Cytological Surveillance Management Pathways for Women with a Low-grade Abnormal Cervical Smear

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ABBREVIATIONS

AIC, Akaike Information Criteria

ALTS, ASCUS-LSIL Triage Study

aOR, Adjusted Odds Ratio

ASCUS, Atypical Squamous Cells of Undetermined Significance

BIC, Bayesian Information Criteria

BMI, Body Mass Index

BNA, Borderline Nuclear Abnormalities

BSCC, British Society for Clinical Cytology

CI, Confidence Interval

CIN, Cervical Intraepithelial Neoplasia

CIN2+, Cervical Intraepithelial Neoplasia grade 2 or higher

CIN3+, Cervical Intraepithelial Neoplasia grade 3 or higher

cOR, Conditional Odds Ratios

DNA, Deoxyribonucleic Acid

GP, General Practitioner

HADS, Hospital Anxiety and Depression Scale

HR, High-risk

HSIL, High-grade Squamous Intraepithelial Lesion

HPV, Human papillomavirus

LOCF, Last Observation Carried Forward

LSIL, Low-grade Squamous Intraepithelial Lesion

MAR, Missing at Random

NHS: National Health Service

OR, Odds Ratio

Pap, Papinacolaou

RCT Randomized controlled trial

STAI, State-Trait Anxiety Inventory

TOMBOLA, Trial of Management of Borderline and Other Low-grade Abnormal cervical smears

United Kingdom, UK United States, US

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ABSTRACT

A conservative strategy for women with a low-grade abnormal cervical smear is continued cytological surveillance by repeat Papinacolaou testing, but there is surprisingly little information on the management of such follow-up. Our objectives were to investigate such management pathways, their determinants, and psychological implications using data from the cytological surveillance arm of the Trial of Management of Borderline and Other Low-grade Abnormal cervical smears. A substantial proportion of participants had ongoing unresolved cytology at last follow-up (42.7%); a policy of following women solely though cytological surveillance to manage these women may be inefficient. A high-risk human papillomavirus test, smoking and age were significantly associated with the management pathways (p-value <0.05). While there were some limitations, our results were reassuring with respect to this group of women with ongoing unresolved cytology, since there were no differences in anxiety and depression scores across the management pathways after thirty months of follow-up.

1. BACKGROUND

1. BACKGROUND

In this chapter, the rationale for the work on management pathways for women with low-grade cervical cytological abnormalities detected as part of cervical cancer screening and managed under a policy of surveillance is presented. This is based on consideration of cervical cancer screening programs as they exist today; the debate regarding the most appropriate management of low-grade (minor) abnormalities detected through such screening; expected outcomes of long-term follow-up through surveillance; risk factors associated with cervical cancer; and the psychosocial impact of long-term follow-up and management pathway. Gaps in previous research were identified, which led to the specific objectives of this thesis; these were pursued by analysis of data from TOMBOLA (Trial of Management of Borderline and Other Low-grade Abnormal cervical smears), a pragmatic randomized controlled trial (RCT) conducted in the United Kingdom (UK).

1.1 Cervical Cancer Screening

Worldwide, cervical cancer ranks as the fourth most common cancer among women in terms of incidence and mortality [1]. Developing countries experience a disproportionate share of the disease burden, accounting for 86% and 88% of all cervical cancer cases and deaths, respectively [2]. However, even in more developed countries, challenges remain. For example, in Canada, it is anticipated that the incidence and disease-specific mortality for cervical cancer will increase over time [3]. Newly diagnosed cervical cancers are expected to increase from approximately 1500 cases in 2015 to 2200 cases in 2030, and in the same time period, cervical

cancer deaths are expected to increase from 430 deaths to 620 deaths [3]. Further, based on 2010 statistics, the incidence rate of cervical cancer was 8.1 per 100,000 women, and the disease-specific mortality rate was 2.2 per 100,000 women in Canada [4]. Cervical cancer continues to affect women in Canada due to lower rates of screening among immigrants, refugees and First Nations women [5,6], factors associated with low uptake of human papillomavirus (HPV) vaccination [7,8], and due to prevalence of risk factors for cervical cancer [9].

The Papinacolaou (Pap) test was introduced for cervical cancer screening within Canada in 1949. It detects precancerous and malignant lesions at an early, pre-symptomatic stage, when treatment is most effective. The sensitivity of a single Pap test for detecting CIN Grade II or higher (CIN2+) is moderate at approximately 55%, with a high specificity at 97% [10-13]. Despite the low sensitivity of the Pap test, there has been substantial reduction in cervical cancer incidence and mortality in the past due to uptake of screening at regular intervals [14]. In Canada, the age-standardized incidence rate of invasive cervical cancer declined from 22.3 to 9.4 cases per 100,000 women (58%) between 1972 and 2006, and its age-standardized mortality rate declined from 7.7 to 2.2 cases per 100,000 women (71%) in the same period [15]. A similar trend was seen in the UK with the age-standardized incidence and mortality rate declining from 15 to 9 cases per 100,000 women (43%), and 8 to 2 cases per 100,000 women (70%) between 1971 and 2011 [16].

Cytological changes on the Pap test are classified on a scale of increasing severity using standard terminology, which differs between countries and has been revised over time. Historically, Canada has used the Bethesda classification to report cervical cytology, and the UK has used the British Society for Clinical Cytology (BSCC) classification [17]. However, these

schemes are broadly comparable as presented in Table 1 [17, 18]. In this thesis, the UK terminology in use up to 2013 was used, to be consistent with other articles based on TOMBOLA. Also, borderline nuclear changes and low-grade dyskaryosis smear test results were classified as "low-grade abnormalities" to achieve the objectives of this thesis.

A high-grade Pap smear test result may lead to a colposcopy referral, during which a detailed examination of the cervix is performed with a binocular low-power microscope. A biopsy may be taken to confirm the diagnosis, and these histopathological findings are graded as Cervical Intraepithelial Neoplasia (CIN) Grade I, II, or III, which correspond to Low-grade Squamous Intraepithelial Lesion (LSIL) and High-grade Squamous Intraepithelial Lesion (HSIL) (Figure 1). These high-grade lesions are treated by local excision (surgical removal of the abnormal area), cryosurgery (freezing), or laser surgery (high-intensity light) [19].

Table 1. Classification of cervical cytology, 2013

Canada's Bethesda classification	UK's BSCC classification	Thesis
Negative	Negative	Negative
Atypical Squamous Cells of Undetermined Significance (ASCUS)	Borderline (nuclear) change or Borderline Nuclear Abnormalities (BNA)	Low-grade abnormalities
Low-grade Squamous Intraepithelial Lesion (LSIL)	Low-grade (mild) dyskaryosis	
High-grade Squamous Intraepithelial Lesion (HSIL)	High-grade dyskaryosis (moderate or severe)	High-grade dyskaryosis
Unsatisfactory for evaluation	Inadequate	Inadequate

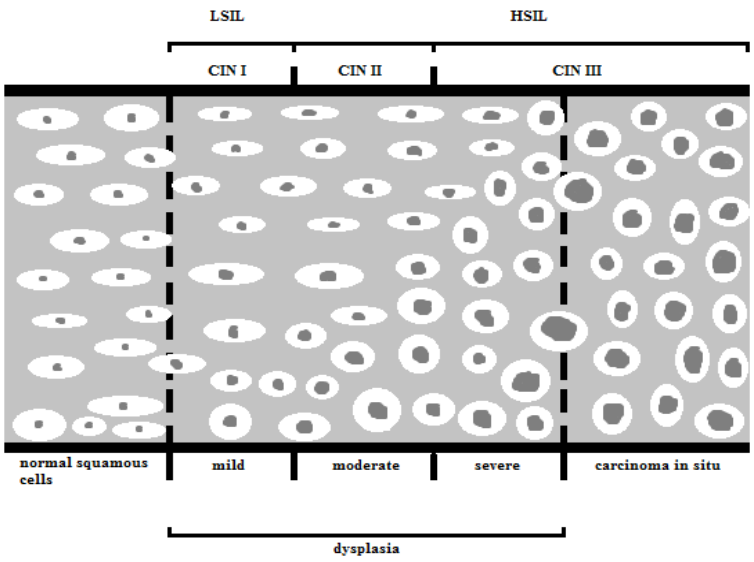


Figure 1. Progression of Cervical Intraepithelial Neoplasia (CIN) (Adapted from the Canadian Cancer Society) [20]

1.2 Cervical Cancer Screening Programs

In Canada, cervical cancer screening policy and organization occurs at the provincial and territorial level. Historically, its delivery has been mainly opportunistic rather than organized, and depends on the initiative of the woman or her doctor [11]. Opportunistic screening is distinguished from organized screening on the basis of whether invitations are issued from centralized population registers, and whether or not all eligible women are personally invited to attend screening [21]. Guidelines for an organized screening program include: an explicit screening policy for the defined target population; a population-based register to identify the individuals; recruit measures to guarantee high coverage; adequate facilities for screening, diagnosis and treatment; a quality assurance structure; and a surveillance system for comparing incidence and mortality in screened

and unscreened populations. However, in practice, organized and opportunistic screening programs often co-exist and may be complementary [22].

By 2013, all Canadian provinces had at least partially organized cervical screening programs, with the exception of Quebec, and two provinces had organized programs that included population-based recruitment and recall systems [11]. Figure 2 illustrates the cervical cancer screening program process in Canada; the Pap test is the primary screening tool for cervical cancer in all Canadian programs [11].

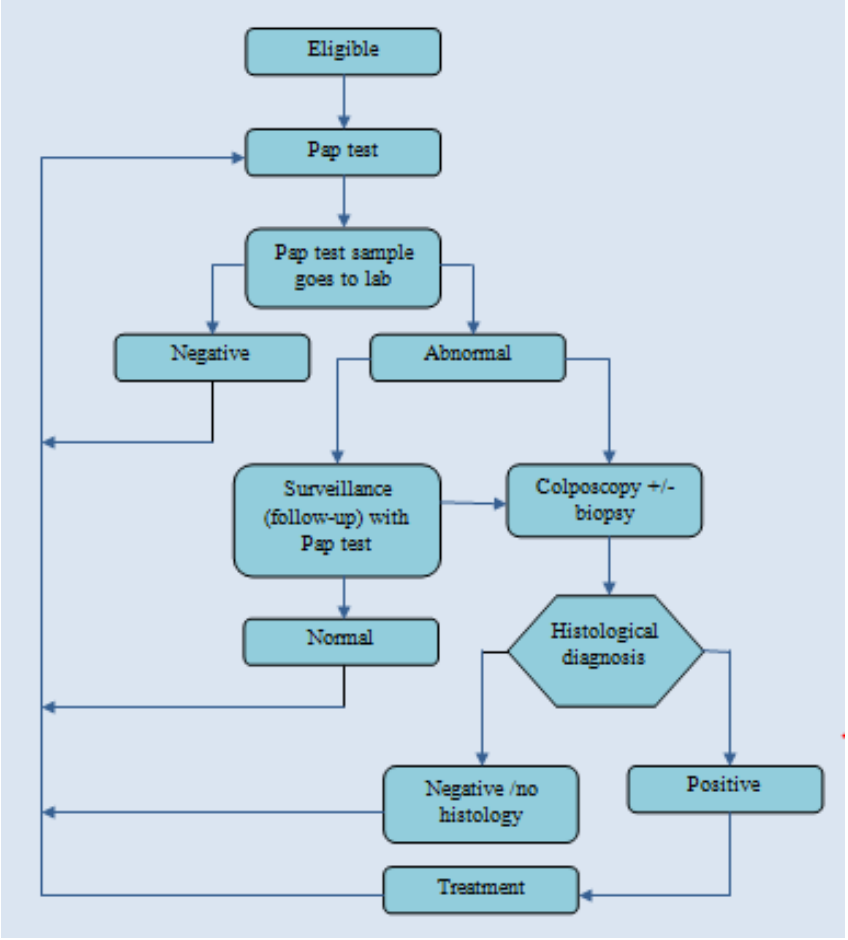


Figure 2. Cervical screening process, Canada (Adapted from Canadian Partnership Against Cancer) [11]

HPV deoxyribonucleic acid (DNA) has recently emerged as a suitable candidate to replace cytology as the primary cervical cancer screening test. Compared with the Pap test, HPV testing is less specific (94% versus 97%) but much more sensitive (95% versus 55%) in detecting high-grade precancerous lesions, less susceptible to human error, and more reproducible across settings [13]. Further, maintaining cytology as the primary screening test in settings with established programs or infrastructure in place to ensure adequate coverage might become less efficient as the prevalence of precancerous lesions is expected to decline with increasing uptake of HPV vaccination. As the prevalence of squamous abnormalities (ASCUS and LSIL) attributable to HPV types 16 and 18 declines, the positive predictive value of cytological screening will decrease [23]. Nevertheless, there will still be questions of cytology triage in systems that use HPV testing as the primary screening test [13].

