Statistical analysis plan (SAP) for clinical research

VACCAIN-P study

Version 1.0, 18 oktober 2019

Template version 1.0, 17 April 2019.

Rebecca Holman[1], Marije Wolvers[1], Maruschka Merkus[1], Rob de Haan[1], Koos Zwinderman[2].

Amsterdam UMC, University of Amsterdam, Clinical Research Unit[1], Department of Clinical Epidemiology, Biostatistics and Bioinformatics[2], Meibergdreef 9, Amsterdam, Netherlands.

Section 1a. Title.

What is the title of the statistical analysis plan?

Statistical analysis plan for the VACCAIN-P study: a multicentre, randomised, double-blinded trial to assess whether quadrivalent HPV vaccination prevents recurrence of high-grade AIN in HIV+ men who have sex with men.

Section 1b. Names and Signatures.

What are the names, affiliations and roles of contributors to this statistical analysis plan?

Role of contributor	Name and full affiliation	Signature	Date of signature
Principal investigator	Prof. dr. J.M. Prins, Amsterdam University Medical Centers, Department of Infectious Diseases		18/10/2019
	Prof. dr. H.J.C. de Vries, Amsterdam University Medical Centers, Department of Dermatology		18-10-2019
Researchers who will perform the statistical analysis	Drs. K.C.M. Gosens, Amsterdam University Medical Centers, Department of Dermatology		18-10-2019
	R.P. van der Zee, MSc., Amsterdam University Medical Centers, Department of Infectious Diseases		18-10-2019
Senior statistician consulted	Prof. dr. M.G.W. Dijkgraaf, Amsterdam University Medical Centers, Department of Clinical Epidemiology, Biostatistics and Bioinformatics	i.o. (06-45161807)	18-10-2019

Section 1c. Revision history of the statistical analysis plan.

What versions of the statistical analysis plan have been approved and filed and what was the reason for producing each version?

This is the first version of the statistical analysis plan dated 18 October 2019 and was based on the study protocol version 5.1 based on the statistical section of the protocol which was agreed upon when drafting up the study protocol.

This version is approved by the PIs, clinical research coordinators and senior statistician on 18-10-2019 and filed in the TMF.

Updated statistical analysis plan version	Protocol version	Section number(s) changed	Description of and reason for changes	Date of approval
1.0	5.1	-	-	18-10-2019

Section 1d. Administrative Information.

1.1. What is the trial registration number?

Eudra-CT nummer: 2013-002009-70
ABR nummer: NL45200.018.13
METC nummer: 2013_194

1.2. What is the planned period of observation?

The date of the inclusion of the first patient was 27-03-2014. The date of the completion of follow-up for the last patient was 20-02-2019. Database completion and verification is planned at the beginning of October 2019. Deblinding is planned half October 2019.

1.3. What is the date and version number of the current statistical analysis plan?

This statistical analysis plan is version 1.0, dated 18-10-2019.

1.4. What is the date, version number and reference number of the protocol used when writing this statistical analysis plan?

This statistical analysis plan is based on the protocol with reference number NL45200.018.13 version 5.1, dated 06-09-2016.

Section 2. Introduction.

2.1. What is the background and rationale for the study?

Since the introduction of combination antiretroviral therapy (cART), human immunodeficiency virus (HIV)-related morbidity and mortality have considerably decreased. However, as a result of the significantly prolonged life span, new causes of morbidity and mortality have become evident. In particular, anal cancer incidence has increased dramatically in HIV-positive men. Like cervical cancer, anal cancer is causally linked to infections with high-risk papillomaviruses, and is preceded by precursor lesions: anal intraepithelial neoplasia (AIN). Over 90% of HIV-positive MSM (men who have sex with men) have persisting anal HPV (human papilloma virus) infection, and high-grade (HG) AIN is present in 30% of all HIV+ MSM.

