Quality Control & Audit Committee Annual Report Season 2019/2020

DRIVE

Development of Robust and Innovative Vaccine Effectiveness

QCAC – Quality Control & Audit Committee

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Version	Date	Description
V0.1	06 July 2020	First QCAC draft
V0.2	21 July 2020	Second QCAC draft prior to SC review
V0.3	04 Sep 2020	Third draft following SC review

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List of abbreviations

DMP	Data Management Plan
DMR	Data Management Report
DQR	Data Quality Report
DRIVE	Development of Robust and Innovative Vaccines
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
ESSA	Electronic Study Support Application
GPP	Good Pharmacoepidemiology Practice
QCAC	Quality Control and Audit Committee
SAP	Statistical Analysis Plan
SC	Steering Committee
SOP	Standard Operating Procedure
WP	Work Package

Executive summary

Why has a Quality Control and Audit Committee been set up in DRIVE and what are they doing?

Through a **public-private partnership**, DRIVE aims to build a sustainable study platform to generate robust brand specific influenza vaccine effectiveness estimates for all influenza vaccines used in the European Union (EU) each season. **The data generated through DRIVE is expected to increase the understanding of influenza vaccine effectiveness, lead to enhanced monitoring of influenza vaccine performance by public health institutes and allow manufacturers to fulfil regulatory requirements.**

To guarantee the scientific independence of the studies, the role of each partner is clearly defined and traceable. As part of the study platform, two committees have been established – the **Independent Scientifc Committee (ISC)** and **Quality Control and Audit Committee (QCAC).** Vaccine manufacturers provide written comments on the scientific deliverables to the ISC who evaluates and endorses them. Since Vaccine manufacturers are responsible for the quality of what they are reporting to European Medicine Agency (EMA), the QCAC has been set up with quality control and assurance experts from manufacturers partners. Their mission is to evaluate the quality of the study conduct, data reporting and the pooled analysis, in order to further ensure that reliable data are delivered or if necessary, identify the areas for improvement.

At the site level, the focus of the QCAC evaluation is on quality management. It is not an assessment of the scientific integrity of the sites' study design neither analysis nor interpretation of the study results. Rather, the QCAC evaluates compliance with regulatory quality requirements, quality of data collected from study sites, availability of procedures describing these processes and related documentation. The sites participating in the DRIVE study platform are **independent researchers public sector providing data** to fulfil the pooled analysis objective of DRIVE. Because the sites are otherwise not subject to the specific quality mechanisms applicable to manufacturers as per regulatory requirements, the QCAC is thus seeking for reasonable and feasible mechanism to enhance the quality management. The **QCAC aims to provide guidance and support sites** to get the relevant study documentation and quality management system in place to ensure that reliable observational data are integrated into the pooled analysis and that activities are in place at site level to prevent, detect, correct and control potential errors.

Within the 5 year project, it is planned that the QCAC will develop, adjust and integrate each year the lessons learnt from the sites evaluation and their feedback to get a comprehensive adequate picture and what could be requested to sites in a context of observational studies to satisfy EMA regulatory requirements imposed to vaccine manufacturers partners of DRIVE.

Based on the **first-year evaluation QCAC made several recommendations to the sites for the season 2019-20:**

<u>Study protocol development and management</u>:

1. The Ethical Committee (EC) approval or Institutional Review Board (IRB) documentation should be appropriately stored or a rationale for a waiver well documented.
2. Study sites should have a documented process of managing protocol deviations and a documentation in case of actual protocol deviation, including the EC/IRB feedback, if applicable. In case of protocol deviation, the site should promptly inform the DRIVE WP7 thus allowing to evaluate the potential impact for the pooled analyses. DRIVE will provide some guidance to harmonise the identification of protocol deviation and reporting of protocol deviation and will provide it to the sites.

Personnel qualifications and Training records:

3. Professional qualifications of core study team members should be documented in their Curriculum Vitae (CV) and evidence of the qualifications should be appropriately stored and available in case of audit, E.g. training certificates, licences, registration number, etc.

4. Job descriptions should be available for each core study team member or at minimum, a description of delegated activities within the study which can be compared to the professional qualifications.

Data Management specifications:

5. A report for data management will have to be completed by the sites. DRIVE will provide a template that can be used to provide the critical information regarding the approach used for data management. This report is expected to contain amongst others, a written procedure describing the flow of the research data from acquiring, validating, storing and processing of data to ensure the accessibility, reliability and timeliness for users.

1. Publishable summary

This is an annual report covering the 2019/2020 season which summarises the improvements incorporated from the 2018/2019 season and the activities performed and findings and recommendations of a remote quality evaluation of sites that have participated in DRIVE during this period and of central processes in relation to the pooling of the data and analysis of the results by P95, a public partner in DRIVE.

The QCAC evaluation is performed in order to determine whether there are any limitations from a quality perspective which may have impacted quality of the study conduct, data reporting and the pooled analysis. The evaluation focused on study conduct which incorporates compliance with regulatory requirements, quality of data collected from study sites, availability of procedures describing these processes, maintenance of documentation and data reporting including the key deliverables generated by P95 and the pooled analysis. The evaluation is focused on quality management systems and is not an assessment of the scientific integrity of the sites' study design and analysis and interpretation of the study results.

The review was conducted by developing a four-step workplan:

- Step 1 activities consisted of a review of the Quality Management Questionnaire (designed to perform evaluations of site studies' quality and feasibility) developed by Work Package 3 (WP3), which local study sites conducting vaccine effectiveness surveillance were requested to complete. QCAC designed a quality checklist to conduct a quantitative assessment of each of the questionnaire responses provided by the study sites. The quality checklist included a scoring system applied to each of the questions determined to have an impact on the overall study evaluation.