Cancer Care Ontario updated its guidelines in 2012 for follow-up of women with abnormal cytology results on Pap test, by recommending HPV testing for use in triage in some sub-groups (Figure 3). Specifically, for women with a pap smear indicating Atypical Squamous Cells of Undetermined Significance (ASCUS), HPV triage is not recommended for those < 30 years of age. Instead, cytology (a Pap test) should be repeated in 6 months and if the results continue to indicate at least ASCUS, a colposcopy should be performed. If the result is negative for two more cytology tests performed every six-month interval in that group, then the women can be returned to routine Pap test screening every three years. For women ≥ 30 years of age with a pap smear indicating ASCUS, HPV triage is recommended if available. A positive HPV test result is reason for a colposcopy, and a negative HPV test result is reason for a repeat cytology in 12 months, after which the woman can be returned to routine screening if the test result is negative; otherwise a

colposcopy is recommended [24]. According to the guidelines, if HPV testing is not available for a women aged >=30 years with an ASCUS result on Pap smear, then cytology should be repeated in six-months again as for women <30 years of age. This is important to note, as HPV testing is not currently funded by the Ministry of Health and Long-Term Care.

For women with a LSIL result based on a Pap test, the evidence suggests that either repeat cytology or colposcopy are acceptable management options, as reflected in the Ontario guidelines (Figure 3)[24]. However, low-grade abnormalities, particularly in young women, often regress and thus, may be best managed by surveillance via repeat cytology. Women with an HSIL smear test result should be referred for colposcopy without repeat cytology, whereas if the Pap test result is unsatisfactory for evaluation, then cytology should be repeated in 3 months [24].

Following the HPV Sentinel Site Project, HPV triage and "test of cure" have also been introduced into the cervical screening programmes across England in 2012. For all cytology samples classified as "low-grade" abnormalities (i.e. borderline nuclear changes and low-grade dyskaryosis), HR-HPV testing is now performed: if the HPV test is positive, then these women are referred for colposcopy; whereas if the HPV test is negative, then these women are returned to routine recall. HPV test of cure uses a woman's HR-HPV status to assess her risk of having residual/recurrent disease after treatment for CIN2, along with cytology [25]. In Northern Ireland, both HPV triage and "test of cure" have been adopted, whereas only test of cure has been introduced in Wales and Scotland [26].

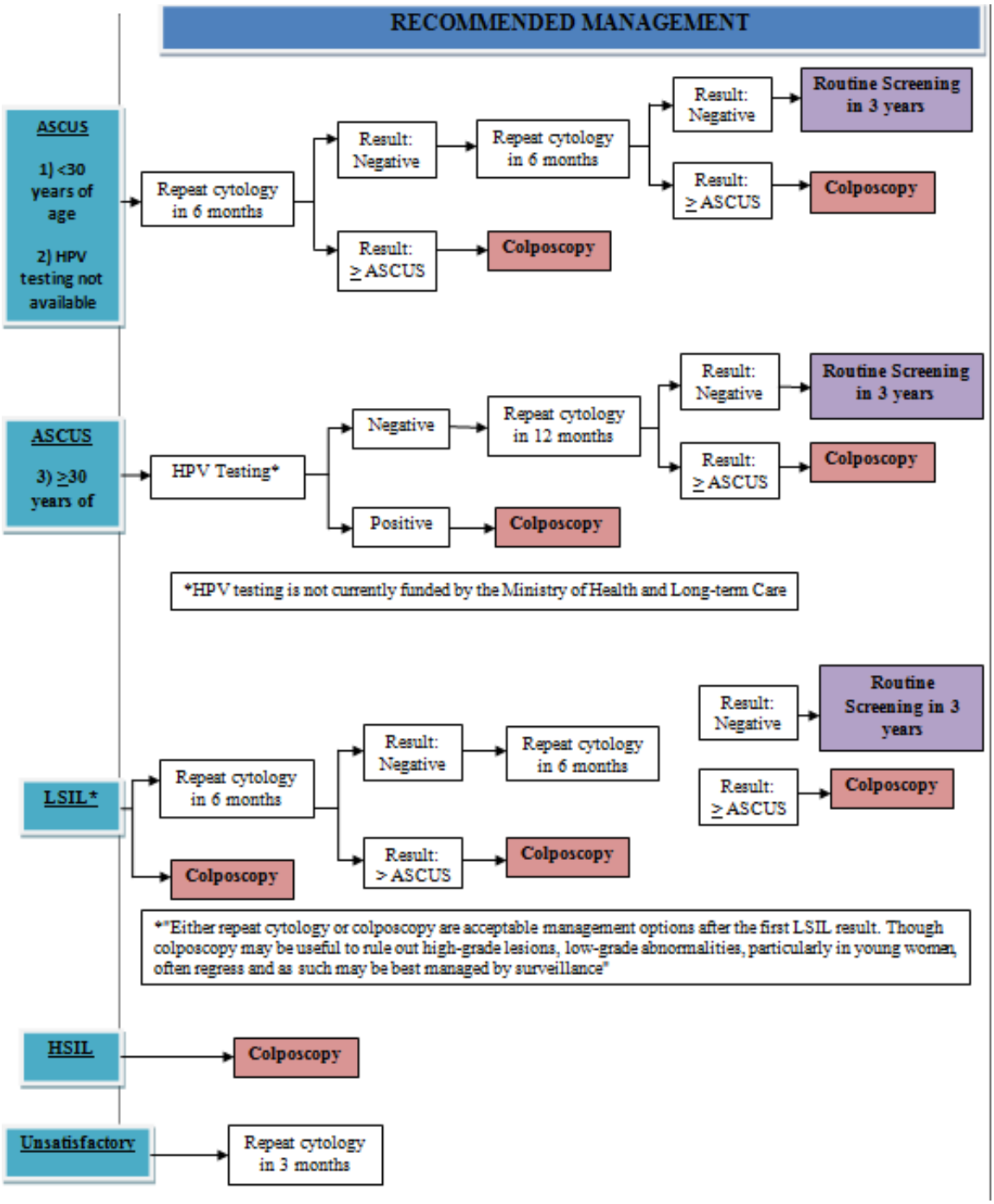


Figure 3. Ontario recommendations for follow-up of abnormal cytology, 2012

(Adapted from Cancer Care Ontario)

1.3 Low-grade Abnormalities and their Management

For cervical cancer screening to be effective in a population, large numbers of healthy people have to be tested, many of whom will be found to have abnormalities, most of which are not cancers or their precursors [27] – i.e., despite the test's high specificity, there are large numbers of false positives, owing to the low prevalence of cervical cancer. Indeed, Pap test screening for cervical cancer results in the identification of large numbers of women with low-grade cytological abnormalities, many of which are false positives, and questions remain about the best strategy for managing and resolving these results. In Canada, for example, it has been estimated that between 115, 000 and 290, 000 cytological smears show low-grade abnormalities annually. This variation is based on rates of LSIL or worse in Canada and the number of women that undergo a Pap test each year in Canada[14]. Similarly, in the UK, approximately 250,000 women show low-grade abnormalities every year [28]. Furthermore, approximately 10% of all specimens processed by cytotechnicians in the United States are flagged for abnormalities [29]. Most of these women do not have an underlying invasive cancer but are required to undergo follow-up, which may require repeated investigations over a number of years [30]. This poses a major health burden to women themselves and in terms of utilization of health care system resources [14].

Clearly, the management of low-grade smears presents a clinical dilemma. There has been debate since the late 1980's as to the best management of low-grade abnormalities. There are two options: six monthly repeat Pap smears in primary care (i.e. cytological surveillance) with referral to colposcopy for diagnosis only if the abnormality persists or progresses, or immediate referral to a hospital-based colposcopy (where the cervix is examined and biopsy or treatment undertaken if

indicated). It has been suggested that approximately one third of women found to have low-grade cytological abnormalities have an underlying high-grade histopathologic lesion (CIN2+) [31].

In 1995, in response to the debate regarding the most appropriate management of women with low-grade cervical abnormalities, the Medical Research Council and Department of Health called for a RCT to compare alternative management policies.

TOMBOLA resulted from that call [28]. One of its aims was (i) to examine the effectiveness of cytological surveillance (i.e. repeat pap testing) in primary care compared with immediate referral for colposcopy examination in women with low-grade abnormal results on cervical cytology tests. Another aim of TOMBOLA was (ii) to evaluate the contribution of a single HPV test in making decisions on management of women with low-grade abnormal cervical smears, in view of the role of certain types of HPV in the aetiology of cervical cancer.

With respect to the first aim of TOMBOLA, the cumulative incidence of CIN2+ was 79 per 1000 person years in the immediate colposcopy arm and 58 per 1000 person years in the cytological surveillance arm (relative risk 1.37, 95% confidence interval (CI): 1.19 – 1.57). This difference was attenuated for CIN grade III or worse (CIN3+), and it was speculated that there may have been spontaneous regression of some cases of CIN2+ in the surveillance arm [32]. The difference in cumulative incidence between the trial arms was apparent only for women aged under 40 years. Similar proportions of cases of CIN2+ were diagnosed at the time of immediate colposcopy, and detected during the surveillance period. However, a higher proportion of women in the colposcopy arm reported after effects such as pain, bleeding, and discharge, and these were

of longer duration and more severe. The authors concluded that a policy of referral for colposcopy after low-grade cervical abnormalities conferred no clear benefit as compared to cytological surveillance. Although colposcopy detected more CIN2+, it may lead to over treatment with associated after effects in young women, and no clear psychological benefit [32].

With respect to the second aim of TOMBOLA, there was no significant interaction between trial arm and high-risk (HR)-HPV status at recruitment in relation to the cumulative incidence of CIN2+. Thus, in women with mild dyskaryosis or borderline nuclear abnormalities (BNA) who were HPV positive, there was no advantage of immediate colposcopy over cytological surveillance (p=0.76). The sensitivity of the HPV test for detecting CIN2+ decreased with increasing age, whereas the specificity increased. The authors concluded that a single HPV test would not be useful in younger women with low-grade abnormal cervical cytology in determining who should be referred for colposcopy; however, in women aged 40 years or older, a negative HPV test could be used to rule out further investigation [18].