As in cervical intraepithelial neoplasia, early diagnosis and treatment of AIN have been advocated to prevent malignancy. Electrocoagulation/ cauterization is standard of care for intra-anal AIN, but after treatment, recurrence of lesions occurs in approx. 50% of cases. This is a major problem in an effective screening program for AIN.

In a nonconcurrent, non-blinded cohort study qHPV (quadrivalent human papilloma virus) vaccination significantly (HR 0.50) reduced HG AIN recurrence among MSM successfully treated for AIN. This is in accordance with findings in women treated for cervical intraepithelial neoplasia. Previous vaccination with quadrivalent HPV vaccine among women who had surgical treatment for HPV related disease significantly reduced the incidence of subsequent HPV related disease, including high grade disease.

Therefore, a strategy that is worth investigating is vaccination with the qHPV vaccine to prevent recurrences in HIV+ MSM who were successfully treated for HG AIN.

For further details see pages 11 to 12 of the protocol.

2.2. What are the objectives of the study?

Primary objective:

To assess the efficacy of qHPV vaccination in preventing recurrence of high-grade AIN in HIV+ MSM with CD4 counts > 350 x 10E6/l who were successfully treated in the past year for high-grade intra-anal AIN.

Secondary objectives:

- To assess the safety of vaccination in this patient group
- To assess the efficacy of qHPV vaccination in preventing occurrence of low-grade AIN
- To assess the efficacy of qHPV vaccination in preventing occurrence of anogenital warts
- To assess the causative HPV genotype of recurrent HGAIN lesions
- To assess the HPV type-specific antibody response after vaccination, and relate this to the efficacy parameters

Section 3. Study Methods.

3.1. What is the study design?

Study design:

This study is a multicenter, randomised, double-blind clinical trial in three hospitals in the Netherlands. Vaccination was done in month 0, 2, and 6 with the qHPV vaccine or a matching placebo.

Study setting:

The study was performed at both the Internal Medicine department as well as the Dermatology department of 3 hospitals in Amsterdam:

- Amsterdam University Medical Centers (Amsterdam UMC), location Academic Medical Center (AMC)

- DC Klinieken Oud Zuid

- Onze Lieve Vrouwe Gasthuis

Study duration:

Patients were vaccinated three times during this study. High-resolution anoscopy (HRA) was be performed at inclusion, at the moment of the last vaccination, and at 6 and 12 months afterwards.

3.2. Will randomization be performed in this study?

Patients were randomised (randomisation ratio 1:1) to be vaccinated 3 times with the qHPV vaccine (Gardasil ®) or matching placebo at months 0, 2 and 6.

An independent central randomisation, ALEA Clinical software version 16 (FormsVision, Abcoude, The Netherlands) was used for computer generated tables per centre to allocate treatment. Randomisation was stratified for complete response versus partial response (from HG AIN to LG AIN) of the initial HG AIN lesion, for treatment less than 6 months ago versus treatment 6 months and longer ago, and for AMC versus other hospitals.

In this study the patients and treating physicians were blinded to treatment allocation. Blinding was maintained because the randomisation, preparation and delivery of the allocated medication (qHPV vaccine or placebo) was performed by an independent pharmacist.

3.3. How was the sample size calculated?

The total sample size for the RCT was estimated to be 125 patients based on the following assumptions:

- Expected recurrence rate was 50% within 12 months in this study population. This recurrence rate was observed in our earlier studies (1, 2).

- In a previous non-concurrent cohort study qHPV (quadrivalent human papilloma virus) vaccination significantly (HR 0.50) reduced HG AIN recurrence rate among MSM successfully treated for AIN. (3)

- A superiority test will be performed to test a 50% relative reduction in recurrence rate. However, a 25% absolute reduction is also considered clinically relevant.

- A two group (not for continuity corrected) chi-square test with a 0,05 two-sided significance level will have 80% power to detect the difference between a recurrence rate of 50% in the palcebo group and 25% in the vaccination group when the sample size in each group is 58.