- Step 2 activities consisted of an evaluation of P95 processes used on data provided by the sites and was performed via a review of the Data Quality Reports (DQRs) for compliance against the Data Management Plan (DMP) and Minimal Data Requirements as defined in the Statistical Analysis Plan (SAP).

- Step 3 consisted of a plan to conduct an evaluation of P95 processes used to perform the pooled analysis and develop the report.
- Step 4 consisted of a review of the implementation of recommendations made from the 2018/2019 season QCAC evaluation.

Eleven (11) out of 14 sites responded to the Quality Management Questionnaire. The responses from the study sites provided an indication of the standards of each responding site's quality management and no issues were identified to trigger a recommendation for a site visit or a formal audit.

Recommendations for improvement will be made primarily in the areas of Data Management regarding maintenance of technical specifications of the site-level study specific database, the use of standard forms to collect original data for the vaccine effectiveness studies and the maintenance of a report to document events or changes which occurred during the study conduct in relation to the study database. The review enables a high-level assessment of the quality management systems in place at each site and the site's understanding of good research practices, but as the responses and the content of documents such as local SOPs cannot be verified, the limitations of this type of review must be acknowledged.

The documents provided to QCAC by P95 were in compliance with the principles for Data Management and Reporting as described in Guidelines for Good Pharmacoepidemiology Practice (GPP) (2016). No major concerns were identified regarding the content of the DQRs.

Key Recommendations:

- The 2018-19 QCAC annual report recommended an independent evaluation to be carried out of P95 processes by a Data Management / Programming/ Biostatistics expert with a focus on the set-up of the software (ESSA), data transfer processes, generation of the datasets/listings and pooled analysis. Due to COVID-19 pandemic and other priorities engaged in the project; it has been decided to re-discuss that for the season 2020-21. Five sites had greater than 10% of data excluded from the data analysis for not meeting the required criteria (refer to § 6.2 §6.3 and §6.4 for more details on Step 2). It is recommended this is explored by the SC and P95 whether this is in relation to technical constraints in relation to collection/upload of data or sites' understanding of study protocol and DRIVE Data Management requirements.

The conclusions and recommendations will be discussed with the Steering Committee and WP 3 including improvements required for future seasons.

2. QCAC composition

Clinical Quality Assurance Representatives:

- Ann-Marie KIRBY (GlaxoSmithKline)
- Claire POPE (Seqirus)
- Sophie GILLES (Sanofi Pasteur)

3. Mission

The mission of the QCAC is to evaluate the quality of the study conduct, data reporting and the pooled analysis. The QCAC will assure that reliable data are delivered to the Independent Scientific Committee, to the Steering Committee (SC) and ultimately to European Medicines Agency (EMA).

4 Methods

The QCAC evaluation was performed in order to determine whether there were any limitations from a quality perspective which may have an impact on the study results or compliance to applicable requirements.

A workplan was developed by QCAC and states a commitment to approach the quality evaluations in 4 steps as summarised below:

- Evaluation of the quality of the study conduct for compliance with regulatory standards, site protocols and local SOPs based on the quality of information collected from the sites in their responses in the "DRIVE Quality Management Questionnaire" during the influenza season".
- Evaluation of P95 processes used on data provided by the sites: review of the DQRs for compliance against the Minimal Data Requirements as defined in the SAP.
- Evaluation of the quality of the data analysis for compliance with the SAP through review of the pooled analysis report produced by P95.
- Review of the implementation of recommendations made from the 2018/2019 season QCAC evaluation.

5 Step 1: Evaluation of the quality of the study conduct

Site-specific results of the quality assessments will be shared with each individual site participating to the DRIVE studies in September 2020. Where the evaluations are indicative of sub-optimal or deficient quality management systems/processes, then recommendations to perform improvements and/or additional quality related activities are provided to the study sites individually. In the event that overall QCAC evaluation of the individual study sites identifies critical impact to study results or compliance to applicable requirements, then QCAC would advise the DRIVE SC that a site visit or an audit would need to be conducted by a third party.

Methodology used to perform the evaluation was performed via a Quality Management Questionnaire amended from the 2019 questionnaire and composed of a total of 62 questions (mostly multiple choice) covering the following 7 section categories:

1. Protocol Development and related documents
2. Personnel and Training
3. Data Management
4. Document Management
5. Compliance
6. Security and confidentiality
7. Ethics and Ethics Committee

WP 3 and QCAC improved the questionnaire from the 2018/2019 version based on feedback from the sites and lessons learned from the 2019 analysis of the survey responses to focus the questions on key compliance areas. The aim of the questionnaire remained the same as the previous season - to inquire about the quality management systems and processes established at organizational/ functional and study levels at each site. Fourteen (14) study sites participated in the 2019/2020 DRIVE season and eleven (11) study sites responded to the Quality Management Questionnaire. The three (3) sites that did not respond this year: ISS (responded last year), Luxemburg (did not respond on time last year) and La Paz is new participating site this year.

Confidential web-questionnaires were issued to study sites listed as DRIVE study participants with acknowledgement of the fact that local study conduct may involve (collaboration across) multiple local parties. Involvement of those parties was left to the discretion of the participating study sites to support the response to the questionnaire. It was requested that each organization reflect in their responses how they apply their various respective quality management related activities performed in the context of the influenza vaccine effectiveness studies, i.e., if an institution also conducts clinical trials or vaccine safety monitoring, they were requested not to reflect quality management for those activities in their responses (unless these also apply to the influenza vaccine effectiveness studies).

