Protocol amendment no. 3

Benefits and harms of the HPV vaccines: systematic review with meta-analyses of trial data in clinical study reports

Comparison of clinical study reports with trial registry reports and journal publications

12 March 2018

Lars Jørgensen (lj@cochrane.dk), [1,2]
Peter Christian Gøtzsche (pcg@cochrane.dk), [1]
Tom Jefferson (tj@cochrane.dk), [1]

The protocol for the underlying systematic review is registered on PROSPERO:
https://www.crd.york.ac.uk/PROSPEROFILES/56093_PROTOCOL_20170030.pdf

Protocol amendments no. 1 and no. 2 for the systematic review are registered in PROSPERO
https://www.crd.york.ac.uk/PROSPEROFILES/56093_PROTOCOL_20171116.pdf

The underlying index of the HPV vaccine studies is published here:
https://systematicreviewsjournal.biomedcentral.com/articles/10.1186/s13643-018-0675-z

[1]The Nordic Cochrane Centre, Rigshospitalet 7811, Tagensvej 21, 2100 Copenhagen, Denmark
[2]Corresponding author: lj@cochrane.dk; ORCID: 0000-0002-9737-0555; ResearcherID: T-6254-2017

Amendment no. 3:

We have submitted our systematic review of the human papillomavirus (HPV) vaccines for publication (see our protocol and the 1st and 2nd protocol amendments on PROSPERO). The review included 24 clinical study reports of 24 randomised clinical trials.

This is the 3rd protocol amendment of our systematic review. In the work described in this amendment we aim to compare the 24 clinical study reports with their corresponding trial registry reports identified on ClinicalTrials.gov (https://clinicaltrials.gov/) and primary journal publications that we identified in peer-reviewed biomedical journals via journal publication databases (the Cochrane Collaboration's Central Register of Controlled Trials, Google Scholar and PubMed) (4). The 24 clinical study reports were obtained from EMA and/or GlaxoSmithKline (5). We identified trial registry reports from ClinicalTrials.gov for all 24 trials and journal publications for 23 trials. For the remaining journal publication (the minor trial HPV-003 of 61 participants), the manufacturer had previously confirmed that no journal publication have been published (4).

Two researchers (LJ and TJ; PCG will arbitrate) will independently carry out the data extraction and comparisons of clinical study reports with their corresponding trial registry reports and journal publications. For each trial document, we will assess: date, availability, protocol (including pre-specified outcomes), reporting of trial design (including PICO criteria) and post-hoc changes to reporting of primary outcomes. We will extract and compare data on the primary outcomes that we assessed in our systematic review (5). As our review contained nearly 200 meta-analyses, we will only compare the following 20 most clinically important outcomes (or statistically significant outcomes, P<0.05): [1]all-cause mortality, [2]HPV related cancer mortality, [3]HPV related cancer incidence, [4]HPV related carcinoma in situ, [5]HPV related moderate intraepithelial neoplasia, [6]HPV related moderate intraepithelial neoplasia or worse, [7]HPV related referral procedures, [8]fatal harms, [9]serious harms (including those judged as 'definitely associated' with [10]CRPS or [11]POTS [see protocol amendment no. 1] and the [12]nervous system disorders that were MedDRA classified in this system organ class), [13]new onset diseases (including [14]back pain and [15]vaginal infection, and the [16]vascular disorders that were MedDRA classified in this system organ class) and [17]general harms (including [18]fatigue, [19]headache and [20]myalgia). Similar to our systematic review, we will only analyse results of intention to treat populations, histological benefit outcomes irrespective of involved HPV types, and the most detailed harms account (for example, if harms are registered separately per harm, we will count and summarise them). As the clinical study reports mainly focused on per-protocol results, we will compare reporting of primary per-protocol outcomes with reporting of primary intention to treat outcomes (irrespective of involved HPV type).

Similar to our systematic review, risk ratios will be calculated with the random effects inverse variance method and we will compare random effects with fixed effects, as we are concerned by the influence of small trials. We will perform sub-group analysis and control for possible confounding factors (age, gender, type of HPV vaccine and comparator).

We aim to publish our findings in the same open access biomedical journal as our systematic review.