Intended for ealthcare professionals

Rapid response to:

Analysis

Restoring invisible and abandoned trials: a call for people to publish the findings

BMJ 2013; 346 doi: https://doi.org/10.1136/bmj.f2865 (Published 13 June 2013) Cite t is as: BMJ 2013;346:f2865

Rapid Response:

Call to action: RIAT restoration of a previously unpublished methodology in Gardasil vaccine trials

We write to issue a call to ction to restore the reporting of multiple trials in erck's clinical deve opment program for qu driv lent hum n papillom virus (HPV) vaccine (Gardasil) vaccine. These tri ls inc ude:

FUTURE II (NCT00092534), pub ished s FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent ig -grade cervical lesions. N Engl J ed. 2007 May 10;356(1):1915–27.

FUTURE III (NCT00090220), published as Muñoz N, Mana astas R Jr, itisuttithum P, Tresukosol D, Monsonego J, Au t K, et l. Safety, immunogenicity, nd effic cy of qu driva ent human papi lomavirus (types 6, 11, 16, 1) recombinant vaccine in women aged 24–45 ye rs: randomised, double-b ind trial. L ncet. 2009 Jun 6;373(67):1949–57.

These ig ly influenti l publications (tot lling over 1300 citations together, according to publishers' websites) report the results of two pre-m rketing c inical trials of Gardasil th t involved over 15,000 women between the ges of 15 nd 45.[1,2] These were pivota trials th t underpin the approva of t e vaccine.

However t ese trial public tions have incompletely reported important methodo ogica details and in ccurately describe t e formulation that the contro arm received, necessit ting correction of the record.

We intend to restore the written record for these trials in accord nce with the principles of t e Restoring Invisible and Ab ndoned Tri ls (RIAT) initi tive, of w ic we are founders.[3]

Our ration le for correcting t e record

Both tri l publications state t at they are reports of "placebo-controlled" tria s.[1,2] However particip nts in the control rm of t ese tri ls did not receive an inert substance, such s s line injection. Inste d, they received an injection containing amorp ous aluminium hydroxyphosphate (AAHS), a proprietary djuvant system that is used in Gardasil to boost immune response.

The use of a comparator that was neither an inert substance nor an efficacious vaccine against another disease demands explanation. The clinical rationale for such a decision is unclear, as the trial arms do not mimic the real life choice of deciding whether or not to receive HPV vaccine, and it is incompatible with established ethical principles regarding the use of placebo in vaccine trials.[4] However, in at least two key trial publications, of the FUTURE II[1] and FUTURE III[2] trials, the rationale for the use of AAHS-containing control is unstated. Trial registration entries for these trials also lack a rationale on the selection of this control.

Furthermore, because AAHS is not inert, the choice of AAHS-containing control complicates the interpretation of efficacy and safety results in trials. While there is no evidence or reason to believe that AAHS adjuvant can induce efficacy on its own without the HPV virus like participles (VLPs) present in the approved vaccine, AAHS is understood to have a harms profile.[5] For example, in a phase 2 study testing multiple doses of potential Gardasil formulations (V501-007), the manufacturer included two active AAHS-containing adjuvant dose arms, “for appropriate safety comparisons.”[6] Concerns about the safety profile of AAHS-containing control and the impact on interpretation of results is also evidenced by the fact that the FDA directed Merck to conduct a 6 month safety study comparing 3 doses of Gardasil against a non-aluminum containing placebo, according to the company’s submission to Japanese regulators.[7] At the time of Gardasil’s 2006 approval in the US, trial V501-018 was the only study to compare Gardasil with a non-aluminum containing placebo,[8] and the FDA medical officer referred to the control used in this trial as “true placebo,”[9] in contrast to the control used in other trials.

The FUTURE II and FUTURE III trial publications however do not discuss how AAHS-containing control could affect the interpretation of results.

We consider the omission in journal articles, of any rationale for the selection of AAHS-containing control, to be a form of incomplete reporting (of important methodological details), and believe the rationale must be reported. We also consider that use of the term “placebo” to describe an active comparator like AAHS inaccurately describes the formulation that the control arm received, and constitutes an important error that requires correction. If trial participants were told they could receive “placebo” (widely defined as referring to an “inactive”[10,11] or “inert”[4] substance) without being informed of all non-inert contents of the control arm injection, this raises ethical questions about trial conduct as well.