For the majority of questions, a follow-up field was offered where additional information could be provided in free text to invite further explanation to aid QCAC understanding of the situation. Where descriptions were requested, sites were asked to include the key elements in 5 to 10 sentences.

5.1 Method of evaluation of questionnaire results

QCAC designed a quality checklist to assess each of the questionnaire responses provided by the study sites. The quality checklist consisted of a scoring system applied to each of the questions determined to have an impact on the overall study evaluation. The scoring system methodology utilized in 2019 was simplified to a colour-coding, 'Green/Amber/Red/Unable to Assess' system. The scoring criteria are provided in ***Table 1***.

Table 1. Quality management questionnaire response results - scoring criteria

Level of Control	Score
Green – suitable level of control/best practice	1
Amber – some level of control but improvements could be made	1
Red – unsuitable level of control	1
Response missing/unable to assess	0
Question with no impact on the evaluation (pre-identified by QCAC) *	N/A (Not Applicable)

*Questions pre-identified by QCAC as having no impact on the evaluation: Q1, Q5 and Q46.

A number of questions related to collaboration across multiple partnering entities/commercial parties outside the site's organization were also scored N/A if no other parties were involved. These were Q13, Q14, Q15, Q44, Q54 and Q58. (refer to Appendix 1)

For repeat responder sites, answers from the 2019 survey were assessed based on the information provided in the 2020 survey response: Q10 to Q15, Q17 to Q20, Q27 to Q29, Q34 to Q44 and Q46 to Q56.

For each site A score of 1 was applied to each predefined category (Green/Amber/Red) and 0 when Unable to Assess (Table 2, Quality management results per site). These were agreed by QCAC and documented in the quality checklists.

When the web-questionnaire responses were received by QCAC (12th May 2020), they were randomly divided and distributed amongst QCAC members ready to be evaluated. Moderation of the questionnaire response results was subsequently performed together by the QCAC to ensure consistency, alignment and fairness of the questionnaire response evaluations.

The overall outcome of each site was assessed as Good, Average or Insufficient (criteria provided by the SC) and the results for the hospital setting-based sites were incorporated into the DRIVE 2020-2021 Call for tender Evaluation Template to be assessed as part of the site selection process.

5.2 Results of Step 1 Evaluation

The results of the Step 1 evaluation are summarized in ***Table 2*** and ***Table 3***. As the number of questions answered differed across the sites e.g. depending on whether the site was new to the DRIVE initiative this year and questions which did not always require a response (e.g. whether informed consent or ethics committee approval was required) the results of the QCAC assessment are presented as absolute number of responses assessed and percentage of responses assessed as Red/Amber/Green/Not Able to Assess. The QCAC overall assessment of each site – Good/Average/Insufficient, (based on the criteria provided by the SC as part of the call for tender – sites selection process) is also presented in ***Table 2***.

The overall response rate was 79% with 11 of the 14 sites responding. No critical concerns were identified from the questionnaire results. Thirteen (13) of the 14 sites had an overall assessment as "Good" with 76% or more of the responses assessed as "Green" (Suitable level of control/best practice). One site (MUV) was assessed as "Average" with 65% of responses assessed as "Green" and 25% "Unable to Assess" where the respondent had not provided a response to several questions.

Table 2. Quality Questionnaire QCAC Assessment Score Results Per Site

Study Sites that Provided a Response to the Quality Questionnaire	QCAC Assessment Score Results			
	Number of responses assessed as "Red"	Number of responses assessed as "Amber"	Number of responses assessed as "Green"	Number of responses assessed as "Not able to assess"
Spain - Val D'Hebron University Hospital, (VHUH)	5	2	35	0
Italy -CIRI-IT BIVE	0	0	46	0
Spain - University Hospital Germans Trias I Pujol (HUGTP)	4	3	32	3
Spain - FISABIO	0	3	43	1
France, INSERM REIVAC	1	1	46	0
Austria - Medical University Vienna (MUV)	2	3	31	12
Italy - CIRI-IT GP	0	0	46	0
Finland - Helsinki University Hospital (HUS)	1	3	43	1
Romania - National Institute Infectious Disease (NIID)	0	0	43	0
Finland - National Institute Health & Welfare (NIH THL)	3	1	31	0
UK, University of Surrey, RCGP	2	4	31	0

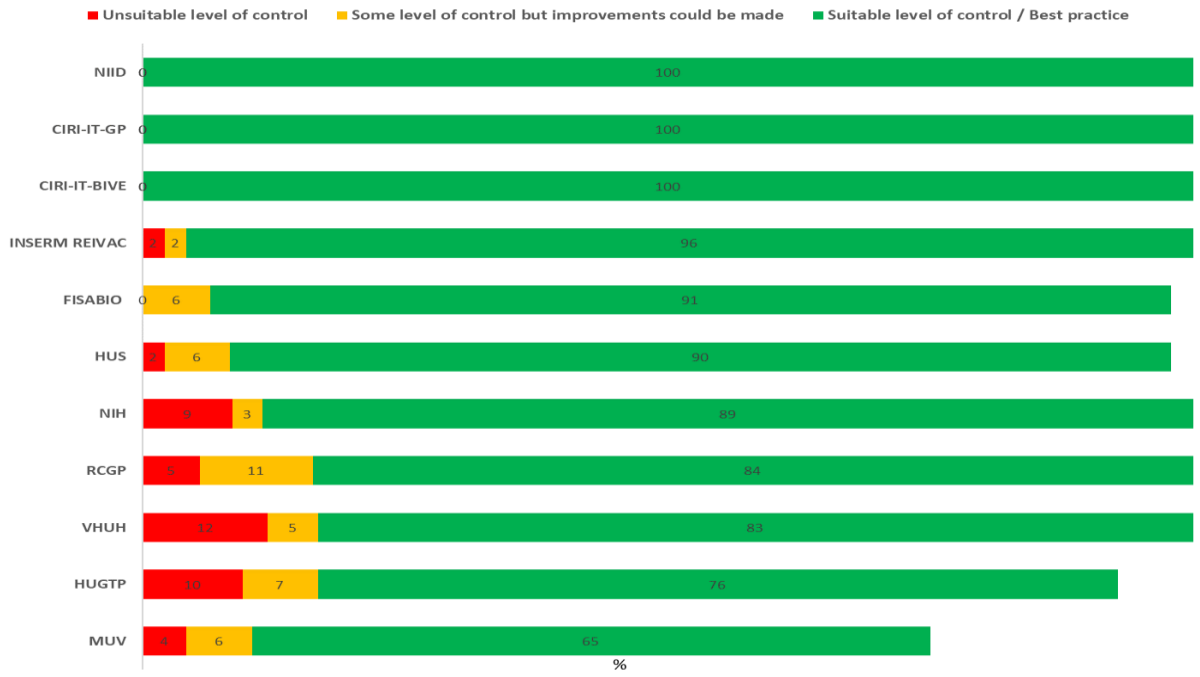
Responses were not provided by the following 3 sites: ISS (responded last year), Luxembourg (did not respond on time last year) and La Paz (new participating site this year).

