Statistical Analysis Plan

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Abbreviations

CRF ..... Case report form
GP ..... General practitioner
HPV ..... Human papillomavirus
HPVv ..... Human papillomavirus vaccination
ITT ..... Intention-to-treat analysis
MMR ..... Measles, mumps, rubella
TBE ..... Tick-borne encephalitis
PPA ..... Per-protocol analysis

1 Introduction

1.1 Background and Rationale

The human papillomavirus (HPV) vaccination coverage rate in Switzerland is below the target rate of 80% that has been set as a goal by the ministry of health. We assume that a multifaceted, targeted educational intervention with focus on teaching a presumptive announcement recommendation style on general practitioners (GPs) results in an increase of HPV vaccination (HPVv) rates in Swiss primary care.

1.2 Hypotheses

The primary study hypothesis is that a multifaceted, targeted intervention with a focus on teaching a presumptive announcement recommendation style will result in an increase of HPVv rates of patients aged 18 years and older in Swiss primary care. The analyses presented in this document will assess the efficacy of such an educational intervention aimed at GPs will be included in the final study report.

2 Study Methods

2.1 Trial Design

2.1.1 Study Population

The study population will consist of GPs working in practices in German-speaking Switzerland. Fulfilment of all inclusion-exclusion criteria will be reviewed by the investigator or qualified designee to ensure that subjects qualify for the study.

Inclusion criteria:

i) The GP works in the primary care setting.
ii) The GP has been providing vaccinations according to the Swiss ministry of health (recommended basic and recommended additional vaccinations) for at least six months in their practice before study start. In detail: combined measles, mumps and rubella (MMR), meningococci, pneumococci, HPV, tick-borne encephalitis (TBE), chickenpox, shingles, and hepatitis A/B (combination and single vaccinations).

Exception: GPs not registered in the cantonal HPVv program can be included if they are willing to join the programme and have the eligible patient population in their practice to administer vaccinations.

Note: 'Providing vaccinations' means that a GP (or the practice they work at) in principle offers the vaccination to the patients. There is no need for a minimum number of vaccinated patients in the last six

months before inclusion into the study. For example, GPs registered in the cantonal HPVv program can be included even if they have not administered any HPVv doses during the previous six months.

Exclusion criteria:

- The GP predominantly provides pediatric care (reported by the GP as >50% of consultations).
- The GP predominantly provides gynecological care (reported by the GP as >50% of consultations).
- The GP is a school physician or provides vaccinations on behalf of schools.

2.1.2 Interventions

This study will comprise two arms:

- **Control intervention group**: Participants will receive a general educational session about vaccinations, with no special focus on HPVv. Study participants allocated to this group will be blinded to the aim of the study to increase HPVv specifically.
- **Active intervention group**: Participants will receive an educational session that comprises a targeted, multifaceted intervention. It will consist of i) basic information about HPV and HPVv, ii) information about the announcement communication method in delivering vaccinations, and iii) information about logistics and administrative issues regarding the HPVv. In addition, this educational session will include the same general information about vaccinations as delivered in the control intervention group.

2.2 Randomization

Randomization will occur cluster-wise on level of the practices where the enrolled GPs work. A statistician external to the study group will carry out stratified randomization into the active or control intervention group using the Shiny Balancer tool, which facilitates balanced allocation in cluster-randomised trials (1).

Stratification will occur according to the following factors:

- Participation status in the cantonal HPVv program at inclusion (yes/no).
- Estimated number of HPVv administered during the baseline period (4 categories, see section 3.3.1).

GPs enrolling in the trial when randomization of their practice has already taken place will be allocated to the corresponding study arm. GPs will need to be registered in the cantonal HPVv program before initiation of outcome measurements.

2.3 Blinding

All study participants will be blinded to the respective other intervention. Study participants in the control intervention arm will be entirely blinded to HPVv being the specific topic of the study (i.e., all CRFs and questionnaires will ask information about HPVv together with information about other vaccinations, without emphasis on HPVv).

2.4 Sample Size

According to the study protocol (2), a sample size of 33 GPs, each recruiting 30 patients, will achieve a power of 80% at an alpha of 5% to detect a coverage change of +9.5% in the control group and of +14.9% in the active intervention group (according to a similar study (3))

2.5 Framework

This study is conceptualized as a superiority trial aiming to detect a difference between the active and the control intervention.

