

**Protocol amendment**

**Benefits and harms of the human papillomavirus vaccines: systematic review of industry and non-industry study reports**

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The protocol is registered on PROSPERO:  
[https://www.crd.york.ac.uk/PROSPEROFILES/56093\\_PROTOCOL\\_20170030.pdf](https://www.crd.york.ac.uk/PROSPEROFILES/56093_PROTOCOL_20170030.pdf)

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### **Amendment no. 1: Alternative assessment of harms of special interest**

We have acquired nearly 60,000 pages of clinical study reports (CSRs) of the HPV vaccines randomised clinical trials (RCTs), but the CSRs lack individual participant data (with case report forms and serious harms narratives) and the trial participant identifiers have been redacted.

Consequently, we cannot in an appropriate manner assess potential harms clustering (e.g., in relation to time of onset), verbatim-preferred harms terms, autoimmune, chronic, syndromic harms or harms of special interest, i.e., chronic fatigue syndrome (CFS), complex regional pain syndrome (CRPS), Guillain–Barré syndrome (GBS), postural orthostatic tachycardia syndrome (POTS) and premature ovarian failure (POF), which were reported in relation to HPV vaccination (1–16).

We will report cases of CFS, CRPS, GBS, POTS and POF (as reported in the CSRs). However, some of the harms of special interest are rare heterogeneous syndromes and diagnoses of exclusion (e.g., CFS, CRPS and POTS). Thus, it would be unlikely that these syndromes would have been identified and reported in the CSRs. Therefore, we will also judge and report if an included Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) is part of the diagnostic criteria of CFS, CRPS or POTS (17–21) and summarise the data.

In addition, a blinded physician with clinical expertise in CRPS and POTS will code and judge the MedDRA PTs according to the correlation of the syndromes (i.e., ‘definitely,’ ‘probably,’ ‘probably not’ or ‘definitely not’ correlated). We will synthesize the data for those MedDRA PTs judged ‘definitely’ correlated with CRPS and POTS. We will use this approach, because a post-trial European Medicines Agency (EMA) report on a HPV vaccine (i.e., Gardasil 9) identified three (possibly six) cases of POTS in participants, who received Gardasil 9, and since reports of CRPS and POTS were the main reason for our involvement with the HPV vaccines (22–24).

### **Amendment no. 2: Additional assessment of HPV vaccine-related harms clusters recorded in VigiBase**

Since we cannot assess harms clustering as intended, we will use the three largest harms clusters reported after HPV vaccination (up until 1 January 2015) recorded in the World Health Organization’s (WHOs) VigiBase (<https://www.who-umc.org/vigibase/vigibase/>) (2):

<b>The three largest HPV vaccine-related harms clusters recorded in VigiBase</b>		
Cluster	Number of reports	Reported harms
1	9,938	Headache Nausea Pyrexia Dizziness
2	7,088	Pruritus Urticaria Rash Erythema
3	6,517	Syncope Dizziness Loss of consciousness

We will synthesize the data for the MedDRA PTs that are part of the three clusters to see if they are present in the CSRs and associated with HPV vaccination.

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