Table 3. Quality Questionnaire QCAC Assessment Score Results Represented as Percentage and Overall Rating of Site

Study Sites that Provided a Response to the Quality Questionnaire	QCAC Assessment Score Results Represented as a Percentage (%)				Overall Site Rating (Good / Average / Insufficient)
	Unsuitable level of control "Red"	Some level of control but improvements could be made "Amber"	Suitable level of control / Best practice "Green"	Not able to assess	
Spain - Val D'Hebron University Hospital, (VHUH)	12	5	83	0	Good
Italy -CIRI-IT BIVE	0	0	100	0	Good
Spain - University Hospital Germans Trias I Pujol (HUGTP)	10	7	76	7	Good
Spain - FISABIO	0	6	91	2	Good
France, INSERM REIVAC	2	2	96	0	Good
Austria - Medical University Vienna (MUV)	4	6	65	25	Average
Italy - CIRI-IT GP	0	0	100	0	Good
Finland - Helsinki University Hospital (HUS)	2	6	90	2	Good
Romania - National Institute Infectious Disease (NIID)	0	0	100	0	Good

Study Sites that Provided a Response to the Quality Questionnaire	QCAC Assessment Score Results Represented as a Percentage (%)				Overall Site Rating (Good / Average / Insufficient)
	Unsuitable level of control "Red"	Some level of control but improvements could be made "Amber"	Suitable level of control / Best practice "Green"	Not able to assess	
Finland - National Institute Health & Welfare (NIH THL)	9	3	89	0	Good
UK, University of Surrey, RCGP	5	11	84	0	Good

Figure 1. . Quality Questionnaire QCAC Assessment Score Results Represented as Percentage Per Site



Details of the questions assessed as Red or Amber per site are presented in **Appendix 2**.

5.3 Recommendations for Step 1 evaluation

Seven (7) of 11 sites provided 18 responses assessed as Red.

Data Management section totalized 9 Red responses from 6 sites. The following is recommended:

- the maintenance of technical specifications of study specific database (Q25)
- the use of standard forms to collect original data for the vaccine effectiveness studies (Q19)
- the maintenance of a report to document events or changes which occurred during the study conduct in relation to the study database (Q23).

The 6 remaining sections totalized 9 Red responses. The following is recommended:

- **Document management** (2 Red responses to Q27): the sites should define which documents to retain in the study archive.

- **Protocol development** (2 Red responses to Q2 & Q7): the sites should have written procedures for protocol development and use a standard protocol template for the vaccine effectiveness studies.
- **Personnel & Training** (2 Red responses to Q11 & Q12): Job descriptions should be available, and the sites should also document the study specific roles and responsibilities of the study team members.
- **Compliance** (2 Red responses to Q31 & Q33): the sites should be familiar with the "DRIVE Guidance on Protocol deviations" and internal or external inspections should be conducted to ensure compliance of vaccine effectiveness studies with regulations.
- **Security & Confidentiality** (only 1 Red response to Q42): the sites should make sure that the study team members signed a confidentiality agreement (as part of their employment contract or as separate agreements).

No Red responses were noted in section **Ethics and EC**.

Five (5) sites provided answers assessed as Amber in the **Document management** section (Q28). The standard list of documents to be archived for a typical study was not provided.

5.4 Conclusion for Step 1 evaluation

Quality Management questionnaire responses from the study sites provided an indicative assessment of each responding site's quality management systems, no issues were identified to trigger a recommendation for a site visit or a formal audit. Ten (10) of the 11 sites had an overall assessment as "Good" and 3 sites will receive no recommendations with 100% of responses assessed as Green. Recommendations for improvement are mainly in the area of Data Management. The simplified and more focussed Quality Questionnaire utilized for 2019/2020 facilitated an increased focus on key compliance areas.

The review enables a high-level assessment of the quality management systems in place at each site and the site's understanding of good research practices, but as the responses and the content of documents such as local SOPs cannot be verified, the limitations of this type of review must be acknowledged.

6 Step 2: Evaluation of the P95 processes on the data provided by the sites

6.1 Method of evaluation of DQRs

The evaluation for the 2018/2019 season was performed by review of the following documents:

- DQRs for 13 sites.