Previous studies, such as the ASCUS-LSIL Trial Study (ALTS), found that in women whose index smear showed ASCUS (broadly equivalent to BNA), a conservative management strategy of cytological surveillance with HPV triage resulted in a similar level of detection of CIN3+ as immediate colposcopy, while reducing the proportion of women referred for colposcopy [33]. In contrast, women whose index cytology showed LSIL (broadly equivalent to mild dyskaryosis) would be best managed by immediate colposcopy, as there was no useful triage strategy identified (more than 80% of women were HR-HPV positive) [34].

1.4 Management Pathways within Cytological Surveillance

Many jurisdictions with opportunistic, partially-organized and organized screening systems, including Canada and the UK, continue to use cervical cytology as the primary screening test (Figures 2 and 3). Previous studies have aimed to evaluate the prevalence of specific types of cervical smear results in populations, including recent Turkish [35] and Albanian [36] studies. Other research has evaluated cytology for the detection of invasive cervical cancer, such as determining its positive predictive value to detect at least severe dyskaryosis [37], and long-term risk of CIN2+ among women with ASCUS/LSIL by age, HPV status and genotypes [38]. A very recent published TOMBOLA article sought to investigate the rate of CIN2+ in women with low-grade cervical cytology and a normal colposcopy examination over three years of follow-up [39].

However, relatively little is known about the management pathways of women with low-grade cervical cytological abnormalities who were followed through repeat Pap testing. Within a policy of repeat Pap testing (i.e. "cytological surveillance") as reflected in current practice, over time and without treatment, some low-grade lesions will progress to higher-grade lesions, others will remain stable, and others will regress. On the basis of published screening guidelines (Figure 3), it would be expected that some women will return to routine recall after varying numbers of repeat tests, some women will eventually be referred for a colposcopy, whilst other women will have unresolved cytology at last follow-up; but what proportions of women experience various pathways within a policy of cytological surveillance, and how many repeated tests would be needed to achieve resolution, was unknown. This has important implications for screening as a

system of care, particularly with respect to the need for screening programs to ensure that women continue to receive necessary repeat testing over the full recommended surveillance period.

These pathways will depict the patient journey during screening to inform the management of women with these low-grade abnormalities–from the initial screening and all other follow-up tests–to contribute evidence toward ensuring a system of care that is effective for all screened women. This research may influence service planning in terms of understanding additional services and interventions women will require.

1.5 Risk Factors Associated with Cervical Cancer

The possible relationship between management pathways and characteristics of cancer screening participants has not been previously investigated. It would be expected that risk factors associated with cervical cancer will also be predictive of the eventual pathway women follow through cytological surveillance. Specifically, higher odds of membership in the colposcopy referral management pathway would be expected for women with risk factors associated with cervical cancer. It would also be expected that participants in the unresolved pathway would be more likely to have risk factors associated with cervical cancer, relative to those who returned to routine recall. We therefore investigated these associations.

There are several known risk factors associated with cervical cancer, including human papillomavirus, tobacco smoking, age and oral contraception. There is a conflation of risk factors

for cancer development and risk factors for low uptake of screening or poor adherence to follow-up; women who are not being screened or followed-up are expected to have a higher risk of invasive cancer diagnosis. For example, in a previous TOMBOLA article, risk of non-attendance and late attendance for the first and second surveillance test were significantly higher in one or more of the following: younger women, smokers, those without post-secondary education, non-users of prescribed contraception and those with children [40]. A summary of evidence for each risk factor is presented below.

a) Human Papillomavirus

The causal role of human papillomaviruses has been documented extensively. It is the first ever identified "necessary cause" of a human cancer, implying that cervical cancer will not develop in the absence of the persistent presence of HPV DNA. A systematic review that used Bradford Hill's causal criteria concluded that this association is causal in nature [41]. Of the numerous oncogenic HPV types, 70% of cervical cancer is attributed to HPV 16 and 18 [42]. Because HPV infection is often transient and high numbers of women infected with HPV 16 or 18 do not develop cancer, it is therefore a necessary but not sufficient cause of cervical cancer; other risk factors need to be considered [41].

b) Tobacco Smoking

The International Agency for Research on Cancer has concluded that the evidence that tobacco smoking causes cancers of the uterine cervix is "sufficient" [43]. In a recent large prospective study with a mean follow-up time of nine years, it was found that current smokers, those who smoked ten years or more, and even those who smoked less than ten cigarettes per day, showed a

two-fold increased risk of cervical cancer as compared to never-smokers. Additionally, women who had quit smoking for long periods of time (20 or more years) showed a two-fold decreased risk of cervical cancer as compared with current smokers. In a nested case-control study, consistent associations between smoking and cervical cancer were observed, after adjustment for HPV types 11, 16, 18, 31, 33, 35, 45, 52, 58, and antibodies against Chlamydia trachomatis, and Human Herpes Virus 2 [44]. Another large primary study confirmed that smoking is an independent risk factor for cervical cancer in women infected with HPV types 16 or 18 [42]. Several plausible biological mechanisms explain how smoking could increase risk of cervical neoplasms, including presence of tobacco carcinogens in cervical mucus [42, 44]. Furthermore, the International Agency for Research on Cancer's monograph states that there is some evidence of association between exposure to second-hand tobacco smoke and cancer of the uterine cervix [45]. A meta-analysis also suggested that passive smoking significantly and independently increases the risk of cervical cancer [46].

c) Age

Cancer Research UK reported that cervical cancer risk is strongly related to age, with higher incidence in younger women. There are two peaks in the age-specific cervical cancer incidence rates: in women aged 30-34 (at 20 per 100,000 women), and in women aged 80-84 (at 13 per 100,000 women). The first peak is related to women becoming sexually active in their early twenties, increasing HPV infection [47] . Young age at first intercourse is a risk factor for cervical cancer due to the transformation of columnar epithelium of the cervix into squamous epithelium. During this transformation, large areas of transitional cells are formed, all of which support HPV

replication. Further, young age at first intercourse is usually a predictor of larger number of sex partners, which increases the risk of HPV infection [48].

d) Oral Contraception

In a systematic review of hormonal contraceptive use, the authors reported that the relative risks of cervical cancer increased with increasing duration of use. The summary relative risks were 1.1 (95% CI: 1.1-1.2), 1.6 (95% CI: 1.4-1.7), and 2.2 (95% CI: 1.9-2.4), for durations of less than 5 years, 5-9 years, and 10 or more years, respectively, compared with never use. The limited available data also suggest that the relative risk of cervical cancer may decrease after oral contraceptive use ceases [49]. In another systematic review, the risk of cervical cancer was increased with duration of oral contraceptive use; however, the authors did not conduct meta-analysis because of heterogeneity [50]. Another quantitative review found that long-term (> 5 years), current or recent use was associated with a two-fold excess risk of cervical cancer [51].

e) Socioeconomic Status

Socioeconomic status is often measured based on an individual's income, education level, occupation and/or residence. It has been postulated to play a role in cancer etiology via its association with modifiable risk factors for cancer, such as smoking, physical inactivity and being overweight or obese. Furthermore, socioeconomic status is associated with uptake of cancer screening and adherence to follow-up [52]. For example, the Canadian Cancer Society stated that women with lower income have a higher risk of developing cervical cancer primarily because these women are less likely to receive regular Pap tests [9]. In a previous TOMBOLA study, it was found that women without post-secondary education were at higher risk of non-attendance and late

attendance to recommended follow-up cytology testing [40]. Another primary study found that higher education level (college and above compared with junior middle school or lower) was a protective risk factor for HSIL, adjusted for other risk factors (aOR = 0.79, 95% CI: 0.37 – 0.90) [53].

f) Parity

In a large review, an increased number of full-term pregnancies was associated with an increased risk of invasive cervical carcinoma. The risk was 15% higher in women who had 1 full-term pregnancy versus those who had none. After controlling for age at first full-term pregnancy, the relative risk for invasive cervical carcinoma was 1.76 (95% CI: 1.53-2.02) for 7 full-term pregnancies compared with 1-2 [54]. One biological mechanism to explain the association between parity and invasive cervical carcinoma is that high concentrations of estrogen and progesterone during pregnancy and delivery-related cervical traumas cause the eversion of the columnar epithelium onto the ectocervix, which favours the exposure of the squamo-columnal junction to HPV infection [54]. Several other reports and studies support the role of parity in cervical cancer [9, 55, 56].

g) Marital Status

In a review of data on 13,745 women from the United States 2000 National Health Interview Survey, it was found that cancer screening rates were lower in women who reported being unmarried. This was also seen in other U.S. studies with Latino women, Southern farm-women, Mexican, Vietnamese, Taiwanese and Korean-American women, as reviewed by Alberta Health Services [57].

h) Physical Activity Level

Overall, there is insufficient evidence to draw a conclusion on a possible role of physical activity in the development of cervical cancer [12, 58]. However, one study indicated that recommendations on the maintenance of an appropriate Body Mass Index (BMI) with an emphasis on physical activity could be an important preventive strategy against the development of cervical cancer [12]. Physical activity was inversely associated with CIN2/3 and cervical cancer but not with CIN1. Exercise may act as an immune modulator that induces changes in the activity of macrophages, natural killer cells, lymphokine-activated killer cells, neutrophils, and regulating cytokines; however, a mechanism for the role of physical activity in preventing cervical cancer and high-grade CIN has not been clearly proposed [12].

i) Ethnicity

The Canadian Cancer Society stated that there is a higher incidence of cervical cancer in women of African ancestry compared to Caucasian women [9]. A primary study found that Black or Hispanic populations in the United States (US) have higher cervical cancer incidence rates as compared to Non-Hispanic/White populations [59]. Several other studies within an Alberta Health Services review also demonstrate differences in cervical cancer screening rates among ethnic groups [57]. Rates of cervical cancer screening have been historically low among First Nations women in Canada, increasing the risk of cervical cancer in this population. For example, in Ontario, the incidence of cervical cancer is almost two-fold higher among First Nations as compared to the general population, and there are similar differences in the mortality rate [5].

1.6 Psychosocial Impact of Long-term Follow-up and Trajectory of Cytological Surveillance Testing and Interventions

Understanding what proportion of women experience various pathways within a policy of cytological surveillance leads to questions about the impact this has on women's experiences and their overall well-being. Large numbers of women who participate in cervical screening require follow-up for low-grade cytological abnormalities. The immediate negative psychological impact of receiving an abnormal cytology result are well-known and include raised anxiety, cancer-related worries, body image concerns and concerns about infertility [30,60]. A TOMBOLA study examined psychological distress using the Impact of Event Scales at six weeks specifically within the cytological surveillance arm. Of all of the respondents, 39% scored in the range for significant distress. The authors found that distress varied by cytology result: 36% of those with a negative test result were distressed, 42% with BNA or mild dyskaryosis, and 55% with other results (including high grade and inadequate). After adjusting for the test result, distress was associated with those who had significant anxiety at recruitment, reported experiencing pain after the follow-up cytology, had children, or were dissatisfied with support they had received after their initial BNA test. Substantial proportions of women experienced surveillance-related psychological distress after a follow-up cytology test, even when the result was negative [61]. In a Thai cross-sectional study, the authors found that mean Hospital Anxiety and Depression Scale (HADS) scores were significantly higher in women with abnormal Pap test results who were awaiting colposcopy than in women attending the outpatient clinic for check-up [62].

A few studies have examined longer-term follow-up of women with low-grade abnormal cervical cytology. For example, a primary study showed that although the initial anxiety of receiving an abnormal cervical smear result decreased over time for the majority of the women, 35% of women had clinically meaningful anxiety at 12 weeks (based on the State-Trait Anxiety

Inventory) [63]. Two other studies in Sweden and the Netherlands showed that referral for colposcopy after an abnormal cervical smear does not seem to result in long-lasting anxiety and depression [64, 65]. A systematic review with a meta-analysis showed that screening does not appear to have adverse emotional impacts in the longer term (>4 weeks), and too few studies assessed outcomes before four weeks to estimate the shorter term emotional impact of screening [66]. Of the 12 studies included in that review, six of them involved screening for cancer but none were specific to cervical cancer.