- 5% drop out in both groups.

1. Richel O, de Vries HJ, van Noesel CJ, Dijkgraaf MG, Prins JM. Comparison of imiquimod, topical fluorouracil, and electrocautery for the treatment of anal intraepithelial neoplasia in HIV-positive men who have sex with men: an open-label, randomised controlled trial. Lancet Oncol. 2013 Mar 14. S1470-2045(13) 70067-6.

2. Richel O, Wieland U, de Vries HJC, et al. Topical 5-fluorouracil treatment of anal intraepithelial neoplasia in human immunodeficiency virus-positive men. Br J Dermatol 2010;163:1301-7.

3. Swedish KA, Factor SH, Goldstone SE. Prevention of recurrent high-grade anal neoplasia with quadrivalent human papillomavirus vaccination of men who have sex with men: a nonconcurrent cohort study. Clin Infect Dis. 2012 Apr;54:891-8.

3.4. What is the hypothesis testing framework for this study?

The VACCAIN-P study aims to test whether qHPV vaccination is superior to placebo for preventing recurrence of high-grade AIN in HIV+ MSM who were successfully treated for high-grade intra-anal AIN in the past year (primary outcome). Hence, the primary outcome has a superiority hypothesis testing framework using the superiority margins specified in the sample size calculations.

Secondary outcomes are examined in a superiority hypothesis testing framework as well, except for safety, causative HPV genotype and HPV type-specific antibody response, which due to the observational and descriptive nature of these parameters, do not use a formal hypothesis testing framework.

3.5. Will interim analyses be performed in this study?

No interim analyses were performed and there were no statistical or clinical guidelines for stopping the study early.

3.6. When will the final statistical analysis of the study data be performed?

The statistical analysis of the primary outcome and all secondary outcomes will be performed after the follow-up of the last patient is completed and after all data is entered in the database, followed by data cleaning and locking of the database. It is expected that this will happen six months after the follow-up of the final patient in the study is completed, meaning that we expect that the statistical analyses will be performed in September and October 2019.

3.7. At which time points are the outcomes measured and which "windows" are allowed?

Screening for recurrent AIN was performed at screening (before the first vaccination) and at last vaccination (follow-up 6 months), and repeated at 6 (follow-up 12 months) and 12 months (follow-up 18 months) after the last vaccination. In case of recurrent high grade lesions patients reached the study end point, further follow-up was ceased and patients were referred to the regular AIN care for further treatment.
At the last follow up (18 months), an anal papsmear (cytology) was performed in order to rule out missing HGAIN recurrences by high-resolution anoscopy. In case the cytology indicated HSIL (high grade squamous intraepithelial lesion), high-resolution anoscopy was repeated (re-HRA).
In case of recurrence at the 6 month visit (third vaccination and first follow up), the venous blood samples to assess the HPV type-specific antibody response was still drawn 3 months afterwards.

All visits, except the baseline visit, had a visit window of two weeks before and two weeks after the nominal time points. The window for the re-HRA was preferably within 22 months after first vaccination.

Section 4. Statistical Principles.

4.1. Which level or levels of statistical significance will be used in the study?

Primary and secondary outcomes will be viewed as significantly different between qHPV vaccination and placebo group if the two-sided p-values are less than 0.05.

4.2. Will the analysis adjust for multiplicity of statistical testing to ensure control of type I error rate?

As there is one primary outcome measured at a single time point in this study, the analysis will not adjust for multiplicity of statistical testing.

4.3. Which confidence intervals will be reported?

Ninety-five percent confidence intervals will be provided.

4.4. How is adherence to the intervention, including the extent of exposure, defined and assessed?

Medication adherence is defined as the number of prescribed vaccines actually received by each patient.

4.5. How will adherence to the intervention or extent of exposure be presented?

Vaccination adherence will be reported as the proportion of patients having received either all three vaccines or at least one vaccine for each arm of the study.