The documents were reviewed to evaluate the following:

- Formatting, consistency and content.
- Planned methodology and results.
- DQRs were produced in line with the requirements set out in the Data Management Plan.
- DQRs were produced in line with the principles for data management and reporting as described in the "Guidelines for Good Pharmacoepidemiology Practice (GPP)" dated 2016.
- Each site provided data that can be retained for the analysis (focusing on the attrition diagram available in each DQR).

Out of scope of QCAC Review:

- Review of data listings and data listing quality checks.
- Assessment of P95 associated procedures for data management, analysis and reporting.

6.2 Results for Step 2 evaluation

6.2.1 Outcome of review of DQRs

Table 4. Criteria for Review of the DQRs

Criteria for Review	
General consistency and formatting – document dated, version controlled, version history listed, and author identified.	All Criteria Satisfied
Description of data quality check issues and how they were resolved e.g. duplicates, missing data, minimal data requirements not met, data exclusions etc.	
Datasets generated as per section 9.2 of the DMP*.	
Consistency check between Table 3 (Data for Analysis Characteristics) and Figure 2 – (Visuals)	
Sample spot check - Do numbers in tables correspond to numbers stated in text?	
Tables and Figures contain clear and unambiguous headings and legends	
Narrative of the report matches information provided in Tables and Figures	
Clear identification of study design within the report	
Clear identification of what data will be retained for the statistical analysis.	

*Dataset requirements as per section 9.2 of the DMP:

- Table of outcomes by covariates (sex, age group, chronic condition, pregnancy, number of GP visits, number of hospitalizations, vaccination status previous year, vaccine brand) by influenza strain (A unspecified, A(H1N1), A(H3N2), B unspecified, B(Vict), B(Yam), Non-influenza, A, B, All)
- Table for DQR (total number of subjects, number of subjects with influenza, number of vaccinated subjects)
- Histogram of covariates by controls/cases (case-control studies) or exposed/unexposed persons (cohort studies)
- Histogram of cumulative number of vaccinations over time
- Histogram of infections over time
- Pie chart with distribution of vaccine brands.

All DQRs satisfied the criteria as evaluated above.

Other points evaluated by QCAC are as follows:

1. Helsinki University Hospital (HUS). Number of influenza cases given as 28, whereas attrition diagram mentions 25. High number of data exclusions – 32% of subjects outside of influenza season and 60% of records excluded from the data analysis.
2. INSERM. 13% of subjects excluded from the analysis due to being outside of influenza system.
3. La Paz University Hospital (LPUH). 14% of subjects excluded from the analysis, mainly for “respiratory specimen taken >= 8 days outside the influenza system.”

4. Medical University Vienna (MUV). 24% subjects excluded from the analysis due to being outside of influenza season.
5. National Institute Infectious Disease (NIID). The calculations to summate the total number of cases beneath Influenza A and Influenza B are not correct.
6. FISABIO. 15% of subjects excluded from the data analysis mainly for "missing vaccination status or date."

6.2.2 Review of the attrition diagrams in the data quality reports

Table 5. Outcome of review of attrition diagrams from DQRs

Site	Number of records received	Outside of influenza season	Excluded from analysis *(per exclusion criteria)*	Discarded from analysis *(per missing information)*	Number of records for analysis	Percentage of records used in analysis
Italy -CIRI-IT BIVE	1805	77	62	16	1650	91.4
Italy - CIRI-IT GP	1521	126	5	22	1368	89.9
Finland - National Institute Health & Welfare (NIH THL)					100,942	
Finland - Helsinki University Hospital (HUS)	213	69	1	15	128	60.1
France, INSERM REIVAC	442	56	1	6	379	85.7
Italy, Instituto Superiore di Sanita (ISS)	2033	81	0	25	1927	94.8
Spain - La Paz University Hospital (LPUH)	122	3	17	7	95	77.9
Austria - Medical University Vienna (MUV)	1953	468	99	27	1359	69.6
Romania - National Institute Infectious Disease (NIID)	903	95	4	5	799	88.5
UK – University of Surrey, RCGP	350	25	3	5	317	90.6
Spain - FISABIO	941	66	63	147	665	70.7
Spain - University Hospital Germans Trias I Pujol (HUGTP)	204	8	14	0	182	89.2
Spain - Val D'Hebron University Hospital, (VHUH)	312	22	2	0	288	92.3
TOTAL	**10799**	**1096**	**271**	**275**	**9157**	**84.8***

**excluding THL/NIH, where no data attrition diagram is produced as per the SAP.*

6.2.3 Outcome of the review of the attrition diagrams from DQRs

Initial quality checks were performed by the study sites prior to the P95 data quality checks and the production of the attrition diagrams.

Attrition diagrams were included in 13 study site DQRs produced by P95 which display that data quality

checks were performed on a total of 10,799 records received. From these records, 9,157 (84.8%) were retained for statistical analysis after applying inclusion/exclusion criteria. Individual DQRs display a range of 60.1% - 94.8% acceptable data records.

The following anomalies are highlighted by QCAC from Table 6 above:

- Five (5) sites – HUS, INSERM, LPUH, MUV, FISABIO had greater than 10% of their records excluded from the data analysis with 40% of the records excluded for HUS.
- Discrepancies within the data attrition diagrams for two sites (HUS and NIID).

6.3 Recommendations for Step 2 evaluation

The following is recommended:

1. The 2019 QCAC annual report recommended an independent evaluation to be carried out of P95 processes by a Data Management / Programming/ Biostatistics expert with a focus on the set-up of the software (ESSA), data transfer processes, and generation of the datasets and data listings. Due to the COVID-19 pandemic and other priorities engaged in the project; it has been decided to re-discuss that for the season 2020-21.