Specifically, within TOMBOLA, there were no significant differences in 30-month percentages of significant anxiety (OR=0.97, 95% CI: 0.81-1.16) or depression (OR=0.99, 95% CI: 0.80-1.21) between the cytological surveillance and initial colposcopy arm [30]. Further, among women with low-grade cytology who were randomized to the initial colposcopy arm of TOMBOLA, the cumulative prevalence of significant anxiety was 27% and significant depression was 21% over the thirty-month period. The authors concluded that a normal colposcopy does not appear to provide psychological reassurance for a substantial proportion of women [67].

A TOMBOLA study also investigated whether women's sociodemographic and lifestyle factors were associated with the psychosocial impact of the abnormal smear result at recruitment prior to women knowing how they would be followed up (immediate colposcopy or cytological surveillance). The authors found that women at highest risk of anxiety were younger, had children, were current smokers, or had the highest levels of physical activity [68]. Another TOMBOLA study investigated the association between HPV infection and anxiety among women who were unaware that they had been tested specifically for HPV. They found no association between HPV-positive

status and anxiety among white women; however, among non-white women, anxiety was less common for HPV-positive women than HPV-negative women in the longitudinal analyses (adjusted OR (aOR) = 0.41, 95% CI: 0.22-0.77) [69]. Among non-smokers, cancer worry was more common in HPV-positive women than HPV-positive women, and the opposite association was observed among ex-smokers. Explanations for these observed associations remain unclear, but it is possible that sociodemographic and lifestyle factors other than learning of HPV test results may explain the occurrence of anxiety in this population [69].

Evidently, studies have examined the immediate mental health consequences of receiving an abnormal cervical smear. However, no studies to our knowledge have investigated the psychosocial impacts of long-term follow-up of three years among those undergoing cervical cancer screening, as it relates to the different management pathways, specifically within a policy of cytological surveillance. Moreover, the impact of long-term cervical cancer screening through cytological surveillance on depression was also examined, since comorbidity of anxiety and depression disorders are quite common [70]. If anxiety and depression are of concern at specific time points or within specific management pathways, this may indicate a need for educational or other supports for women managed through cytological surveillance. If such psychosocial impacts are strong, this may raise concerns about how long-term cytological surveillance is implemented as a strategy for managing low-grade abnormal findings.

1.7 Thesis Objectives

Overall, the objectives of this thesis were:

1) To identify and describe management pathways of women with low-grade abnormal cervical cytology randomized to repeat cytology tests ("cytological surveillance") over the three-year follow-up period within the Trial of Management of Borderline and Other-grade Abnormal Smears (TOMBOLA),

2) To identify socio-demographic and clinical characteristics associated with the identified management pathways, and

3) To describe and compare trajectories of anxiety and depression over time and among the identified management pathways.

2. METHODS

2. METHODS

2.1 Summary of TOMBOLA

2.1.0 Study Design

This thesis was a secondary analysis of data from TOMBOLA. TOMBOLA was a pragmatic (i.e. designed to inform decisions about "real-world" practice) RCT nested within the Cervical Screening Programmes in two areas of Scotland (Grampian and Tayside) and one area of England (Nottingham), in which women were followed for three years after receipt of a low-grade abnormal cytology test result. In this thesis, data from TOMBOLA were used to identify and describe the management pathways of women allocated specifically to the cytological surveillance arm, to identify socio-demographic and clinical characteristics associated with the identified pathways, and to examine differences in psychological variables over time and among these pathways. To explain the context of the present study, relevant aspects of the TOMBOLA design are summarized below. Figure 4 provides an overview of the trial design. Full details of the trial design are reported elsewhere [28]. The STrenghtening the Reporting of OBservational studies in Epidemiology Statement was used as a guideline to ensure accurate and complete reporting in this thesis [71].

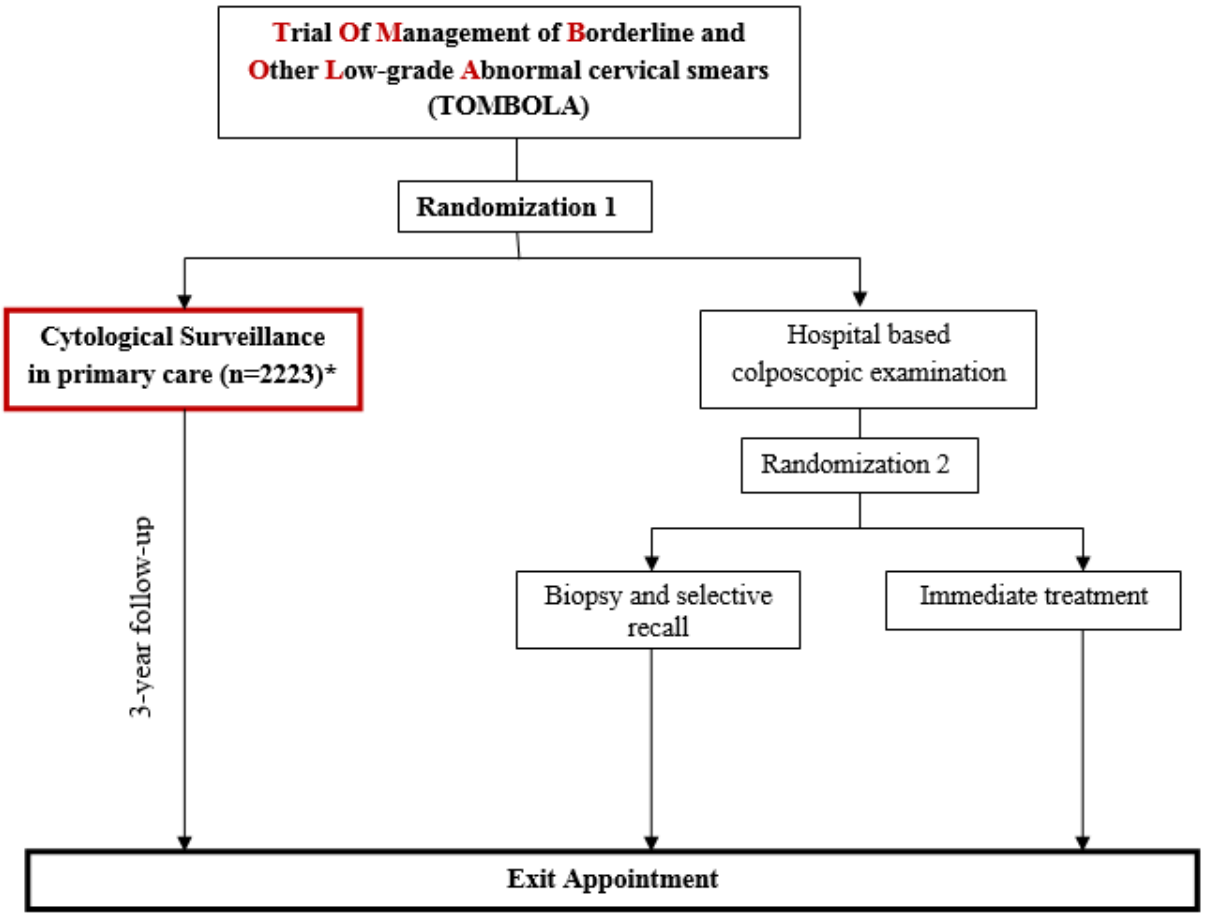


Figure 4. Overview of TOMBOLA trial design

*Present study is based on secondary analysis of data from this arm of the trial.

2.1.1 Eligibility Criteria

Women were eligible if they (1) had a routine (i.e., through cervical cancer screening) Pap smear showing a low-grade cervical cytology result (henceforth termed the 'index' smear) between 1999-2003; (2) were aged 20 to 59 years; (3) were residents of the Grampian, Tayside, or Nottingham areas of the United Kingdom; (4) were not pregnant at the time of recruitment and (5) had no previous treatment for proven or suspected cervical lesions.

There were two phases of recruitment in TOMBOLA, during which different eligibility criteria were in operation. The eligibility criteria in the two recruitment phases are summarized in Table 2 [28]. In the first recruitment phase, October 1999-March 2001, women were eligible if they did not have any abnormal Pap smears in the past three years. Women with a BNA index smear were only eligible if a 'recruitment smear', taken at the TOMBOLA recruitment clinic, indicated BNA or mild dyskaryosis. In the second recruitment phase, March 2001-January 2003, women could have up to one additional BNA smear in the previous three years to be eligible for this study. Women with a BNA index smear were eligible on the basis of the index smear without the need for a recruitment smear.

The rationale for changing the eligibility criteria relating to the smear status in TOMBOLA was primarily due to increasing pressure in the UK to refer women with a single BNA smear to colposcopy; it was important that this was evaluated before there was widespread change in practice [28, 32].

Table 2. Smear history[a], index smear[b] and recruitment smear[c] eligibility criteria

Recruitment phase	Smear history[a]	Index smear[b]	Recruitment smear[c]
Phase 1 (October 1999 – March 2001)	No abnormal smears	BNA	BNA or mild dyskaryosis
	No abnormal smears	Mild dyskaryosis	Not required
Phase 2 (March 2001 – January 2003)	Up to one BNA smear	BNA	Not required
	Up to one BNA smear	Mild dyskaryosis	Not required

[a] Smears taken during the three years prior to the index smear
[b] Smear identified from the cytopathology laboratories databases
[c] Smear taken at TOMBOLA recruitment clinic. Only taken for with women with a BNA index smear during Phase 1

2.1.2 Recruitment

Eligible women were identified from the cytopathology laboratories' (in Aberdeen, Dundee and Nottingham) databases. A letter was sent to the General Practitioner (GP) of each eligible woman informing them that their patient would be invited to participate in TOMBOLA, which gave GPs an opportunity to "opt-out" individual women from the trial. Approximately 30 women were deemed unsuitable for inclusion by their GP due to other medical conditions, language difficulties or difficult personal circumstances. Subsequently, information about TOMBOLA with an invitation to attend a TOMBOLA recruitment clinic was sent to eligible women. At the recruitment clinic, the trial protocol was explained by a research nurse and informed consent sought [28].

2.1.3 Human Papillomavirus Testing

At recruitment, women who consented to participate in the trial were asked if a cervical swab could be taken for "additional testing." The primary purpose of taking this sample was to test for HR-HPV infection. If a participant asked for more specific information about the test, they were informed that the sample was for HPV testing for research purposes and that the result would not be used in their management nor disclosed to the clinicians or to themselves. Less than 1% of the women in the trial asked for more specific information.

The rationale for not disclosing the HPV testing result was three-fold. Firstly, this was done to avoid confounding between management policy and HPV status, as it would have been "impossible to disentangle" the effects of management from the effects of HPV [28]. Secondly, there was insufficient evidence to justify management based on a single HPV test result. Thirdly, it can be argued that it would have been unethical to disclose the nature and result of the test as it could have had a negative psychosocial impact if women were aware of the HPV testing element and their test result, without women understanding its clinical significance [28]. Instead, interactions between HPV test result and the alternative management and treatment policies were tested in relation to cumulative incidence of cervical intraepithelial neoplasia grade 2 or 3 (CIN 2/3) enabling an unbiased evaluation of the role of HPV in triage [72].

Fourteen HR-HPV types–16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68–were tested using the GP5+/6+ general primer system [73]. Women were classified as HR-HPV positive if their sample had an optical density of three times greater than that of the negative controls included in each assay; otherwise they were classified as HR- HPV negative. Samples without recordable levels of DNA were classified as inadequate [28].

