

Participants' baseline characteristics will be summarized using descriptive statistics.

9.2 Safety Analyses

Reactogenicity: The number and percentage of subjects experiencing each type of reactogenicity sign or symptom will be tabulated by severity. For a given sign or symptom, each subject's reactogenicity will be counted once under the maximum severity for all assessments.

Adverse Events: AEs will be coded into Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. The number and percentage of subjects experiencing each specific AE will be tabulated by severity and relationship to study vaccine. For the calculations in these tables, each subject's AE will be counted once under the maximum severity or strongest recorded causal relationship to treatment. A complete listing of AEs for each subject will provide details including severity, relationship to treatment, onset, duration and outcome.

10 SAFETY TABLES, PARTICIPANT LISTINGS, AND FIGURES

10.1 List of Tables

- Enrollment Report
- Demographics and Vaccination Frequencies
- Overall Protocol Status
- Maximum Local and Systemic Reactogenicity Summaries
- Adverse Experiences by Body System and Severity – By Decreasing Frequency
- Adverse Experiences by Preferred Term and Severity – By Decreasing Frequency – Includes Severe, Life-threatening or Fatal Experiences Only
- Adverse Experiences by Preferred Term and Severity – By Decreasing Frequency – Includes Experiences of All Severities
- Adverse Experiences by Preferred Term and Relationship to Study Product – By Decreasing Frequency – Includes Related Experiences Only
- Expedited Adverse Experiences (EAEs) Reported to the Regulatory Support Center (RSC)
- Medically Attended Adverse Events (MAAE)
- Pre-Enrollment Procedure-Related Events
- Pregnancy Listing

Additional tables included in the FSR for Safety:

- Social Impact Summary
- End of Study Diagnostic ELISA Testing Results
- Local Lab Value Summary Statistics
- Local Laboratory Values Meeting Grade 1 AE Criteria or Above

10.2 List of Participant Listings

These participant listings are included in the SMB reports:

- Discontinuation Status
- Pregnancies
- Severe or Life-Threatening Local and Systemic Reactogenicities
- Moderate Erythema and Induration
- Expedited Adverse Experiences (EAEs)
- Adverse Experiences of Special Interest (AESIs)
- Severe, Life-Threatening, or Fatal Adverse Experiences
- Adverse Experiences with Relationship to Study Product

- HIV Infection Results from Lab and Reported by Site
- Study Product Administration Errors
- Device Related Adverse Events

10.3 List of Figures

These graphs are included in the SMB reports and FSR for Safety:

- Maximum Local Reactogenicities
- Maximum Systemic Reactogenicities
- Boxplots for ALT, Creatinine, Hemoglobin, Platelet Count, AST, WBC, Neutrophil Count, Lymphocyte Count, Monocytes, Eosinophils, Basophils, Atypical lymphocytes

11 REFERENCES

1) Agresti A, Coull BA. Approximate is better than "exact" for interval estimation of binomial proportions. Am Stat 1998;52:119-26.

From: Yurdadon, Claudio
To: Yurdadon, Claudio
Subject: RE: [For Signature] HVTN 305 Safety SAP V1.0 For approval
Date: Monday, November 14, 2022 6:42:05 PM
Importance: High

I, Claudio Yurdadon, SRA II, approve HVTN305_Safety_SAP_v1.0.docx and HVTN305_Safety_SAP_v1.0.pdf.
This email is a substitute for a hand written signature.

From: Yurdadon, Claudio <cyurdado@scharp.org>
Sent: Monday, November 14, 2022 6:41 PM
To: Yurdadon, Claudio <cyurdado@scharp.org>
Subject: [For Signature] HVTN 305 Safety SAP V1.0 For approval
Importance: High

Dear,

Please review and approve the attached documents.
If you approve, please respond with the following statement:
"I, Claudio Yurdadon, SRA II, approve HVTN305_Safety_SAP_v1.0.docx and HVTN305_Safety_SAP_v1.0.pdf.
This email is a substitute for a hand written signature."

Thank you,

Claudio Yurdadön
He/They
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Working 9 hours ahead, meeting hours are 8 am – 2 pm PT.

From: Hyrien, Ollivier
To: Kalu, IJ
Subject: Re: [Signature Request] HVTN 305 Safety SAP v1.0
Date: Tuesday, November 22, 2022 7:18:44 AM

"I, Ollivier Hyrien, Professor, approve the Statistical Analysis Plan for Safety v1.0 document for HVTN 305 Protocol v1.0 - A phase-1 open-label clinical trial to evaluate the safety and immunogenicity of synthetic DNAs encoding NP-GT8 and IL-12, with or without a TLR-agonist–adjuvanted HIV Env Trimer 4571 boost, in adults without HIV, dated effective last day of signature. This email is a substitute for a handwritten approval signature of this document."

From: Kalu, IJ <ikalu@scharp.org>
Sent: Tuesday, November 22, 2022 7:07 AM
To: Hyrien, Ollivier <ohyrien@fredhutch.org>
Subject: FW: [Signature Request] HVTN 305 Safety SAP v1.0

Hello Ollivier,

Please review the attachment. If you approve the document and its contents, please respond with the following statement:

"I, Ollivier Hyrien, Professor, approve the Statistical Analysis Plan for Safety v1.0 document for HVTN 305 Protocol v1.0 - A phase-1 open-label clinical trial to evaluate the safety and immunogenicity of synthetic DNAs encoding NP-GT8 and IL-12, with or without a TLR-agonist–adjuvanted HIV Env Trimer 4571 boost, in adults without HIV, dated effective last day of signature. This email is a substitute for a handwritten approval signature of this document."

Best,
IJ

From: Kalu, IJ
Sent: Tuesday, November 15, 2022 12:44 PM
To: Hyrien, Ollivier <ohyrien@fredhutch.org>
Cc: Yurdadon, Claudio <cyurdado@scharp.org>
Subject: [Signature Request] HVTN 305 Safety SAP v1.0

Hello Ollivier,

Please review the attachment. If you approve the document and its contents, please respond with the following statement:

"I, Ollivier Hyrien, Professor, approve the Statistical Analysis Plan for Safety v1.0 document for HVTN 305 Protocol v1.0 - A phase-1 open-label clinical trial to evaluate the safety and immunogenicity of synthetic DNAs encoding NP-GT8 and IL-12, with or without a TLR-agonist–adjuvanted HIV Env Trimer 4571 boost, in adults without HIV, dated effective last day of signature. This email is a

substitute for a handwritten approval signature of this document."

Best,
IJ

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