2.6 Statistical Interim Analysis and Stopping Guidance

Due to the lack of risks associated with the study interventions (2), we will include no stopping criteria nor interim analyses.

2.7 Timing of Final Analyses

We will perform a preliminary descriptive analysis of baseline characteristics of the study population upon transfer of the baseline data of the last included GP into OpenClinica. The final analysis of the study will be conducted after transfer of the last CRF into OpenClinica and after finalization and approval of this SAP.

2.8 Timing of Study Assessments

For each GP included into the study, we define the following timings:

- **Baseline period Pb**: A consecutive period of three months as recent as possible, but entirely before the intervention date Ti. Study participants will be asked to provide estimates of the number of HPVv doses administered during this period, which will be used for stratified randomization (see sections 2.2 and 3.3.1).
- **Intervention date Ti**: The day of delivery of the active and control intervention in the active intervention arm or of the control intervention in the control intervention arm. A questionnaire assessing knowledge on HPV and attitudes concerning HPVv will be administered at Ti, right before delivery of the intervention.
- **Study start T0**: The day of start of vaccination counting, usually scheduled on the 1st of the respective month following Ti. If Ti falls within the first week of a month, T0 is usually scheduled on the 15th of the same month.
- **Follow-up at T3, T6, and T12**: The dates at three, six and twelve months, respectively, after the study start T0. The questionnaire on HPV knowledge and HPVv attitudes will be delivered a second and final time at T6.
- **Study period**: The time interval between T0 and T6, which is the time interval relevant to the primary objective of the study.
- **Follow-up period**: The time interval between T6 and T12.
- **Study end:** The follow-up date T12, which indicates the end of all vaccination documentation.

3 Statistical Principles

3.1 Confidence Intervals and *p*-Values

We will report statistical significance as determined in statistical null hypothesis tests by means of *p*-values. A level of significance of 0.05 will be used throughout the analyses. Accordingly, we will report two-sided 95% confidence intervals of coefficient estimates.

We will use a mixed-effects regression model for assessment of the primary objective and we will base rejection of the null hypothesis (no difference in effect on HPVv counts at T6 between the control and

intervention group related to the study hypothesis (see section 1.2) on statistical significance of a specific fixed effect coefficient estimate (see section 4.2.3).

Secondary outcomes will be assessed in an exploratory manner, and no adjustment for multiplicity will be implemented. We will judge resulting *p*-values with appropriate caution and consider the corresponding effect sizes.

3.2 Analysis Populations

For each of the primary and secondary objectives, we will define an intention-to-treat analysis (ITT) population as the population of all GPs who underwent randomization, regardless of participation in the educational session at Ti and loss to follow-up.

For each of the primary and secondary objectives, a per-protocol analysis (PPA) population will include all GPs who participated in the educational session at Ti.

Handling of missing data in the ITT and PPA populations is described in section 4.3.

3.3 Variables and Measurements

This section describes the variables assessed during the study. The corresponding timings are described in section 2.8 and summarized in Table 1.

3.3.1 Baseline Data

GPs will be asked to provide the total number of vaccination doses administered during Pb for each of the vaccinations that will also be reported during the study and follow-up periods. GPs will be provided the choice among Never; Rarely (1–5 doses); Occasionally (6–10 doses); Regularly (at least 11 doses). For Pb, no information will be collected on demographic data of patients who obtained the vaccination or on whether the vaccinations were administered as first/second/third doses or booster vaccinations.

3.3.2 Outcome Measurements

GPs will document all vaccines administered to patients aged at least 18 years starting on T0 and ending on T12. We will provide enrolled GPs with separate standardized case report forms (CRFs) to report all vaccinations administered during the study period and the follow-up period, respectively. GPs will report the following vaccinations: HPV, MMR, meningococci, pneumococci, TBE, chickenpox, shingles, and hepatitis A/B (combination and individual vaccines). The GPs will send CRFs to the Institute of Primary Care every two months by mail. For the study period and the follow-up period, GPs will report age and sex of patients to whom these vaccines are administered. In addition, only during the study period, they will report whether vaccinations are administered as first/second/third doses or as booster vaccinations as well as whether they are administered upon request by the patient or as recommended by the GP. During the follow-up period, they will only indicate whether vaccinations are administered as first or later doses (without further specification).