Scope of our restoration

After documenting that these deficiencies in reporting were not confined to a single study, but at least applied to two Phase 3 trials in the Gardasil evidence development program, we have decided to systematically correct the record for all Gardasil and Gardasil 9 trials with standalone aluminum-containing control arms. We may therefore discover additional trials in need of restoration for the same reason, and we will include this as part of our work.

Our sources

Our population of trials potentially eligible for restoration is defined as all clinical trials for which we have obtained clinical study reports (CSRs). At present, this population is limited to data received from the European Medicines Agency (EMA) in response to a request by one of the team members (TJ) for all CSRs for Gardasil and Gardasil 9, lodged in May 2014. The process of obtaining CSRs has been previously described in an Index study[12] and Analysis article.[13] All trials for which CSRs of Gardasil and Gardasil 9 vaccine trials were obtained by 1 November 2018 are potentially eligible for inclusion in this restoration.

Following a 2018 ruling in Canadian Federal Court, we anticipate having access to all CSRs for Gardasil and Gardasil 9 and may use these data from Health Canada instead of--or in addition to--what we have received from

EMA, depending on what data are received.

Our holdings include the trial protocol, CSR main body, and informed consent form used during participant recruitment. We also hold correspondence with regulators and manufacturers in which the topic has been discussed.

Questions our restoration aims to answer

1. Has the rationale for using a control arm formulation that contained the aluminium-containing adjuvant known as AAHS been documented? If so, what was it?

2. What was contained in the control arm formulation?

3. How was the control arm formulation described across trial publications, registry entries, CSRs, and informed consent forms?

4. What are the consequences of such a choice for participants and how might it affect the interpretation of the trial results?

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Competing interests: The Laura and John Arnold Foundation funds the RIAT Support Center which supports the salaries of Doshi, Jefferson, Jones, Bourgeois, Spence, Shamseer (until 2018), and Hong. In addition: Peter Doshi has received travel funds from the European Respiratory Society (2012) and Uppsala Monitoring Center (2018); grants from the Laura and John Arnold Foundation (2017-20), American Association of Colleges of Pharmacy (2015), Patient-Centered Outcomes Research Institute (2014-16), Cochrane Methods Innovations Fund (2016-18), and UK National Institute for Health Research (2011-14); and is an editor at The BMJ and unpaid member of the Reagan-Udall Foundation for the FDA. Tom Jefferson (TJ) was a recipient of a UK National Institute for Health Research grant for a Cochrane review of neuraminidase inhibitors for influenza. In addition, TJ receives royalties from his books published by Il Pensiero Scientifico Editore, Rome and Blackwells. TJ is occasionally interviewed by market research companies about phase I or II pharmaceutical products. In 2011-13, TJ acted as an expert witness in litigation related to the antiviral oseltamivir, in two litigation cases on potential vaccine-related damage (including the vaccine Pandemrix (2015-2017) and in a labour case on influenza vaccines in healthcare workers in Canada. He has acted as a consultant for Roche (1997-99), GSK (2001-2), Sanofi-Synthelabo (2003), and IMS Health (2013).In 2014 he was retained as a scientific adviser to a legal team acting on oseltamivir. TJ has a potential financial conflict of interest in the drug oseltamivir. In 2014-16, TJ was a member of three advisory boards for Boerhinger Ingelheim. TJ was holder of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane reviews. TJ was a member of an independent data monitoring committee for a Sanofi Pasteur clinical trial on an influenza vaccine. Between 1994 and 2013, TJ was the coordinator of the Cochrane Vaccines Field. TJ was a co-signatory of the Nordic Cochrane Centre Complaint to the European Medicines Agency (EMA) over maladministration at the EMA in relation to the investigation of alleged harms of HPV vaccines and consequent complaints to the European Ombudsman. TJ is co-holder of a John and Laura Arnold Foundation grant for development of a RIAT support centre (2017-2020) and Jean Monnet Network Grant, 2017-2020 for The Jean Monnet Health Law and Policy Network. TJ is an unpaid collaborator to the project Beyond Transparency in Pharmaceutical Research and Regulation led by Dalhousie University and funded by the Canadian Institutes of Health Research (2018-2022). Mark Jones was a co-investigator on a UK National Institute for Health Research grant for a Cochrane review of neuraminidase inhibitors for influenza; was a co-recipient of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane reviews; and is a paid consultant on a John and Laura Arnold Foundation grant for development of a RIAT Support Center (2017-2020). LS, HL, FB, KH: no competing interests to declare. OS was a recipient of a Maryland CERSI Scholar award from the Food and Drug Administration (grant #1U01FD005946).

11 January 2019

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