2.1.4 Randomization

Participants were randomized 1:1 to either cytological surveillance in primary care (consisting of repeat cervical smears at six monthly intervals) or colposcopy examination at a hospital-based TOMBOLA clinic. A touch-tone telephone randomization service was used.

Randomization was minimized by age group, index smear, HPV result and recruitment centre (Table 3).

Trial participants were monitored for three years after recruitment, during which period all testing and test results were recorded. The participants were invited to an exit appointment at the TOMBOLA clinic, at which point a colposcopy was offered to all women and subsequent treatment offered if necessary [28].

Table 3. Minimization variables and categories for randomization

Minimization Variable	Categories
Age group	20-29 years
	30-39 years
	40-49 years
	50-59 years
Index Smear	*Recruitment Phase 1*
	Mild index[a]
	BNA index with mild repeat smear
	BNA index with BNA repeat smear
	Recruitment Phase 2
	Mild index with no history of abnormal smear[a]
	Mild index with history of previous BNA smear
	BNA index with no history of previous abnormal smear
	BNA index with history of previous BNA smear
HPV result	High-risk HPV positive
	High-risk HPV negative
	Inadequate sample for analysis
	No consent for HPV/no HPV sample available
Recruitment centre	Grampian
	Tayside
	Nottingham

[1]Equivalent groups from first and second recruitment phases
Mild: Mild dyskaryosis; BNA: Borderline Nuclear Abnormalities

2.1.5 Follow-up of Abnormal Cytology–Cytological Surveillance Arm

The procedures and follow-up of TOMBOLA were designed to mimic real-world practice in the National Health Service (NHS) Cervical Screening Programmes. Thus, women who were randomized to cytological surveillance were recommended to have repeat cytology tests every six months in primary care (i.e., at their general practitioner or family planning clinic). They received a letter informing them of their randomization, and of when their next smear was due.

All women entered the study with a low-grade eligible smear. The first surveillance smear was due six months after the eligible smear had been taken. For subsequent smears, the date the smear was due depended on the result of the previous smear, as summarized in Table 4.

Table 4. Summary of action for women randomized to cytological surveillance, National Health Service Cervical Screening Programmes

Smear Result(s)	Action
Inadequate	Repeat cytology test in 1-3 months
Negative	Repeat cytology test in 6 months
Low-grade	Repeat cytology test in 6 months
Moderate dyskaryosis or worse	Refer to NHS colposcopy
Three consecutive inadequate smears	Refer to NHS colposcopy
Three consecutive normal smears	Return to routine screening recall (screening at 3-year intervals)

If the smear was inadequate, a repeat was due one to three months later. If an adequate smear was obtained and the result was negative or low-grade, the subsequent smear was due six months later. If a woman had a cytology test showing moderate dyskaryosis or worse, or three consecutive inadequate tests, she was referred to a NHS colposcopy clinic. For the purpose of this

thesis, once a woman was eligible for colposcopy, her remaining data were not considered for analysis. This is explained in section 2.4. If a woman had three consecutive normal smears, she was eligible for return to "routine recall", i.e. smears at 3-yearly intervals within the screening program.

2.1.6 Hospital Anxiety and Depression Scale (HADS)

Women who consented to participate in the trial were also asked to complete a socio-demographic and lifestyle questionnaire at baseline, and the Hospital Anxiety and Depression Scale (HADS) at five time points: baseline, 12 months, 18 months, 24 months and 30 months– even if they returned to routine recall or were referred for colposcopy at an earlier stage. The HADS questionnaire was offered to women recruited from February 2001 onwards; this subset of the participants were included in the analysis of anxiety and depression [28].

The HADS was a brief self-report measure that was specifically designed to screen for distinct dimensions of anxiety and depression in non-psychiatric hospital departments; somatic symptoms were excluded in order to allow for sufficient distinction between these two mood disorders and to avoid confounding by the underlying physical illness of the patient [74]. Specifically, it was intended for use with medical patients whose experience of anxiety or depression should inform the treating physician. The authors encouraged use of the HADS as a repeated measure to obtain an ongoing picture of a patient's health during the course of medical investigation and treatment [74]. Although the HADS was originally designed to screen for clinically significant depression and anxiety in hospital medical outpatient clinics, it has also been validated in primary

care and community settings [75], and a recent study also established normative HADS data for the UK population [76].

The severity of anxiety and depression was assessed using two subscales each consisting of seven items that were rated on a four-point Likert-type scale. The items for depression focused on the state of reduced ability to experience pleasure (anhedonia), whereas the items for anxiety focused on the psychic manifestations of anxiety neurosis (Appendix A). Scores for each subscale can range from 0-21 with scores categorized as follows: normal (0-7), mild (8-10), moderate (11-14), and severe (15-21); however, the authors indicated that ideally thresholds should be validated in each setting [30, 74]. The results of two literature reviews support its two-factor structure, test-retest reliability, internal consistency and criterion (predictive) validity [77, 78].

2.2 Ethics Approval

This thesis project involved secondary use of research data (previously collected, anonymized data); thus, this study underwent delegated review by the Ottawa Health Science Network Research Ethics Board and received approval (Appendix B). For TOMBOLA itself, ethics approval was obtained from the local ethics committees in each of the study areas prior to the start of the trial. Additionally, the General Practice sub-committees in each area were consulted about the trial.

Anonymized data relating to the women randomized to cytological surveillance were imported from a STATA file into a SAS file. Data cleaning, coding, and analysis were conducted

using SAS 9.3. Annotated log files were maintained throughout. All data were stored securely with password protection.

2.3 Sample Size Considerations

This was a secondary analysis of one arm of the TOMBOLA trial and as such, the sample size (n=2223) was determined by the objectives of the original trial. Therefore, no formal power calculation was carried out for this thesis. However, the available data were examined to determine whether the proposed analyses were feasible. In particular, with respect to the first two objectives of this thesis, namely identifying and describing management pathways of follow-up and identifying baseline sociodemographic and lifestyle characteristics associated with these pathways, multivariable regression analysis was used. A commonly used rule of thumb for multivariable regression analysis is that the effective sample size divided by the number of predictors should be at least 10 or 20 to avoid over-fitting. For a dichotomous outcome, Harrell [79] showed that the effective sample size is the minimum of either the number of subjects with the event of interest or the number of subjects without. There were twenty two predictors of interest in this thesis counting dummy variables for all categorical predictors; thus, we needed to ensure that there were at least 220 – 440 women in each of the management pathways to allow fitting the multivariable regression model.

2.4 Identifying Specific Management Pathways (Objective 1)

As a first step, data cleaning and descriptive analyses were carried out. The trajectories of testing and sequences of test results were identified for women in the cytological surveillance arm of the trial using flow charts (Figure 5 and Appendix C), and subsequently classified into overall management pathways. The smear test results were grouped into four major categories for the purposes of analysis: (1) negative, (2) low-grade (BNA and mild dyskaryosis), (3) inadequate and (4) high-grade (moderate dyskaryosis, severe dyskaryosis, and glandular abnormalities).

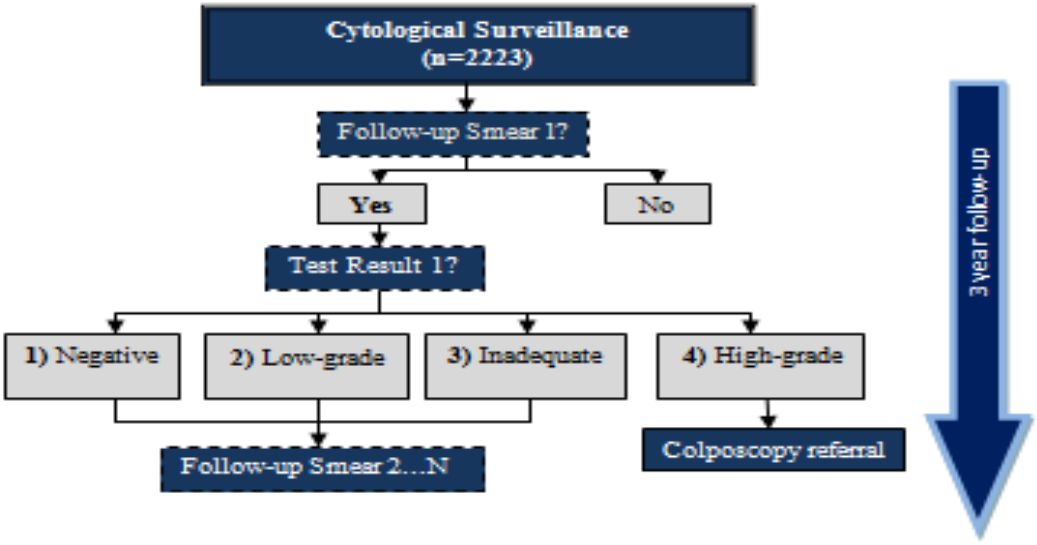


Figure 5. Flow charts to visualize the trajectory of testing and cytology test results

The individual trajectories of test results were examined to identify specific clinical management pathways of interest within the cytological surveillance arm (section 3.2). Due to the longitudinal nature of this study, all of the information available for each woman was used to best summarize the experiences of the trial participant, regardless of the number of smears a woman had within the three years of follow-up. All women who had at least one follow-up surveillance

smear were classified into one of the identified management pathways based on their cytology test results. An additional pathway, namely women who failed to have at least three follow-up surveillance smears before reaching resolution, was identified but not considered further in the present study because a previous publication from the trial addressed the issue of participant drop-out/losses to follow-up in detail [40].

Further, the analysis focused on the test results of women who remained within the cytological surveillance arm. Specifically, once a woman had a "high-grade" test result, she should have received a referral for colposcopy, and would have therefore been ineligible for a repeat cytology test. Thus, it was expected that she would have received the intervention and not to have been followed-up by cytological surveillance beyond that point. To test this expectation, women with a high-grade test result were monitored up to the third follow-up surveillance smear to determine if they (1) did indeed receive a colposcopy examination, (2) had another smear, or (3) did not attend for any further testing. If more than 5% of the women who should have received a referral for colposcopy were found not in fact to have received a colposcopy examination, then it was planned to conduct a sensitivity analysis to exclude those women who did not receive the intervention from the psychosocial analysis. On the basis of identifying management pathways, other deviations from TOMBOLA protocol up to the third surveillance smear–specifically a colposcopy referral for reasons other than a high-grade test result or three consecutive inadequate test results–were also examined.

Next, the frequency and proportion of women with each management pathway were determined, together with 95% CIs as an indication of precision of the estimated prevalence of these management pathways.

2.5 Characteristics Associated with the Identified Management Pathways (Objective 2)

Associations between each management pathway and three categories of variables were investigated: socio-demographic (recruitment age, trial centre, deprivation level, marital status, number of children); lifestyle (smoking status, use of prescribed contraception, physical activity level); and HR-HPV test results at recruitment. The variables investigated have been identified as risk factors for cervical cancer or low uptake of cervical cancer screening, and were an appropriate number given the sample size.

Frequencies and proportions were used to describe the characteristics of the participants in each management pathway. Bivariable tests (Pearson's chi-square tests of association) were conducted to examine differences in participant characteristics between the pathways. Frequencies on the tables were checked to determine whether Fisher's exact test was required ($n \leq 5$). A p-value <0.05 was taken to indicate statistical significance.

A multivariable logistic regression model allowed for the simultaneous assessment of participant characteristics as predictors of management pathways, thus providing an estimate of the independent association of each explanatory variable with the pathway as the outcome.