2. Five (5) sites which had greater than 10% of data excluded from the data analysis for not meeting the required criteria. It is recommended this is explored by the SC and P95 whether this is in relation to technical constraints in relation to collection/upload of data or sites' understanding of study protocol and DRIVE Data Management requirements.

6.4 Conclusion for Step 2 evaluation

1. The DQRs have been produced in line with the requirements set-out in the DMP and the SAP.

2. Five (5) sites which had greater than 10% of data excluded from the data analysis for not meeting the required criteria. It is recommended this is further explored by the SC and P95.

7 Step 3: Evaluation of the pooled analysis

Evaluation of the quality of the data analysis for compliance with the SAP through review of the pooled statistical analysis report produced by P95.

According to P95, the scripts used in the 2019/2020 season were largely based on those developed for the 2018/2019 season. In the 2018/2019 season the scripts were developed and reviewed by two P95 statisticians. In the autumn of 2019, the scripts were then subsequently streamlined by a P95 IT engineer and these changes were subsequently reviewed by a P95 statistician. During 2020 only some minor additional changes were made (e.g. relabelling of some figures). To ensure data integrity and to have a change log the codebase has been tracked using a version-control system (git) since March 2020.

For the season 2020-21, it is planned to conduct an independent evaluation of the P95 processes which will be carried out by a Data Management / Programming/ Biostatistics expert and will focus on the set-up of the software (ESSA), data transfer processes, generation of the datasets/listings and pooled analysis. This independent evaluation will be part of the investment into the sustainability of the study platform

8 Step 4: Review of the adoption of QCAC 2018/2019 Recommendations

- Recommendation 1:
  - Third-party Data Management/Programming/Biostatistics expert(s) to conduct an evaluation of P95 processes (set-up of the software (ESSA), data transfer, datasets and data listings generation).
  - *2020 status update: This evaluation activity was not conducted for the 2019/2020 due to the impact of COVID-19 on the initiative and remains a QCAC recommendation for next season.*

- Recommendation 2:
  - Communicate and agree expectations and timings of the documentation for QCAC evaluation upfront with P95 and WP3 for the 2019/2020 season
  - *2020 status update: DRIVE timelines for 2020 were effectively communicated to the QCAC by the SC.*

- Recommendation 3:
  - Update DMP each season to identify the participating sites and ensure alignment with current good practice
  - *2020 status update: DMP was received in advance of the DQRs and was updated in December 2019 identifying all participating sites as recommended.*

- Recommendation 4:
  - Revise questions from the Questionnaire sent to sites based on feedback from the sites and QCAC first experience of evaluation/scoring. The use of this information as part of the site tender/site selection could also be considered by the SC. The QCAC will evaluate the scoring system to assess how this can be improved such as weighting the different quality categories and whether a threshold could be implemented which would trigger a recommendation for a site visit.
  - *2020 status update: The Quality Management Questionnaire was updated by WP3 and reviewed by QCAC for the 2019/2020 season. Improvements were made in reducing the number of questions to make it more user friendly for the sites to complete and simplification of terminology based on feedback from the sites. Modifications were made to the QCAC scoring system and evaluation process to a colour coded rating for easier interpretation of the results. In addition, an overall site assessment was given based on the criteria provided by the SC for the site tender/selection process.*

9 Limitations of QCAC assessment

This is the second season that QCAC has performed its annual evaluation and the QCAC recognizes that further improvements are required for future seasons. The review continues to have the following limitations:

1. As this was a remote assessment, there is no mechanism to verify the accuracy of the responses provided by the sites for the Quality Management questionnaires and the sites provided differing levels of detail in the responses. The simplified and more targeted Quality Questionnaire utilized for 2019/2020 incorporated lessons learned and feedback from the sites which allowed for a more simplified assessment whilst still focussing on key compliance aspects.

2. Items that could not be assessed because of absence of information/lack of response from the sites. This continues to be an issue with 3 sites out of 14 not responding to the questionnaire. The SC had implemented a requirement for responding to the Quality Questionnaire being mandatory as part of the

site tender/selection process in 2020 however due to the impact of COVID-19 this requirement was not enforced.

3. There was limited insight in the way that the original data collection from the sites was managed (i.e. paper, eCRF) and how sites managed changes based on the P95 quality checks. It is recommended the percentage of data excluded from the analysis for not meeting defined criteria is further explored by the SC and P95.

4. Membership of the QCAC is currently industry partners only due to lack of corresponding clinical quality compliance roles in the public sector.

10 Conclusion

The Step 1 evaluation provided an indication of the standards of each responding site's quality management systems and the simplified and more focussed Quality Questionnaire utilized for 2019/2020 enabled focus on key compliance areas. No issues were identified to trigger a recommendation for a site visit for the responding sites, or a formal audit and recommendations are mainly in the area of Data Management. The review enables a high-level assessment of the quality management systems in place at each site and the site's understanding of good research practices, but as the responses and the content of documents such as local SOPs cannot be verified, the limitations of this type of review must be acknowledged.

The documents provided to QCAC by P95 were in compliance with the principles for Data Management and Reporting as described in Guidelines for Good Pharmacoepidemiology Practice (GPP) (2016). No major concerns were identified regarding the content of the DQRs. It is recommended that the percentage of data excluded from certain sites is reviewed and assessed by P95 and the SC.

The conclusions and recommendations will be discussed with the SC, ISC and WP3 including the limitations of this type of review and improvements required for future seasons.