3.3.3 Questionnaires

We will assess knowledge about HPV and HPVv and attitudes towards HPVv with a questionnaire administered at Ti (right before the educational session) and at T6. In order to preserve blinding of the control group with respect to HPVv, the survey will be the same for all participants and will include analogous questions about other vaccinations (herpes zoster, pneumococci, and TBE).

The HPVv-specific section of the questionnaire will comprise

– Nine questions on attitudes towards HPVv (4.1–4.9). Of these, 7 questions (4.1–4.3, 4.5–4.8) are Likert-type (levels Disagree/Rather disagree/Neutral/Rather agree/Agree), one is multiple-choice (4.4), and one is single-choice (4.9). Both the single- and multiple-choice question have a free-text option. The sections specific to all other vaccinations will contain the same questions.
– Five single-choice questions on knowledge about HPV (4.10–4.14). Of these, two questions (4.11, 4.12) consist of 7 sub-questions with respectively identical answer options each.

Table 1. Overview of study timings. The inclusion period refers to the time frame between approaching the GP for eligibility and delivery of the intervention.

Event/Variable	Inclusion period	Ti	T0	T3	T6	T12
Eligibility determination						
Recruitment						
Randomization						
Baseline characteristics of GPs						
Baseline HPVv count						
Questionnaires						
Delivery of intervention						
Start of HPVv documentation						
Reporting of HPVv documentation						
End of HPVv documentation						

4 Analysis

4.1 Objective Definitions

4.1.1 Primary Objectives

(1) To compare the first-dose HPVv counts at T6 between the intervention group and the control group.

4.1.2 Secondary Objectives

(1) To compare the first-dose HPVv counts at T3 and T12 between the intervention group and the control group.
(2) To compare the number of overall HPVv counts at T3, T6, and T12 between the intervention group and the control group.
(3) To compare the change of overall HPVv counts at T3, T6 and T12 with respect to Pb between the intervention group and the control group.
(4) To compare the change in HPV-related knowledge at T6 with respect to Ti (before delivery of the intervention) between the active intervention group and the control group.
(5) To compare the change in attitudes towards HPVv at T6 with respect to Ti (before delivery of the intervention) between the active intervention group and the control group.
(6) To describe demographic characteristics of patients obtaining HPVv (gender and age).
(7) To describe the following characteristics of administered HPVv: first dose or later vaccination, request of patient or recommendation by GP (or both), and HPVv administered alone or in combination with other vaccines.

4.2 Analysis Methods

4.2.1 Descriptive and Baseline Analyses

For all descriptive analyses, we will report counts and percentages for categorical variables and extreme values (minimum and maximum), means and standard deviations, and medians and upper/lower quartiles for continuous variables.

We will provide descriptive summaries for demographic characteristics of participating GPs (age, gender, years of experience in practice, type of practice, type of employment, and workload) and for characteristics of patients who will be administered HPVv (age and gender).

To assess differences in baseline characteristics of GPs in the ITT population among the study arms, we will use Pearson's chi-squared and Fisher's exact tests for categorical variables and Student's *t*-tests and Wilcoxon rank-sum tests for continuous variables as appropriate. The same tests will be performed to assess differences between GPs of the ITT population and GPs lost to follow-up.

We will assess differences of HPVv counts during the study period between the study arms using Pearson's chi-squared and Fisher's exact tests. Cochran Armitage trend test will be used for comparison of HPVv counts between the study arms using the measurement time point as an ordinal variable (with levels T3, T6, T12).

4.2.2 Analysis of Questionnaire Responses

We will provide descriptive summaries of the questionnaire answers to all vaccinations at Ti (before delivery of the intervention) and T6. No stratification into study arm will be implemented. Answers to questionnaire items containing free-text options will be categorized in either one of the provided answer options, if applicable, or as "other answer".

For questionnaire items expressed as Likert-type scales, we will assign integer scores to the responses ranging from 1 for "Disagree" to 5 for "Agree". We will provide a measure of internal consistency by means of Cronbach's alpha. The test-retest reliability will be assessed by calculating Pearson correlation coefficients between each GP's summated scores at Ti and T6, in each study arm separately.