Multinomial logistic regression modelling was used, since it was anticipated that there would be more than two management pathways identified within the cytological surveillance arm. An unordered multinomial model was used as there was no natural hierarchy in the identified pathways [80]. All variables of clinical relevance, regardless of statistical significance in bivariable testing, were included as independent variables in the model.

Multicollinearity was examined using tolerance and variance inflation factors. Tolerance scores below 0.4, or corresponding variance inflation factors above 4.0 were considered indicative of multicollinearity. If multicollinearity was found, the variable with less scientific evidence and/or with less information was dropped from the full model.

The fit of the multinomial logistic regression model to the data was assessed using deviance and Pearson goodness of fit statistics. In order to obtain a basic measure of overall accuracy, the area under the Receiver-Operating Characteristic curve (also known as the C-statistic) was calculated, with a 95% CI around this estimate, for each pair of management pathways, using conventional logistic regression.

2.6 Trajectories of Anxiety and Depression over Time and Among the Identified Management Pathways (Objective 3)

2.6.1 Descriptive Analysis

The extent of missing data on HADS measures was described. Results were presented over time and within subgroups, defined by management pathways identified in objective 1. Range checks were made to ensure that the scores were between 0 and 21. We graphed raw individual anxiety/depression profiles for participants as well as mean anxiety over time in each management pathway. The individual profiles helped to identify outliers, describe heterogeneity, as well as identify general trends within subjects. The group profiles illustrated the relationship between anxiety/depression and management pathway over time.

Previously, it had been observed that the HADS scores from TOMBOLA were strongly positively skewed [30], so the distribution of HADS scores was examined using visual inspection of histograms. In cases of substantial skewness or departures from normality, normalizing transformations (log and square-root) were considered.

2.6.2 General Linear Model

A general linear model was used to investigate changes in repeated measures of anxiety and depression scores (as continuous variables) over time and across management pathways, and to determine whether there were differences among groups defined by management pathways in

their trajectories of anxiety or depression scores over time. The main predictors of interest in the model were time, management pathway, and their interaction. The analysis adjusted for baseline factors thought to be associated with anxiety and depression; these covariates were high-risk HPV infection at recruitment, smoking status, age group, trial centre, contraception prescribed by the general practitioner, number of children, deprivation, marital status and physical activity. Multiple imputation to account for missing data on the response was not used; instead, a complete case analysis of all available data was carried out. In an attempt to adjust for bias due to attrition under the assumption of "missing at random" (MAR), covariates thought to be potentially associated with anxiety and depression were included in the multivariable regression analysis as main effects.

Time was modelled as categorical rather than continuous, to allow for arbitrary patterns in the mean response to anxiety and depression over time (no specific time trend was assumed). The advantage of this approach is that results are more robust against model misspecification. A disadvantage is that there could be a substantial loss in degrees of freedom with many categories of time; however, in this analysis there were only five measurement times and a large sample size. On the other hand, if the mean response was modelled using parametric or semi-parametric curves, time would have been regarded as a continuous variable, and would have imposed an explicit structure on the mean responses (e.g., linear or quadratic trend) over time. There was no a priori rationale for assuming that the trend was linear or quadratic.

2.6.3 Identifying the Best-fitting Covariance Structure

Longitudinal data analysis requires specification of an appropriate covariance structure to account for correlation in repeated measures on the same participant over time. Selecting an appropriate covariance structure is essential to obtaining valid inferences: if the chosen structure is too simple, the risk of type I error rate is increased, whereas if the chosen structure is too complex, power and efficiency will be sacrificed. Potential covariance models considered were: Unstructured, Compound Symmetry Heterogeneous, and Spatial Power as these structures allow for unequally spaced time intervals. The Unstructured covariance has the advantage of allowing any arbitrary pattern of covariances among the repeated measures; however, the number of covariance parameters can be too large relative to the sample size. In our case, there were 5 measurement occasions, which implies $5(5+1)/2 = 15$ unique covariance parameters. The Compound Symmetric structure, also called "Exchangeable correlation," assumes constant correlation, regardless of distance between time points. In the heterogeneous Compound Symmetry structure, the variances are allowed to vary over time, although covariances remain fixed. In general, compound symmetry is not appropriate for longitudinal data as correlations are rarely constant over time. Spatial Power structures allow for unequal spacing of the repeated measures and the correlation between repeated measures is allowed to depend on time.

The relative fit of various covariance structures was compared using Information Criteria–specifically the Bayesian Information Criterion (also called the Schwarz criterion) and Akaike's Information Criterion–and likelihood ratio tests (see section 3.4 of Results chapter).

2.6.4 Statistical Inferences

If the interaction between time and management pathway was non-significant (indicating no significant differences among the groups over time), the model was re-estimated excluding the interaction term. Adjusted least square means, together with 95% confidence intervals, were then obtained from the reduced model that included the main effects of time, management pathway and the covariates. These means were used to examine changes over time within each of the management pathways.

3. RESULTS

3. RESULTS

This chapter presents the management pathways of 2223 women with low-grade cervical cytological abnormalities randomized to the cytological surveillance arm of the TOMBOLA trial (section 3.2), and relates these to risk factors for cervical dysplasia (section 3.3) and measures of psychological distress (section 3.4).

3.1 Characteristics of the Participants

The baseline characteristics of the participants included in the analysis are presented in Table 5. Just over 50% of the women had HR-HPV negative infection at recruitment. Over 40% of the women were aged 20-29 years, and over 50% of the women were married and had children. The majority of women (95%) self-identified their ethnic group as white. Just over half of the women were from areas classified to be the most deprived according to the Carstairs quintiles (4 & 5), and half of the women had full-time employment and vocational training or a college diploma. Further, 47% of the women reported that they had never smoked, 40% exercised less than once a week, and 54% reported that they did not use contraception prescribed by their GP. Lastly, 42% of the women came from trial centre A. The proportion of women for whom baseline socio-demographic and lifestyle information was missing or unknown was very low, at most 3% (for the number of children).

Table 5. Characteristics of women with low-grade cervical cytological abnormalities

Characteristic *(n for whom data available)*	Frequency	%[1]	% Missing
HPV infection at recruitment *(n=2223)*			0
High-risk HPV negative	1147	51.6	
High-risk HPV positive	875	39.4	
Inadequate/Missing	201	9.0	
Age group *(n=2223)*			0
20 – 29 years	982	44.2	
30 – 39 years	596	26.8	
40 – 49 years	459	20.7	
50 – 59 years	186	8.4	
Marital status *(n=2193)*			1.3
Married/Common-Law	1235	56.3	
Divorced/Separated/Widowed	298	13.6	
Single	660	30.1	
Ever had children *(n=2191)*			1.4
Yes	1238	56.5	
No	953	43.5	
Number of children *(n=2191)*			1.4
0	953	43.5	
1	370	16.9	
2	492	22.5	
3	224	10.2	
4-7	119	5.4	
Not reported	33	1.5	
Ethnicity *(n=2210)*			0.6
White	2112	95.6	
Non-white	98	4.4	
Deprivation quintile *(n=2223)*			0
1 (Least deprived)	318	14.3	
2	418	18.8	
3	354	15.9	
4	565	25.4	
5 (Most deprived)	569	25.6	
Employment Status *(n=2212)*			0.5
Full-time	1096	49.5	
Part-time	512	23.1	
Student	207	9.4	
Not in paid employment	397	17.9	
Level of post-secondary school education *(n=2204)*			0.9
None	620	28.1	
Vocational training/College diploma	1082	49.1	
Degree	502	22.8	

Table 5 Continued

Characteristic *(n for whom data available)*	Frequency	%[1]	% Missing
Smoking status *(n=2193)*			1.3
Never smoked	1027	46.8	
Ex-smoker	383	17.5	
Current smoker	783	35.7	
Physical activity *(n=2183)*			1.8
<1 time/week	879	40.3	
1-3 times/week	534	24.5	
>3 times/week	770	35.3	
Contraception prescribed by GP* *(n=2213)*			0.4
Yes	1014	45.8	
No	1199	54.2	
Trial centre *(n=2223)*			0
A	932	41.9	
B	738	33.2	
C	553	24.9	

Notes
[1]Calculated with missing data excluded
*General Practitioner

3.2 Identifying and Describing Management Pathways (Objective 1)

Three main characteristics of the observed cytology test result and visit patterns informed our characterization of management pathways. Firstly, there was substantial heterogeneity of test results. In particular, although a large proportion of women were eligible for return to routine recall based on having three consecutive negative test results (n=625) after a low-grade abnormal cervical smear at recruitment, the rest of the women had a heterogeneous mixture of smear results, consisting of negative, low-grade and inadequate test results in several different sequences. Secondly, there was a varying number of smears. For example, 827 women had three smears whereas 86 women had six smears, as illustrated in Figure 6. Thirdly, there was substantial loss to follow-up; approximately 21% of women (n=468) were lost to follow-up before having at least three consecutive smears or a high-grade test result.

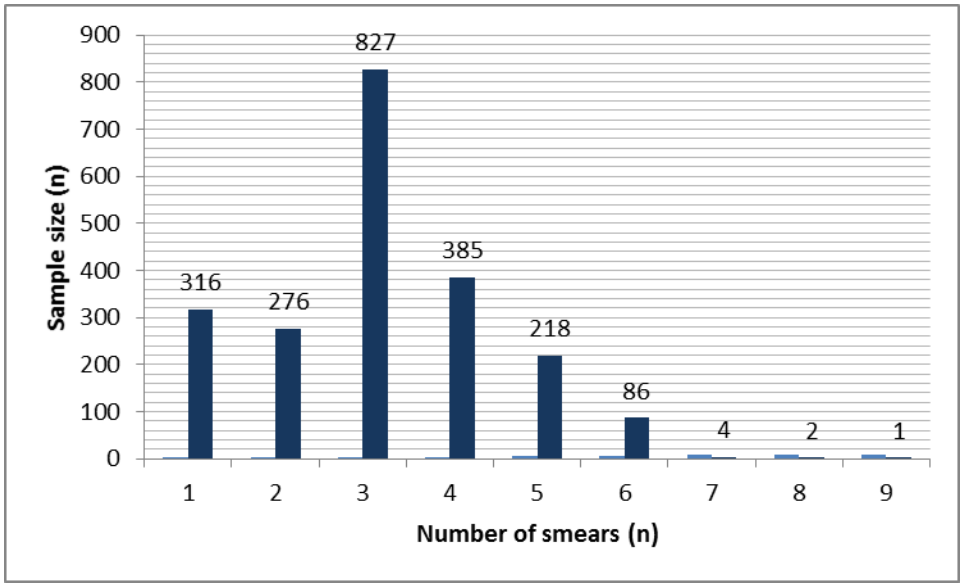


Figure 6. Number of smears women had in the cytological surveillance arm over the three-year follow-up period.

There were 108 women (4.9%) who did not have at least one follow-up smear. These women were excluded from the management pathway analysis, as they did not contribute any information on the trajectory of testing and test results.

On the basis of examining the trajectories of testing for the remaining 2115 women, three mutually exclusive management pathways were identified (Figure 7). The management pathways were: (1) being eligible for return to routine recall, (2) being eligible for colposcopy referral, and (3) having continued unresolved cytology at last follow-up. The first pathway comprised women who had three consecutive negative smear test results, and therefore were eligible for return to routine recall. The second pathway comprised women who had either a high-grade smear test result or three consecutive inadequate test results, and therefore were eligible for a colposcopy referral during the study period. Third, if women were not classified into either of these pathways, then

they were considered to have a management pathway for a sequence of cytology results that was "unresolved." Thus, they had some combination of (1) negative and low-grade or inadequate, or (2) low-grade and inadequate, test results. Appendix D shows a breakdown of the management pathways.

