# Table of Contents

ABBREVIATIONS .......................................................................................................................... IX

CHAPTER 1. SUMMARY OF IARC/NCI EXPERT MEETING ON PRIMARY END-POINTS FOR PROPHYLACTIC HPV VACCINE TRIALS ................................................................. 1
1.1 EXECUTIVE SUMMARY ............................................................................................................. 1
1.2 BACKGROUND ......................................................................................................................... 2
1.3 RATIONALE FOR THE IARC/NCI EXPERT MEETING ON PRIMARY END-POINTS FOR PROPHYLACTIC HPV VACCINE TRIALS ............................................................ 4
1.4 EXPERT MEETING ON PRIMARY END-POINTS FOR PROPHYLACTIC HPV VACCINE TRIALS ........... 5
1.5 RECOMMENDATIONS OF VACCINE END-POINTS ....................................................................... 9
REFERENCES ...............................................................................................................................11

CHAPTER 2. NEXT-GENERATION HPV VACCINES – POTENTIAL FOR ALTERNATIVE END-POINTS ............................................................................................................................... 21
2.1 INTRODUCTION .....................................................................................................................21
2.2 LICENSED PROPHYLACTIC HPV VACCINES ...........................................................................21
2.3 NEXT-GENERATION VACCINES ..............................................................................................22
2.4 VACCINE END-POINTS ..........................................................................................................23
2.5 NATURAL HISTORY OF HPV INFECTION IN THE GENITAL TRACT .............................................23
2.6 PERSISTENT INFECTION AS A SURROGATE END-POINT FOR HIGH-GRADE CERVICAL DISEASE .24
2.7 VACCINE-INDUCED IMMUNE RESPONSES .............................................................................30
2.8 MONITORING VACCINE-INDUCED IMMUNITY – SERO-ASSAYS .................................................30
2.9 IMMUNOGENICITY ..................................................................................................................31
2.10 IMMUNOGENICITY AND SECOND-GENERATION VACCINES .......................................................32
REFERENCES ...............................................................................................................................32

CHAPTER 3. METHODOLOGICAL ISSUES FOR TRIALS OF VACCINE EFFICACY AGAINST HPV TYPES 16 AND 18 ........................................................................................................ 39
3.1 INTRODUCTION .....................................................................................................................39
3.2 VALIDATED AND NON-VALIDATED END-POINTS ...................................................................39
3.3 ARE RANDOMIZED CONTROLLED TRIALS WITH CIN2/3 END-POINTS FEASIBLE FOR THE FUTURE GENERATION OF HPV VACCINES? .........................................................42
3.4 BENCHMARKING PROTECTION AGAINST HPV 16 AND 18 .........................................................43
3.5 CONCLUSIONS .......................................................................................................................45
REFERENCES ...............................................................................................................................45

CHAPTER 4. TRIALS OF VACCINE EFFICACY AGAINST CERVICAL OUTCOMES ASSOCIATED WITH HPV TYPES OTHER THAN HPV 16 AND 18 ............................................................47
4.1 INTRODUCTION .....................................................................................................................47
4.2 MAIN OPEN ISSUES ...............................................................................................................48
4.3 DISCUSSION ..........................................................................................................................50
CHAPTER 8. HPV VACCINES AND POTENTIAL PREVENTION OF HPV-POSITIVE HEAD AND NECK CANCER ................................................................. 86

8.1 INTRODUCTION ........................................................................................................... 86
8.2 HPV ETIOLOGY OF CERVICAL VERSUS OROPHARYNGEAL CANCERS ....................... 86
8.3 SEX-BASED DIFFERENCES IN INCIDENCE OF HPV-POSITIVE OROPHARYNGEAL CANCERS .......... 87
8.4 SEX-BASED DIFFERENCES IN NATURAL HISTORY OF ORAL HPV INFECTION ..................... 87
8.5 HISTOPATHOLOGICAL PROGRESSION OF CERVICAL CANCER VERSUS OROPHARYNGEAL CANCER ......................................................................................................................... 88
8.6 PREVENTION OF ORAL HPV INFECTION AND ASSOCIATED CANCERS ......................... 88
REFERENCES .......................................................................................................................... 90

DISCLOSURES OF INTERESTS .................................................................................. 93

TABLES

Table 1.1 End-points for placebo-controlled trial of a licensed HPV VLP vaccine: three doses ........ 14
Table 1.2 End-points for development of a new HPV VLP vaccine similar to a licensed product or products: three doses .......................................................... 15
Table 1.3 End-points for development of a new polyvalent VLP vaccine containing additional HPV types compared with a licensed product or products: three doses ........ 16
Table 1.4 End-points for one or two doses for an HPV VLP vaccine approved for three doses, for situations in which immunological non-inferiority can be demonstrated .... 17
Table 1.5 End-points for one or two doses for an HPV VLP vaccine approved for three doses: alternative approach for situations in which immunologic non-inferiority cannot be demonstrated ............................................................. 18
Table 1.6 End-points for cross-protection against non-vaccine types for any VLP vaccine ........ 19
Table 1.7 End-points for non-VLP vaccines ........................................................................... 20
Table 2.1 Vaccine efficacy against high-grade cervical lesions associated with HPV 16/18 (according-to-protocol [ATP] cohort) in the PATRICIA trial ................... 27
Table 2.2 Vaccine efficacy against virological end-points associated with HPV 16/18 (according-to-protocol [ATP] cohort) in the PATRICIA trial ....... 27
Table 2.3 Studies of the quadrivalent HPV (qHPV) vaccine in women that assessed persistent infection ................................................................. 28
Table 2.4 HPV 16/18-related CIN2 or worse by prior infection with the same HPV type (subjects naive to the relevant type receiving placebo) ...... 29
Table 3.1 End-points based on HPV 16 and 18 virological and lesion frequencies in the placebo arm of the Costa Rica Vaccine Trial and associated sample size requirements .......................................................... 43
Table 4.1 Main questions and answers in relation to vaccine end-points associated with HPV types other than HPV 16 and 18 .......................................................... 48
Table 4.2 Prevalence rate of HPV 16 and other high-risk HPV types (X) as a percentage of HPV-positive women, in CIN2 and CIN3 ...................................................... 54
Table 4.3 Effect of selection of end-point on vaccine efficacy against (i) HPV 31/33/45, (ii) other non-HPV 16/18 carcinogenic HPV types, and (iii) all carcinogenic HPV types, in an according-to-protocol (ATP) analytic cohort .................................. 55