For each GP, we will calculate an HPV knowledge score as the sum of all correct answers to the knowledge-related questions as well as an HPVv attitude score as the sum of all Likert-type answer scores to the attitude-related questions. We will use Wilcoxon signed-rank tests to assess for differences in HPV knowledge and HPVv attitude scores between Ti and T6.

4.2.3 Analysis of the Primary Objective

To analyze the primary objective, we will model the count of first administered HPVv doses at T6 using mixed-effect Poisson regression. The outcome variable will be the count of first HPVv doses administered by each GP at each of the time points T3 or T6. GP-level random intercepts will account for intra-GP correlation. The following fixed effects will define the grouping variables of the data set:

- Study arm (binary with levels control; active)
- Time point (binary with levels T3; T6)
- Baseline HPVv count (categorical with levels Never; Rarely (1–5 doses); Occasionally (6–10 doses); Regularly (at least 11 doses))
- GP gender (binary with levels male; female)
- GP age in years (continuous)
- GP workload (categorical with levels < 60%; 60–79%; 80–100%; based on the distribution of consultation counts according to workload in Swiss primary care (4))
- GP participation status in the cantonal HPVv program at inclusion (binary with levels yes; no)
- Patient gender (binary with levels male; female).

Each fixed effect other than the study arm will be included in the final model if a corresponding univariate analysis results in a p-value ≤ 0.2.

The Poisson regression model will be assessed for overdispersion based on an asymptotic chi-squared test for the sum of squared residuals (5, 6). If the null hypothesis of no overdispersion is rejected at the 0.05 level, we will replace the Poisson model by a negative binomial model with the same fixed- and random-effect structure. A quasi-Poisson model will be considered as an alternative in case of an observed linear variance-to-mean relationship (7).

Rejection of the null hypothesis related to the primary objective (the effect associated with the study arm is equal to zero) will be based on the parameter estimate of study arm and its 95% confidence interval in the final model.

4.2.4 Analysis of the Secondary Objectives

For the secondary objectives, we will use the following procedures:

(1) Analogous models as for the primary objective, using the first HPVv dose count at the respective time point and assessing the coefficient estimate of the study arm together with 95% confidence intervals.
(2) Analogous models as for the primary objective, but using the count of all administered HPVv doses instead of the number of first HPVv doses at the respective time points as the outcome variable. We will base assessment of this objective on the estimated coefficient of the study arm for the respective time points together with 95% confidence intervals.
(3) We will model this objective with logistic regression. The binary outcome variable will indicate whether the overall count of administered HPVv doses at T6 will have increased with respect to the value indicated for Pb. Model covariates will include GP gender, workload (categorized as for the primary objective), and participation status in the cantonal HPVv program at inclusion.
(4) To assess this objective, we will use logistic regression on a binary outcome indicating, for each GP, whether their HPV knowledge score will have increased from Ti to T6. The model will include the following covariates: study arm, baseline HPV knowledge score, GP gender, GP workload (categorized as for the primary objective), and participation status in the cantonal HPVv program at inclusion.
(5) We will assess this objective by a logistic regression model analogous to the model for secondary objective 4. The binary outcome variable will indicate, for each GP, whether their HPVv attitude score will have increased from Ti to T6. Adjustment will occur for the baseline HPVv attitude score instead of the HPV knowledge score.
(6) Tabulation and assessment of group differences as described in section 4.2.1.
(7) Tabulation and assessment of group differences as described in section 4.2.1.

For each of the fitted regression models, we will report the results and inferred implications of standard model diagnostics procedures, such as assessment for overdispersion, residual and random effect analyses, influential point analyses, and checks for multicollinearity. Accordingly, we will adapt models as necessary (e.g., by log-transforming continuous variables, by excluding ill-defined variables from the model equations or by considering non-parametric alternatives where deemed appropriate).

4.2.5 Sensitivity Analyses

We will conduct all analyses described in sections 4.2.1 to 4.2.4 on the ITT population. Analyses of the primary and secondary study objectives will be repeated on the PPA population.