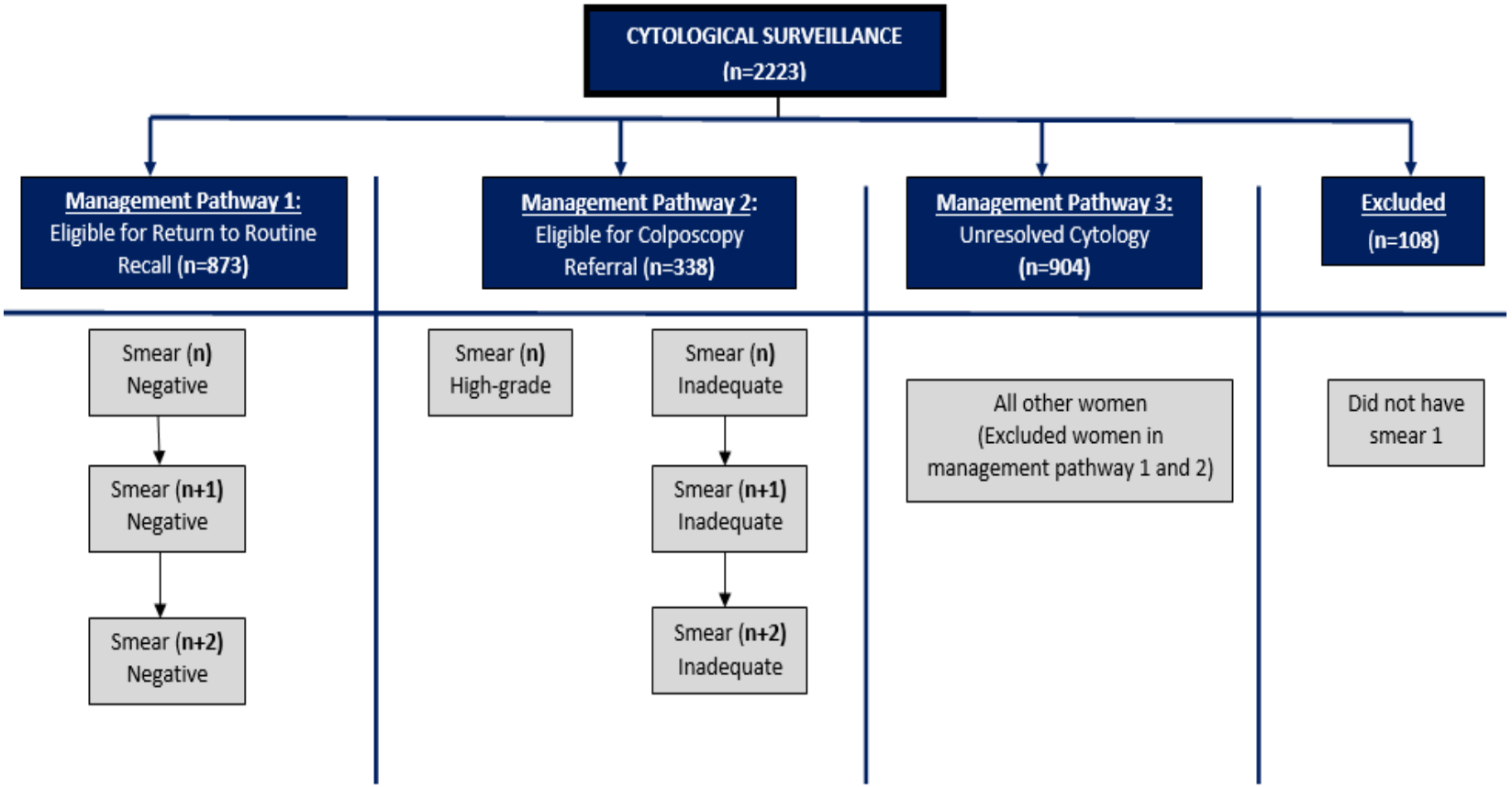


Figure 7. Summary of the management pathways identified in the cytological surveillance arm of the TOMBOLA trial

The proportion of women with each management pathway is presented in Table 6, together with 95% CIs. Of the 2223 women recruited into the cytological surveillance arm of TOMBOLA, 2115 women had at least one follow-up cervical smear after recruitment; 873 [41.3% (95% CI: 39.2 - 43.4)] of the 2115 women were eligible for return to routine recall, while 338 women [16.0% (95% CI: 14.4 - 17.5)] were eligible for referral to colposcopy. Finally, 904 [42.7% (95% CI: 40.6 - 44.9)] continued to have unresolved cytology at last follow-up.

Table 6. Proportion of women in the management pathways over the three-year follow-up period within TOMBOLA, with 95% CIs

Management Pathway	Frequency	Proportion (%) (95% CI)
1. Eligible for Return to Routine recall	873	41.3 (39.2 - 43.4)
a) Eligible after 3 smears	625	71.6
b) Eligible after 4 smears or more	248	28.4
2. Eligible for Colposcopy Referral	338	16.0 (14.4 - 17.5)
a) Eligible after 3 smears	283	83.7
b) Eligible after 4 smears or more	55	16.3
3. Unresolved Cytology	904	42.7 (40.6 - 44.9)

Of the 625 women who were eligible for return to routine recall after the first three consecutive smears, 577 (92.3%) did indeed return to routine recall, 45 (7.2%) had another smear, and 3 received a colposcopy referral (0.5%) (Table 6; and Figure 10c of Appendix C). Almost all women (278 of 283 - 98.2%) who were eligible for a colposcopy referral after the first three smears did indeed receive a colposcopy referral and subsequent colposcopy examination (Table 6; and Figures 10a-e of Appendix C).

Deviations from the TOMBOLA protocol, specifically a colposcopy referral for reasons other than a high-grade test result up to the third follow-up surveillance smear, were also examined (Table 7). Only 50 women deviated from the TOMBOLA protocol when they were due for their first, second or third follow-up surveillance smear. Stated reasons for a colposcopy referral that did not meet the protocol criteria for such a referral were: one or more borderline nuclear abnormalities (14/50, 28.0%), mild dyskaryosis (19/50, 38.0%) or inadequate test results (2/50, 4.0%); bleeding complications (9/50, 18.0%); and a wart /polyp (3/50, 6.0%) on the cervix. Other stated reasons for women deviating from the TOMBOLA protocol were: randomization to the cytological surveillance arm in error so participant was offered colposcopy, the GP was unable to take smears, and clinical suspicion after one BNA and one negative test result (3/50, 6.0%).

Table 7. Prevalence of women who deviated from the TOMBOLA protocol up to the third follow-up surveillance smear

Deviated time point	Frequency	Eligible Women*	%
1. Due for follow-up smear 1	10	2115	0.5
2. Due for follow-up smear 2	23	1956	1.2
3. Due for follow-up smear 3	17	1726	1.0

Notes
*Women who were eligible to have a follow-up surveillance smear, i.e. did not have a high-grade smear test result

Interestingly, almost two thirds of the 50 women whose management deviated from protocol were from areas classified to be the most deprived according to the Carstairs quintiles (4 & 5), and were in the youngest age group (age 20-29) at recruitment (Appendix E).

3.3 Characteristics Associated with the Identified Management Pathways (Objective 2)

The characteristics of participants within each of the three management pathways, and Pearson's chi-square tests of association between these characteristics and the pathways, are presented in Table 8. All characteristics, with the exception of physical activity, were statistically significantly associated with management pathway. The proportion of women with HR-HPV positive infection at recruitment was higher (65%) among those who were eligible for colposcopy referral relative to those with on-going unresolved results (42%) and those eligible for return to routine recall (27%). A similar trend was apparent when considering smoking status: 46% of participants eligible for colposcopy referral were current smokers, compared with 38% among those with unresolved results, and 29% who were eligible for return to routine recall. Interestingly, there was a much lower proportion of women aged 20-29 years among those who were eligible for return to routine recall (30%) than those in the other two management pathway groups. There was also a higher proportion of women in trial centre A who had unresolved cytology at last follow-up relative to those eligible for return to routine recall and those eligible for a colposcopy referral.

Furthermore, there was a lower proportion of women who were prescribed contraception by their general practitioner (39%), and did not have children (36%) among those eligible for return to routine recall relative to those women in the other two management pathways. Lastly, there was a higher proportion of women who were least deprived, and were married or in a common-law relationship, among those eligible for return to routine recall.

Table 8. Bivariable associations between participant characteristics and management pathways

	Management Pathway			
Characteristic (*n*)[1]	**Eligible for Return to Routine Recall (n=873)**	**Eligible for Colposcopy Referral (n=338)**	**Unresolved Cytology (n=904)**	**p-value[2]**
HPV infection at recruitment *(2115)*				**p<0.0001***
High-risk HPV negative	555 (63.6%)	89 (26.3%)	453 (50.1%)	
High-risk HPV positive	234 (26.8%)	220 (65.1%)	377 (41.7%)	
Inadequate/Missing	84 (9.6%)	29 (8.6%)	74 (8.2%)	
Smoking Status *(2085)*				**p<0.0001***
Never smoked	442 (51.1%)	127 (38.1%)	407 (45.9%)	
Ex-smoker	175 (20.2%)	52 (15.6%)	140 (15.8%)	
Current smoker	248 (28.7%)	154 (46.3%)	340 (38.3%)	
Age group *(2115)*				**p<0.0001***
20-29 years	264 (30.2%)	182 (53.9%)	468 (51.8%)	
30-39 years	262 (30.0%)	97 (28.7%)	44 (23.8%)	
40-49 years	225 (25.8%)	41 (12.1%)	176 (19.5%)	
50-59 years	122 (14.0%)	18 (5.3%)	45 (5.0%)	
Trial centre (*2115*)				**p= 0.0011***
A	329 (37.7%)	139 (41.1%)	411 (45.5%)	
B	309 (35.4%)	100 (29.6%)	302 (33.4%)	
C	235 (26.9%)	99 (29.3%)	191 (21.1%)	
Contraception prescribed by GP (*2105)*				**p<0.0001***
No	532 (61.1%)	160 (47.3%)	450 (50.2%)	
Yes	339 (38.9%)	178 (52.7%)	446 (49.8%)	
Ever had children *(2083)*				**p<0.0001***
No	309 (35.9%)	151 (45.2%)	432 (48.7%)	
Yes	552 (64.1%)	183 (55.0%)	456 (51.4%)	
Number of children (2052)				**p<0.0001***
0	309 (36.5%)	151 (45.9%)	432 (49.3%)	
1	148 (17.5%)	64 (19.5%)	148 (16.9%)	
2	234 (27.7%)	67 (20.4%)	170 (19.4%)	
3	101 (11.9%)	32 (9.7%)	82 (9.4%)	
4-7	54 (6.4%)	15 (4.6%)	45 (5.1%)	

Table 8 Continued

	Management Pathway			
Characteristic (*n*)[1]	**Eligible for Return to Routine Recall (n=873)**	**Eligible for Colposcopy Referral (n=338)**	**Unresolved Cytology (n=904)**	**p-value[2]**
Deprivation quintile *(2115)*				**p=0.0088***
1 (Least deprived)	147 (16.8%)	39 (11.5%)	116 (12.8%)	
2	175 (20.0%)	62 (18.3%)	166 (18.4%)	
3	153 (17.5%)	55 (16.3%)	133 (14.7%)	
4	213 (24.4%)	83 (24.6%)	248 (27.4%)	
5 (Most deprived)	185 (21.2%)	99 (29.3%)	241 (26.7%)	
Marital status *(2086)*				**p<0.0001***
Married/Common-law	557 (64.6%)	177 (53.0%)	460 (51.7%)	
Divorced/Separate/Widowed	116 (13.5%)	44 (13.2%)	118 (13.3 %)	
Single	189 (21.9%)	113 (33.8%)	312 (35.1%)	
Physical activity *(2075)*				p=0.5491
<1 time/week	356 (41.3%)	142 (43.2%)	345 (39.0%)	
1-3 times/week	211 (24.5%)	83 (25.2%)	216 (24.4%)	
>3 times/week	295 (34.2%)	104 (31.6%)	323 (36.5%)	

Notes

[1]Number for whom data available

[2]p: Pearson's Chi-Square Test of Association

* (and bold font): Statistically significant (p-value <0.05)

The results of the multinomial logistic regression analysis to identify independent factors associated with classification into one of the three relevant management pathways are presented in Table 9. As a first step, we examined multicollinearity by examining tolerance values less than 0.4 in the regression model. As expected, we found that women who ever had children, and number of children were collinear, with tolerance values less than 0.4; thus, the variable, women who ever had children, was not included in the full model. No other variables in the model were collinear.