Appendix 1 – DRIVE Site Quality Questionnaire

1	Q1(2) Responder Information
2	Q2 If your organisation has written procedure(s) which describe the process for the protocol development for the vaccine effectiveness studies, please detail which aspects are covered in these documents. Tick all that apply.
3	Q3 'Does the protocol for the vaccine effectiveness studies undergo review by an expert (or review committee) – before the ethics committee review?
4	Q4 'Is the review/approval of a protocol by the expert (or review committee) documented? (by email or letter)
5	Q5 Are technical aspects of the study in scope of the Ethics committee review, such as methodology, statistics?
6	Q6 (24) In Chapter 1 of the DRIVE document “Standard Operating Procedures (SOPs) and Templates: Guidance and Recommendations” responsibilities are described for the sites with respect to: Study design and planning, Study Set-up, Study Conduct and Study archiving. Has the organization implemented these responsibilities for the vaccine effectiveness studies?
7	Q7 (35) Did your organization use the “DRIVE generic protocol template” or another standard template to guide protocol development for the vaccine effectiveness studies?Please find here the “DRIVE generic protocol template” for test-negative and population-based cohort design.
8	Q8 (45) Beyond the protocol, are there any of the following study specific documents or plans created that describe the operational aspects of a study in more detail?(i.e. documents processes/instructions/plans with contain more detailed instructions for the study staff how to perform the study in real-life). Note: the document management plan and data management plan are addressed later in this survey. Tick all that apply.
9	Q9 For repeat responders only (else leave blank)
10	Q10 (47) Please describe briefly how professional qualifications of study team members are verified, records maintained and updated. Please consider aspects of educational degree, work and skills certifications, professional certifications, maintaining and updating CVs etc. (5-10 sentences)
11	Q11 (49) Are Job Descriptions of personnel available within the organization? (i.e. a job description describes the general (not-study specific) tasks, or other related duties, and responsibilities of a specific position/role)
12	Q12 (51) Does the organisation document the study- specific roles and responsibilities of study team members (for example in the protocol, study plan or charter)?
13	Q13 (54) If the annual vaccine effectiveness studies involve a collaboration across multiple partnering entities outside your organization (i.e. coordinating center, hospital/GP, laboratory), is the role of each of the partners described in writing?
14	Q14 (56) Do any commercial parties (i.e. suppliers) have a critical role in the vaccine effectiveness study conduct (for example for the testing of the swab samples, or conduct of the data management)?
15	Q15 (58) If any commercial parties (i.e. suppliers) have a critical role in the vaccine effectiveness study conduct, please describe which critical activities such commercial suppliers perform (5-10 sentences).
16	Q16 For repeat responders only (else leave blank)
17	Q17 (28) Has the organization used the DRIVE written procedure on “Data management” for the vaccine effectiveness studies?Please find here the DRIVE written procedure on ““Data management” – chapter 3.
18	Q18 (30) Has the organization used the DRIVE written procedure on “Data quality assessment” in the context of the vaccine effectiveness studies?Please find here the DRIVE written procedure on ““Data quality assessment” – chapter 4.
19	Q19 (64) Are standard forms used for the original data collection for the vaccine effec
20	Q20 (71) In addition to the quality and consistency checks devised by the “DRIVE Electronic Study

	Support Application", does the organisation perform any additional local quality and consistency checks of the data?
21	Q21 For repeat responders only (else leave blank)
22	Q22 Does the organisation use any dictionaries, code books or other instructions to guide the data entry into the local study database?(this is separate/in addition to the DRIVR code book)
23	Q23 Does the organisation maintain a report or otherwise document events or changes which occurred during the study conduct in relation to the study database (i.e. identified inconsistencies, applied changes etc)? Tick all that apply:
24	Q24 If your organisation has written procedure(s) for data management or a study-specific data management plan applicable for the data management of vaccine effectiveness studies, please detail which aspects are covered in these documents. Tick all that apply:Note: these can be in addition to the DRIVE Data Management procedures as in question 17 and 18.
25	Q25 If you maintain a technical specification of the study-specific database design, please detail for which aspects documentation is maintained. Tick all that apply:
26	Q26 Does the organisation have any written procedures on the document management or maintain a study specific document management plan which describes any of the following aspects? Tick all that apply:
27	Q27 (82) Has the organisation defined which documents should at minimum be retained in the study archive?
28	Q28 (84) If available, please upload the standard list of documents to be archived for a typical study (only the list of document types/titles – not the actual documents) or send by email to Roberto Bonaiuti (roberto.bonaiuti@unifi.it).
29	Q29 (87) Does the organisation maintain a regular back-up during the study conduct of the electronic data (i.e. server) and is this back-up in a different location than the location of the primary server?
30	Q30 For repeat responders only (else leave blank)
31	Q31 Has the organization used the DRIVE "Guidance on Protocol Deviations"? Please find here the DRIVE "Guidance on Protocol Deviations".
32	Q32 If the "DRIVE Guidance on Protocol Deviations" was not applied, please describe briefly how deviations from the protocol are handled, i.e. how these are documented, who is informed, how are actions decided (5-10 sentences)
33	Q33 Does the organization conduct internal/external inspections to check if the activities performed by your organization for the vaccine effectiveness studies are compliant with the applicable regulations?
34	Q34 (26) Has the organization used the DRIVE written procedure on "Integrity and transparency" for the vaccine effectiveness studies?Please find here the DRIVE written procedure on "Integrity and transparency" – chapter 2.
35	Q35 (91) If your organization has any written procedure(s) covering security, please indicate which aspects are covered by such written procedures. Tick all that apply:
36	Q36 (92) Is access to physical storage locations of paper study documents "controlled"? (i.e. controlled meaning that it is possible to restrict access to authorized personnel to a place or other resource, that previous access is logged (manually or by a system) etc.)
37	Q37 (94) Is access to laboratory sample storage "controlled"? (i.e. controlled meaning that it is possible to restrict access to authorized personnel to a place or other resource, that previous access is logged (manually or by a system) etc)
38	Q38 (96) Is access to the main server locations "controlled"? (i.e. controlled meaning that it is possible to restrict access to authorized personnel to a place or other resource, that previous access is logged (manually or by a system) etc.)
39	Q39 (98) Does the organisation maintain access logs for systems where study data is processed (excluding applications provided by DRIVE)?
40	Q40 (100) Does the organisation apply password access for individual work stations (i.e. laptops, desktops)?
41	Q41 (102) Does the organisation require password access to electronicsystems/ applications relevant for study conduct (not considering the applications provided by DRIVE)?