4.6. What are defined as protocol deviations in this study?

Protocol violations are defined as:
- Inadequate or delinquent informed consent
- Inclusion/exclusion criteria not met
- Unreported serious adverse events
- Improper breaking of the blind
- Use of prohibited medication
- Incorrect or missing tests
- Mishandled samples
- Any visits missed or outside permissible windows
- Materially inadequate record keeping
- Intentional deviation from protocol, Good Clinical Practice, or regulations by study personnel
- Subject repeated non-compliance with study requirements

Protocol deviations are defined as:
- Minor deviation from study visit windows
- Inappropriate documentation
- Study procedure is not exactly done per protocol

4.7. How will protocol deviations be presented in the reporting of this study?

All protocol violations will be line-listed according to treatment group. In addition, the number and percentage of patients in each treatment group experiencing one or more protocol violations will be presented.

4.8. Which analysis populations will be defined?

Statistical analysis will be based on the intention-to-treat principle. Outcomes will be evaluated for all patients who have been randomized (intention-to-treat, ITT), and for patients who received all three vaccinations and completed the follow-up (per protocol).

Section 5. Study populations.

5.1. Which data were collected from participants, who were screened for eligibility for inclusion in the study, and how these data will be presented in study reports?

Screening data will be presented as the number of patients asked, screened, the number fulfilling the inclusion criteria and the number approached for informed consent.
Date and hospital of screening, age, STI history, HIV history (year of diagnosis, nadir CD4 count, last measured CD4 and viral load including date, starting year and current regimen of cART), immunosuppressant use, allergies, AIN treatment history and last treatment including dates, smoking, physical complaints, blood pressure, heart rate, presence of genital, perianal or inguinal condylomata acuminata, routine blood tests, intra- and perianal presence of AIN and digital rectal examination were collected for all patients screened, fulfilling the inclusion criteria and giving informed consent.
Baseline assessments and outcome parameters will be summarized using simple descriptive statistics. Categorical variables will be summarized with frequencies and percentages. We will present the mean and standard deviation of normally distributed continuous variables, and the median and interquartile range of non-normally distributed continuous variables for all patients fulfilling the inclusion criteria.

5.2. What are the inclusion and exclusion criteria for the study?

Inclusion criteria

In order to be eligible to participate in this study, a subject had to meet all of the following criteria:

- Written informed consent.
- Age ≥ 18 years.
- HIV+ MSM, CD4 count > 350/ul (maximum 6 months before screening visit).
- Biopsy-proven intra-anal high-grade AIN successfully treated in the past year with cauterization, cryotherapy, Efudix, imiquimod or another form of local treatment. A maximum interval of 1 year between last treatment and first vaccination is allowed. Lesions with regression from HG to LG AIN (AIN 1) will also be eligible.
- Lesions (still) in remission.
    - Remission has to be established by 2 independent HRA anoscopists.
    - A maximum interval of 3 months is allowed between the first of these HRAs and the first vaccination, and a maximum interval of 6 weeks is allowed between the second of these HRAs and the first vaccination.
    - Biopsies of suspect lesions need to be obtained in one of the HRA sessions.
- Good performance status (a Karnofsky performance score of ≥ 60 [on a scale of 0 to 100, with higher scores indicating better performance status]).
- Pre-treatment haematology, and plasma ASAT, ALAT and creatinine levels compatible with study inclusion (maximum 6 weeks before screening visit).

Exclusion criteria

In order to be non-eligible to participate in this study, a subject had to meet at least one of the following criteria:

- Immunosuppressive medication or other diseases associated with immunodeficiency.
- Life expectancy less than one year.
- Previous HPV vaccination.
- History of anal cancer.
- Other diseases not compatible with study participation.
- Allergy against constituent of Gardasil ® vaccine.
- Currently peri-anal AIN2 or 3.

5.3. Which information will be presented in the flow chart for this study?

The mock-up of the CONSORT flow diagram is presented in the appendix to this statistical analysis plan.