In addition, we will repeat analysis for the primary study objective by using a random-effect structure consisting of GP-level random intercepts nested within practice-level random intercepts to assess for clustering due to GPs working in the same practice.

Sensitivity analyses related to missing data are described in section 4.3.

4.2.6 Subgroup Analyses

We will conduct a subgroup analysis for the baseline HPVv count by repeating the primary outcome analyses on data sets restricted to the categories of baseline HPVv count as defined in section 3.3.1. We will report the estimated coefficients together with 95% confidence intervals.

4.3 Missing Data

Missing data may potentially occur on two levels:

- GPs: baseline (including demographic) characteristics, failure to undergo the intervention, failure to return CRFs (including loss to follow-up) or questionnaires.
- Patients (data from the CRFs): demographic characteristics, type of vaccination.

To analyze the study objectives, we will use the following procedures to handle missingness in the ITT and PPA population data sets:

- Loss to follow-up of GPs: complete-case analysis.
- Missing baseline characteristics of GPs and missing patient-level characteristics: complete-case analysis.

For each study objective, we will conduct a sensitivity analysis on the IIT population using multilevel chained equations-based multiple imputation with 5 datasets and 20 iterations. We will restrict use of multiple imputation to this sensitivity analysis and use a complete-case approach for the main analysis due to the low anticipated drop-out rates (2).

For other analyses not belonging to a study objective, we will handle missing data by pairwise deletion (i.e., by omitting only cases with missing values of variables relevant to the current analysis).

The nature and frequency of missing data will be reported for all analyses. Differences in loss to follow-up frequencies between the study arms will be assessed using Pearson's chi-squared and Fisher's exact test.

4.4 Data Management

The received paper clinical report forms (CRFs) will be handled as source data. Data concerning administered HPVv doses will be transcribed from the paper CRF to a digital database using the software OpenClinica version 3.11 (OpenClinica LLC and collaborators, Waltham, MA, USA, www.OpenClinica.com). OpenClinica is a well-established and GCP-conform clinical data management system. An audit trail is available within the software.

The study nurse will transcribe data from the pen-and-paper CRFs, baseline and follow-up questionnaires into OpenClinica. Another member of the study team will validate all transcribed data manually, and a further member of the study team will conduct sample checks. OpenClinica will run on a separate computer with no network connection (due to security reasons) located in the Institute of Primary Care of the University of Zurich. To gain access to the software and to the data a password will be needed and available to selected members of the study team only. All users of the software will be granted specific rights (for example, the study nurse will be allowed to enter data but not to edit or export it). The study statistician will not be granted access to OpenClinica. Backups of the data will be stored on a computer connected to the network of the University Hospital Zurich.

A member of the study team will provide the statistician with anonymized data exports from OpenClinica in form of comma-separated values files and Excel spreadsheets (Microsoft Excel, Microsoft Corporation, Redmond, WA, USA, https://office.microsoft.com/excel) after blinding for the study arm.

4.5 Statistical Software

Statistical analysis will be performed with the software R version 4.1.0 or higher (R Foundation for Statistical Computing, Vienna, Austria) (8).

5 Safety Analyses

This study will include no safety analyses, since no safety data collection will be required (2).

6 Reporting Conventions

For summary statistics, we will use one decimal place more than for the data from which they originate. We will make exceptions were deemed appropriate, such as for reporting of extremal values, where we will use the same number of decimal places as for the data from which they originate.

We will report quantities derived from regression models (coefficient estimates with confidence intervals and variance estimates) and values of test statistics up to three decimal places. We will report *p*-values of at least 0.001 up to three decimal places, and *p*-values smaller than 0.001 as "< 0.001".

7 Summary of Changes to the Protocol

The following points needed changes with respect to indications in the study protocol:

- Included GPs will not be asked for a precise number of administered vaccinations during Pb, but will provide a categorical estimate.
- Accordingly, the primary and secondary outcomes will not compare changes from T0 to the respective time points, but will assess the absolute HPVv uptake between T0 and the respective time points.
- Duration of Pb will be reduced from 6 months to 3 months due to practicability reasons.
- Accordingly, to ensure comparability with HPVv numbers during the baseline period, the measurements at 2 and 4 months after T0 will be replaced by one single measurement at 3 months after T0.

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