42	Q42 (104) Does the organisation obtain confidentiality agreements of the study team members (as part of their employment contract or as separate agreements)?
43	Q43 (106) Does the organisation obtain confidentiality agreements of the colloborting partners if they have access to study data?
44	Q44 (108) If a third party has access to sensitive study data (i.e. clinical information), for example because they perform the data management, does the third party then sign a confidentiality agreement before study start?
45	Q45 For repeat responders only (else leave blank)
46	Q46 (2) Is the influenza vaccine effectiveness (IVE) study conducted by your unit nested into the national influenza surveillance system?
47	Q47 (7) How are study subjects explicitly informed about the use of data? If not, why (i.e. arranged through a specific waiver, etc.)?
48	Q48 (8) Is ethics committee approval required for performing IVE studies?
49	Q49 (10) Which ethics committee has been consulted? Tick all that apply:
50	Q50 (11) Which of these professionals compose the ethics committee? Tick all that apply:
51	Q51 (12) Is informed consent needed?
52	Q52 (13) If you answered no to the previous question (51), is a legally valid waiver for informed consent approved by an Ethics Committee?
53	Q53 (14) If you answered yes to the previous question (52), is the approval of waiver for informed consent study-specific or general for vaccine effectiveness surveillance?
54	Q54 (16) What was the feedback received from the Ethics Committees on the protocol used in the 2019/2020 influenza season?
55	Q55 (20) Is personal information anonymized or pseudoanonymized and security of all data guaranteed?
56	Q56 If you answered yes to the previous question (55), please detail in which way your data is pseudonymized/anonymized and if standard procedures are available
57	Q57 For repeated responders only (else leave blank)
58	Q58 Does your study involve (or could it involve) sending biological samples outside your institution and/or abroad?
59	Q59 If you answered yes to the previous question (58), which authorizations / transfer agreements are required to send samples outside?
60	Q60 Please upload here the informed consent
61	Q61 Please upload here the patient information sheet
62	Q62 Please upload here the ethics committee approval

Appendix 2 – Detailed Overview of Questions Assessed as Red or Amber Per Site

Study Sites that Provided a Response to the Quality Questionnaire	Detailed Overview of Questions Assessed as Red or Amber Per Site
Spain - Val D'Hebron University Hospital, (VHUH)	• Five responses assessed as Red. No written procedures for protocol development, standard forms not used for original data collection, no audit trail maintained of study database, no technical specification of study-specific database design is maintained, no internal/external inspections conducted for vaccine effectiveness studies. • Two responses assessed as amber - no standard list of documents to be archived provided and organisation maintains a back-up but has no information on its location.
Italy -CIRI-IT BIVE	• No responses assessed as Red or Amber
Spain - University Hospital Germans Trias I Pujol (HUGTP)	• Four questions assessed as Red. No audit trail of study database is maintained, no technical specification of study-specific database design is maintained, site not familiar with “Guidance on Protocol Deviations”, no confidentiality agreements obtained from study team members. • Three questions assessed as Amber. No information provided on how professional certifications are updated and maintained after hiring, no procedures or plans are available which describe how documents for a study should be managed, no standard list of documents to be archived provided.
Spain - FISABIO	• Three responses assessed as Amber. Expert review of protocol is conducted by expert or review committee but review/approval not documented. No standard protocol template for vaccine effectiveness studies applied. Lay person/patient representative not listed as part of ethics committee composition.
France, INSERM REIVAC	• One response assessed as Red - no technical specification of study -specific database is maintained • One responses assessed as Amber, no standard list of documents to be archived provided.
Austria - Medical University Vienna (MUV)	• Two questions assessed as Red. Organisation does not document the study-specific roles and responsibilities of study team members, no technical specification of the study specific database design is maintained. • Three questions assessed as Amber. Review/approval of a protocol by the expert (or review committee) is not documented, no standard list of documents to be archived provided, ethics committee approval not uploaded.
Italy - CIRI-IT GP	• No responses assessed as Red or Amber
Finland - Helsinki University Hospital (HUS)	• One response assessed as Red, no job descriptions are available • Three responses assessed as Amber. No standard list of documents to be archived provided, no internal/external inspections of vaccine effectiveness studies conducted, HUS has written procedure on patient security but it does not specifically address clinical studies.
Romania - National Institute Infectious Disease (NIID)	• No responses assessed as Red or Amber
Finland - National Institute Health & Welfare (NIH THL)	• Three responses assessed as Red. Organisation does not apply any standard protocol template for the vaccine effectiveness studies, no technical specification of the study database is maintained, organisation does not define which documents at minimum should be retained in the study archive • No responses assessed as Amber
UK, Surrey, RCGP	• Two responses assessed as Red. Standard forms not used for the original data collection, organisation does not define which documents at minimum should be retained in the study archive. • Four questions assessed as Amber. Not all DRIVE SOPs have been implemented in their original form, beyond the protocol there are no study specific documents or plans which describe the operational aspects of a study in more detail, location of the back-up for electronic data is located in the same location as the primary storage, internal/external inspections are conducted but activities related to the vaccine effectiveness studies are not in scope