5.4. What is the expected level of, timing of and reasons for withdrawal from the intervention and/or from follow-up and how will this be presented in the study reports?

We expect 5% of patients to have been lost to follow-up or dropped out of the study before assessment of the primary outcome was complete. We replaced patients who did not receive all 3 vaccines, but according to the study protocol these patients remained in follow-up.
We will report the number and percentage of patients in each study arm who: stopped receiving vaccinations before having received all 3 vaccines; or dropped out before assessment of the primary outcome was complete. For the drop out patients, we will present line listings of the reasons for withdrawal or loss to follow-up.

5.5. Which baseline characteristics of participants will be presented?

- Age at screening
- Sex (% male)
- MSM (% yes/no)
- Treatment centre (n, %)
- Years living with HIV
- % on cART and years on cART at screening
- Nadir CD4 count in cells / µl + number of years between measurement and screening
- Current CD4 in cells / µl + weeks before screening
- Recent viral load (copies/ ml or undetectable) + weeks before screening
- STI history (number of STI + which STIs)
- Smoking status (current smoker/ ex-smoker/ never smoked)

- Modus of last treatment type for intra-anal HG AIN, incl. no of treatments
- First vaccination within 6 months OR between 6 months to a year after last treatment
- Previous treatment type(s) for intra-anal HG AIN
- Presence at screening of genital, perianal or inguinal condylomata acuminata + location
- Presence at screening of intra- and perianal LG AIN yes/ no + location
- Digital rectal examination suspected for AIN

A mock-up of the baseline characteristics table is presented in the appendix to this statistical analysis plan.

5.6. How will the baseline characteristics be summarized?

Categorical baseline characteristics will be summarized by presenting the number and percentage in each category. Continuous, normally distributed variables will be summarized by presenting the mean and standard deviation. Continuous, non-normally distributed variables will be summarized by presenting the median and interquartile range.

Section 6. Analysis.

6.1. How are the outcomes of this study defined?

The primary outcome is the proportion of patients experiencing recurrence of intra-anal or peri-anal HG AIN at 12 months after last vaccination, as assessed by HRA, with biopsies taken of suspect lesions.

Secondary outcomes (no order of importance):

- The proportion of patients experiencing recurrence of HG AIN at last vaccination and 6 months afterwards.
- The proportion of patients with occurrence of LG AIN at 12 months after the last vaccination. The patients with LG AIN at screening are excluded from this analysis.
- The proportion of patients with occurrence of anogenital warts at 12 months after the last vaccination. The patients with anogenital warts at screening are excluded from this analysis.
- Safety: number of and severity of reported adverse effects
- Causative HPV types in recurrent HGAIN lesions will be described.
- HPV type-specific antibody response (titer levels) 3 months after the last vaccination, in patients with or without recurrent lesions, will be summarized.

6.2. Will any calculations or transformations be used to derive any outcome from the original data?

All outcomes will be compared for absolute differences between the vaccine and placebo arm. No calculations or transformations will be performed, unless data cleaning and distributional properties suggest otherwise (see paragraph 6.4).

6.3. What analysis method will be used and how the treatment effects will be presented?

The primary outcome will be evaluated for patients who have been randomized (intention-to-treat, ITT), and for patients who received all three vaccinations and completed the follow-up (per protocol).

For both sets, the main analysis of the effect of qHPV vaccination on the binary primary outcome at 12-months after the last vaccination in the two groups will be performed with a Chi-square test with a 0.05 two-sided significance level. In addition, the crude proportions and absolute differences in proportions with associated 95% confidence intervals will be presented.
A logistic regression model with treatment arm on recurrence of intra-anal or peri-anal HG AIN will be performed, correcting for the stratification factors 'treatment centre group', 'complete or partial response (from HG AIN to LG AIN) of the initial HG AIN' lesion and 'treatment less or equal/more than 6 months ago'. In a second step, a maximum of two baseline variables most predictive (if any) of recurrence will be added to the model. Adjusted odds ratios with 95% confidence interval will be reported.

