Appendix 1: Pregnancy Methods [posted as supplied by author]

During the clinical development of GSK's HPV-16/18 VLP AS04 vaccine, pregnancy was a contraindication for vaccination, and pregnant and lactating women were not enrolled until after lactation was complete. At the enrollment visit, women of child-bearing potential were instructed by study personnel during the informed consent process about the importance of using an effective birth control method. Only those who agreed to practice effective contraception for the 9-month period between 30 days before first vaccination until 60 days after the last vaccination and were otherwise eligible were enrolled in the study. Methods of birth control deemed effective included abstinence; surgical sterilization; hormonal contraceptives; the intrauterine contraceptive device; and diaphragm or condom; PATRICIA but not CVT required spermicide use in conjunction with diaphragm or condom.

Data collection. Trial staff gathered data on pregnancy start and outcome according to protocols designed for evaluation of the safety profile of the vaccine. Immediately before each study vaccination, each participant, regardless of reported sexual experience, gave a urine sample for a sensitive pregnancy test. PATRICIA and CVT used One Step Pregnancy Test Strip (*ACON* Laboratories, Inc., San Diego, CA) test of urine for human chorionic gonadotropin (hCG), a hormone produced at the time of implantation. The test kit had a sensitivity of 25 mIU/mL (PATRICIA) or 10 mIU/ml (CVT).

After each vaccination the participants are reminded of the continuing need for birth control until two months after the last vaccination. Vaccination was

discontinued for women with a positive pregnancy test or known pregnancy. Other study procedures continued at the discretion of the investigator. In CVT, participants with equivocal pregnancy tests were deferred for 15 days. At the request of the Costa Rican IRB, beginning on August 12, 2005, any participant in CVT with a negative pregnancy test but who reported menstrual delay (five days late for women with regular menses and more than 35 days late after previous menses for women with irregular menses) was deferred for a minimum of seven days to provide additional reassurance that pregnant women were not vaccinated. If the urine pregnancy test after the minimum deferral period was negative, the woman was vaccinated.

Study protocols specified how data on pregnancy and pregnancy outcomes were recorded throughout the entire study period. Specifically, immediately after learning that a woman was pregnant, study staff completed a form documenting the expected delivery date based on report of her last menstrual period. In addition, study staff contacted the woman after her expected delivery date to learn the pregnancy outcome. Staff coded information on gynaecological history, last menstrual period date, pregnancy end date, gestational age, whether the delivery was vaginal or Caesarean, delivery outcome and weight, length, sex, Apgar score, and outcome of the baby. In addition, women were instructed to report serious adverse events at any time during the trials to investigators. Any abnormality during the pregnancy or delivery and any medical condition of the baby at birth were documented using appropriate forms and reported according to the local regulation and the Good Clinical Practice guidelines. All adverse events were coded with

MEDRA preferred codes for PATRICIA and using Spanish edition of ICD-10 for CVT.