In case of missing end-point data on recurrence, the two groups for the ITT analysis will be compared using Kaplan-Meier survival (or life tables if more appropriate) analysis. The difference between the fractions free of recurrence at 6, 12 and 18 months since inclusion will be assessed for statistical significance based on the widths of the corresponding confidence intervals. Additionally, we will perform best-case (last observation carried forward) and worst-case (assuming that all lost to follow up patients have recurrent HGAIN) scenarios for missing data to assess what might happen in case of violation of the assumption in survival analysis that patients with missing end-points have the same probability of recurrence during the remainder of the survival period as the other non-recurrent patients at the moment of loss-to-follow-up.
A Cox proportional hazards regression model with treatment arm on the time to recurrence of intra-anal or peri-anal HG AIN will be performed, correcting for the stratification factors 'treatment centre group', 'complete or partial response (from HG AIN to LG AIN) of the initial HG AIN' lesion and 'treatment less or equal/more than 6 months ago' as well as for up to two other baseline variables most predictive (if any) of recurrence. The effect sizes from this model will be expressed as an adjusted hazard ratio with 95% confidence interval. In addition, the survival time will be compared in the intention to treat, as treated, and per protocol populations using a log-rank test.

Secondary outcomes
The analysis of the secondary outcomes will only be performed in the intention-to-treat population and will be based on the t-test for continuous, normally distributed outcomes, the Mann-Whitney-U test for continuous, non-normally distributed outcomes.

6.4. Will any assumptions for statistical methods be checked?

Normality will be assessed by visual inspection of histograms and q-q plots. Continuous baseline variables judged to follow a non-normal distribution will be summarized using medians and interquartile ranges. Right skewed continuous baseline variables will be transformed using a natural logarithm (base e) for high kurtosis, square-root for normal kurtosis and inverse transformation for low kurtosis before linear regression is performed. For the Cox proportional hazards regression model we will test the proportional hazard assumption using visual inspection In case of violation of this assumption we will stratify for subgroups.

6.5. Will sensitivity analyses be performed?

We will perform best-case (last observation carried forward) and worst-case (assuming that all lost to follow up patients have recurrent HGAIN) scenarios for missing data to assess what might happen in case of violation of the assumption in survival analysis that patients with missing end-points have the same probability of recurrence during the remainder of the survival period as the other non-recurrent patients at the moment of loss-to-follow-up.

6.6. Will subgroup analyses be performed?

Subgroup analyses will be performed using logistic regression analysis with interaction terms for patients who had a complete response after initial treatment versus those with regression from HG to LG AIN on the one hand and for patients treated in the past 6 months versus those treated 6 months and longer ago on the other hand.

6.7. How will missing data be reported in the study reports and handled in the statistical analysis?

Missing data will be reported descriptively.
In case of missing end-point data on recurrence for the primary outcome, the two groups for the ITT analysis will be compared using Kaplan-Meier survival (or life tables if more appropriate) analysis. The difference between the fractions free of recurrence at 18 months since inclusion will be assessed for statistical significance based on the widths of the corresponding confidence intervals. Additionally, we will perform best-case and worst-case scenarios for missing data to assess what might happen in case of violation of the assumption in survival analysis that patients with missing end-points have the same probability of recurrence during the remainder of the survival period as the other non-recurrent patients at the moment of loss-to-follow-up.

6.8. Will additional analyses on the primary or secondary outcomes be performed?

No additional analyses will be performed on the primary or secondary outcomes.

6.9. How will harms be reported?

We will present line listings of safety outcomes. Adverse events will be graded according to version 4.0 of the Common Terminology Criteria for Adverse Events (CTCAE), which grades events on a scale of 1 to 5, with higher grades indicating greater severity. Safety outcomes will be classified by the clinical research coordinators as: expected complications of qHPV vaccination; suspected unexpected serious adverse drug reactions; and other (serious) adverse events. Each class of safety outcome will be presented using tabulations of counts and percentages of events and of patients experiencing one or more of each type of event for each treatment arm. Adverse effects will be reported using descriptive statistics. No formal statistical testing will be performed.

6.10. Which statistical software will be used to carry out the statistical analyses?

All statistical analysis will be performed in IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp, Armonk, NY).

Section 7. References to literature, standard operating procedures and reporting guidelines.

7.1. Are non-standard statistical procedures to be used, which have not been described in sufficient depth in the previous sections?

Not applicable.

7.2. What is the title, date and version number of the current data management plan?

The current data management plan has the title “Data management plan for the VACCAIN-P study”, version number 1.0, is dated 22-10-2019 and is stored in the trial master file.

7.3. What is the title, date and version number of the current data validation and derivation plan?

Data validation and derivation is implemented in the database program Research Online as documented in the Data Management Plan of Research Online and is stored in the trial master file.

7.4. What is the title, date and version number of the current study master file and where it is stored?

The trial master file has the title “Trial master file for the VACCAIN-P study”, is last updated at 9-9-2019 and is stored on paper at room A0-226 at the Amsterdam University Medical Center, location AMC, Amsterdam.

7.5. Where are the syntax files for data extraction, manipulation and preparation and statistical analysis stored?

The syntax files for data extraction, manipulation and preparation and statistical analysis will be stored at the location *G:\diva\Dermatologie\AIN en proctologie\Overige bestanden niet voor fotografie\VACCAIN-P studie\Statistical Master File.*

7.6. Which standard operating procedures will be adhered to when using and analysing data from this study?

When using and analysing data from the VACCAIN-P study, researchers will adhere to the standard operating procedure AMC RDM001 Research data management.

7.7. Which reporting guidelines will be adhered to when reporting on this study?

When reporting the results of this randomized clinical trial, the researchers will adhere to the SAMPL and CONSORT reporting guidelines.

Appendix. Additional Tables, Figures and Documents.

Figure 1. The flow chart of patients enrolled in the VACCAIN-P.

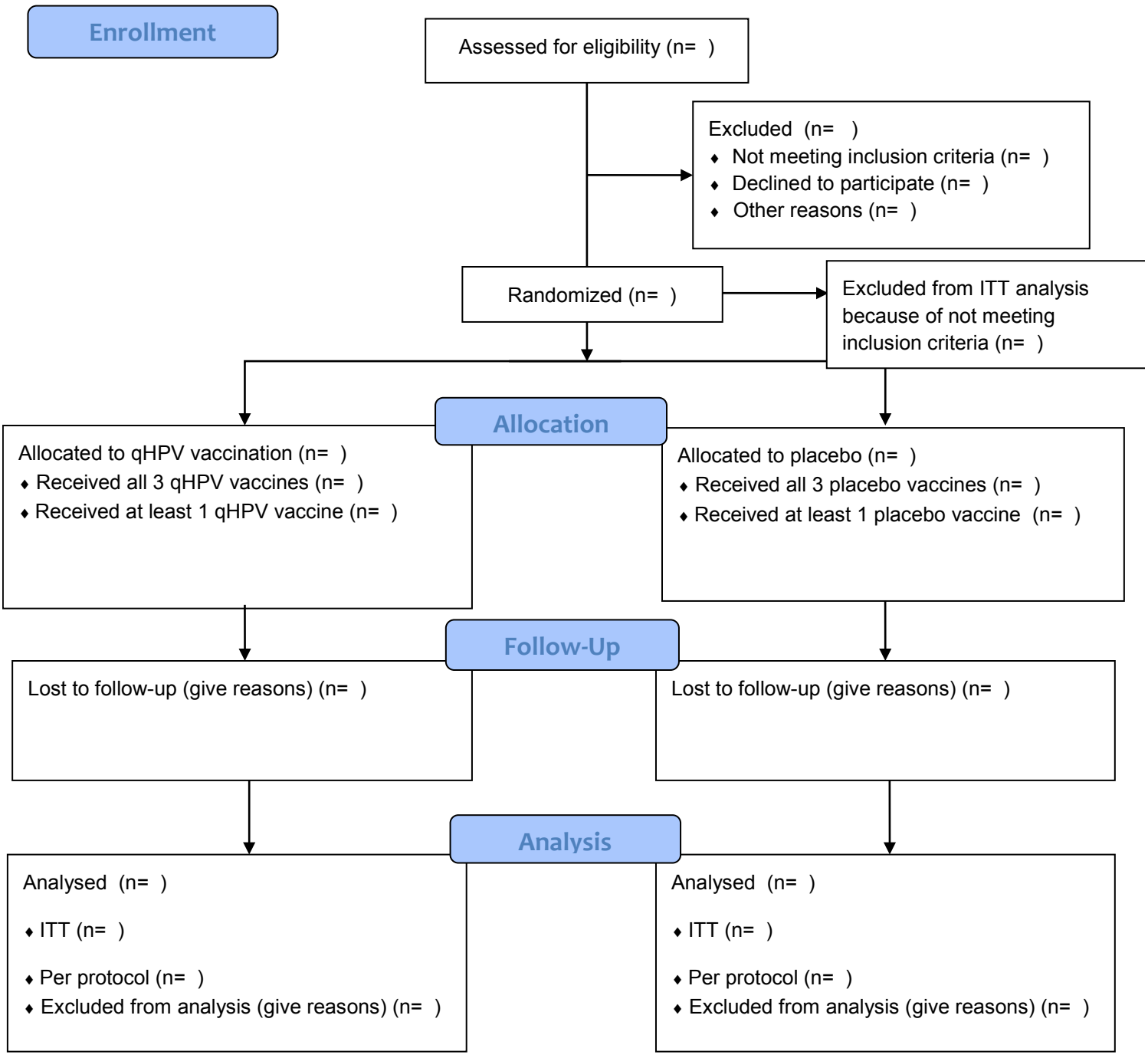

Table 1. The baseline characteristics of patients randomized in the VACCAIN-P study.

	Vaccine	**Placebo**	**P-value**
N=			
Age, years			
Male sex, %			
MSM, %			
Treatment centre - AMC - OLVG - DC			
Years living with HIV			
Nadir CD4 - count (cells / µl) - years before screening			
Current CD4 - count (cells / µl) - weeks before screening			
Recent viral load - copies / ml or undetectable - Weeks before screening			
% on cART and time on cART (years before screening)			
STI history, %, # of STIs - Gonorrhoea - Chlamydia - LGV - Syphilis - Condylomata acuminata - Herpes genitalis - Hepatitis A - Hepatitis B - Hepatitis C - Scabies - STI type unknown - Other			
Smoking % - current smoker - ex-smoker - never smoked			
Modus of last intra-anal HG AIN treatment, # of treatments or # of weeks treated - Cryotherapy - Cryotherapy + podofyllin 10% - Electrocautery/coagulation - Excision - Fotodynamic therapy - Laser - TCA - 5-fluoro-uracil crème - Imiquimod crème -Other			
Timing first vaccination: <6 months OR 6-12 months after last treatment			
Previous treatments for intra-anal HG AIN, %, modus of treatment, # of treatments or # of weeks treated - Cryotherapy - Cryotherapy + podofyllin 10% - Electrocautery/coagulation - Excision - Fotodynamic therapy - Laser - TCA - 5-fluoro-uracil crème - Imiquimod crème -Other			

Presence of condylomata acuminata, % - genital - perianal - inguinal			
Presence of intra and perianal LG AIN (=partial response), % - intra - peri			
Digital rectal examination suspected for AIN, %			