Our findings showed that HR-HPV infection at recruitment, smoking status, age group and trial centre were significantly and independently associated with the management pathways. Compared to women with a negative HR-HPV test result at recruitment, women with a positive HR-HPV test result had a four-fold increased odds of being eligible for a colposcopy referral rather than being eligible for return to routine recall; and a three-fold increased odds of being eligible for a colposcopy referral rather than being in the unresolved cytology management pathway. Similarly, current smokers had a two-fold increased odds of being eligible for a colposcopy referral rather than returning to routine recall as compared to never smokers. Current smokers also had approximately a 40% increased odds of being eligible for a colposcopy referral rather than being in the unresolved group, and a 32% increased odds of continuing to have unresolved cytology versus being eligible for return to routine recall. Furthermore, older women had reduced odds of being eligible for a colposcopy referral or being placed in the unresolved group, versus routine recall, as compared to women aged 20-29 years of age. There was also a significant, independent effect of trial centre on the management pathways. For example, women in trial centre B had reduced odds of being eligible for a colposcopy referral, and of having unresolved cytology versus routine recall, as compared to women in trial centre A.

Table 9. Multivariable, multinomial logistic regression model for characteristics associated with management pathways, with conditional Odds ratios (cORs) and 95% CIs

Characteristic	*Colposcopy Referral vs. Routine Recall*[A]	*Unresolved Cytology vs. Routine Recall*[B]	*Colposcopy Referral vs. Unresolved Cytology*[C]
	cOR (95% CI)	**cOR (95% CI)**	**cOR (95% CI)**
HPV infection at recruitment			
High-Risk HPV negative	Ref		
High-Risk HPV positive	**4.45 (3.24 - 6.12)***	**1.44 (1.14 - 1.80)***	**3.10 (2.28 - 4.23)***
Inadequate/Missing	**1.72 (1.00 - 2.96)***	0.99 (0.68 - 1.45)	**1.73 (1.01 - 2.99)***
Smoking status			
Never smoked	Ref		
Current smoker	**1.85 (1.36 - 2.51)***	**1.32 (1.06 - 1.66)***	**1.40 (1.04 - 1.87)***
Ex-smoker	1.17 (0.78 - 1.74)	0.94 (0.71 - 1.24)	1.24 (0.83 - 1.84)
Age group			
20-29	Ref		
30-39	**0.56 (0.38 - 0.83)***	**0.52 (0.39 - 0.70)***	1.07 (0.73 - 1.57)
40-49	**0.33 (0.20 - 0.55)***	**0.52 (0.37 - 0.74)***	0.63 (0.38 - 1.05)
50-59	**0.27 (0.13 - 0.53)***	**0.26 (0.16 - 0.41)***	1.05 (0.51 - 2.14)
Trial centre			
A	Ref		
B	**0.61 (0.43 - 0.86)***	**0.70 (0.55 - 0.89)***	0.87 (0.62 - 1.21)
C	1.04 (0.73 - 1.46)	**0.63 (0.48 - 0.82)***	**1.65 (1.18 - 2.32)***
Contraception prescribed by GP			
No	Ref		
Yes	0.95 (0.70 - 1.30)	0.98 (0.78 - 1.24)	0.97 (0.72 - 1.31)
Number of children			
0	Ref		
1	1.19 (0.79 - 1.79)	0.99 (0.73 - 1.35)	1.20 (0.81 - 1.77)
2	1.35 (0.87 - 2.09)	0.97 (0.71 - 1.33)	1.39 (0.90 - 2.14)
3	1.68 (0.97 - 2.92)	1.20 (0.81 - 1.77)	1.41 (0.81 - 2.43)
4-7	1.14 (0.55 - 2.33)	1.03 (0.63 - 1.68)	1.10 (0.54 - 2.24)

Table 9 Continued

Characteristic	*Colposcopy Referral vs. Routine Recall*[A]	*Unresolved Cytology vs. Routine Recall*[B]	*Colposcopy Referral vs. Unresolved Cytology*[C]
	cOR (95% CI)	**cOR (95% CI)**	**cOR (95% CI)**
Deprivation quintile			
1 (Least Deprived)	Ref		
2	1.47 (0.89 - 2.43)	1.25 (0.88 - 1.76)	1.18 (0.71 - 1.94)
3	1.54 (0.92 - 2.59)	1.16 (0.81 - 1.67)	1.33 (0.79 - 2.22)
4	1.26 (0.78 - 2.04)	1.33 (0.96 - 1.85)	0.94 (0.59 - 1.52)
5 (Most deprived)	1.40 (0.86 - 2.26)	1.29 (0.92 - 1.81)	1.08 (0.67 - 1.73)
Marital status			
Single	Ref		
Divorced/Separated/Widowed	1.09 (0.65 - 1.83)	1.06 (0.72 - 1.55)	1.03 (0.63 - 1.68)
Married/Common-law	0.93 (0.64 - 1.34)	0.79 (0.60 - 1.04)	1.18 (0.83 - 1.66)
Physical activity			
<Once/week	Ref		
1-3 times/week	1.07 (0.75 - 1.53)	1.01 (0.78 - 1.31)	1.06 (0.75 - 1.50)
>3 times/week	0.91 (0.66 - 1.25)	1.07 (0.85 - 1.35)	0.85 (0.62 - 1.16)

Notes
Ref: Reference category
Colposcopy Referral: eligible for a colposcopy referral; Routine Recall: eligible for return to routine recall
* (and bold font): Statistically significant (p-value < 0.05)

A: cOR > 1 shows an increased odds of colposcopy referral compared to routine recall; and cOR <1 shows a reduced odds of colposcopy referral compared to routine recall.
B: cOR > 1 shows an increased odds of unresolved cytology compared to routine recall; and cOR <1 shows a reduced odds of unresolved cytology compared to routine recall.
C: cOR > 1 shows an increased odds of colposcopy referral compared to unresolved cytology; and cOR <1 shows a reduced odds of colposcopy referral compared to unresolved cytology.

Out of the 2115 observations, 1997 observations (94.4%) were used due to missing values for the explanatory variables.
HPV infection at recruitment, smoking status, age group and trial centre were statistically significant beyond the 0.05 level
Deviance and Pearson Goodness-of-Fit Statistics: p-value: 0.80 and 0.26, respectively, suggesting that the data fitted the model well

Next, the discrimination of the full model was assessed by calculating three separate c-statistics, along with 95% CIs. This was done by fitting three ordinary logistic regression models to each management pathway versus a comparator. For women eligible for a colposcopy referral compared with those eligible for routine recall, the c-statistic was 0.76 (95% CI: 0.73 - 0.79). The c-statistic was lower for the other two pairwise comparisons of the management pathways, i.e. for women with unresolved cytology compared with those eligible for return to routine recall [c-statistic: 0.66 (95% CI: 0.64 - 0.69)]; and for women eligible for a colposcopy referral compared with those with unresolved cytology [c-statistic: 0.68 (95% CI: 0.64 - 0.71)].

3.3.1 Sensitivity Analysis of Possible Impact of Loss to Follow-up

It is possible that the unresolved cytology management pathway identified within the cytological surveillance arm could be very heterogeneous because of inclusion of women who were lost to follow-up from the TOMBOLA study after various number of smears, since, for example, women who did not attend for at least three smears did not have the opportunity to meet the criteria to be returned to routine recall. Thus, some of the differences observed in our analysis may be explained by factors associated with loss to follow-up. To examine whether these findings were robust to the decisions made about the process of identifying these management pathways, a sensitivity analysis was conducted by excluding women who had less than three follow-up surveillance smears in this pathway.

The results from that sensitivity analysis were very similar to the full model, with respect to both direction and magnitude (Table 10). HR-HPV infection at recruitment, smoking status, age group and trial centre were still independently associated with the management pathways identified. There were a few differences to be noted. Firstly, associations with smoking were attenuated in the sensitivity model as compared to the full model. Compared to never smokers, current smokers no longer had a significant increased odds of having unresolved cytology rather than being eligible for return to routine recall. Secondly, older women generally had increased odds of having an unresolved cytology management pathway rather than being eligible for return to routine recall in the sensitivity analysis, though the difference was still in the same direction. Thirdly, women aged 40-49 no longer had a statistically significant reduced odds of having unresolved cytology relative to those eligible for return to routine recall. Lastly, the pairwise discrimination ability, even after excluding women who had less than three follow-up surveillance smears, was very similar to that for the primary analysis (data not shown).

Table 10. Multivariable, multinomial logistic regression model for characteristics associated with management pathways, with conditional Odds ratios (cORs) and 95% CIs–Sensitivity analysis

Characteristic	*Colposcopy Referral vs. Routine Recall*[A]	*Unresolved Cytology vs. Routine Recall*[B]	*Colposcopy Referral vs. Unresolved Cytology*[C]
	cOR (95% CI)	**cOR (95% CI)**	**cOR (95% CI)**
HPV Infection at Recruitment (n=1755)			
High-risk HPV negative (n=923)	Ref		
High-risk HPV positive (n=680)	**4.37 (3.18 - 6.02)****	**1.48 (1.14 - 1.91)****	**2.99 (2.14 - 4.17)****
Unknown/missing (n=152)	**1.70 (0.99 - 2.93)****	0.99 (0.64 - 1.55)	1.73 (0.95 - 3.15)
Smoking Status (n=1734)			
Never smoker (n=834)	Ref		
Current smoker (n=592)	**1.80 (1.32 - 2.45)****	1.15 (0.88 - 1.48)	**1.56 (1.13 - 2.15)****
Ex-smoker (n=308)	1.16 (0.78 - 1.74)	0.83 (0.60 - 1.14)	1.40 (0.91 - 2.16)
Age group (n=1755)			
20-29 (n=699)	Ref		
30-39 (n=490)	**0.56 (0.38 - 0.84)****	**0.61 (0.43 - 0.86)****	0.93 (0.61 - 1.42)
40-49 (n=388)	**0.33 (0.20 - 0.56)****	0.69 (0.46 - 1.04)	**0.48 (0.28 - 0.83)****
50-59 (n=178)	**0.27 (0.14 - 0.54)****	**0.41 (0.24 - 0.69)****	0.64 (0.30 - 1.37)
Trial Centre (n=1755)			
A (n=592)	Ref		
B (n=427)	**0.63 (0.44 - 0.89)****	**0.69 (0.53 - 0.91)****	0.91 (0.64 - 1.29)
C (n=736)	1.04 (0.73 - 1.47)	**0.47 (0.34 - 0.64)****	**2.22 (1.51 - 3.24)****
Contraception prescribed by GP (n=1748)			
No (n=961)	Ref		
Yes (n=787)	0.92 (0.67 - 1.26)	1.15 (0.88 - 1.50)	0.79 (0.57 – 1.10)
Number of children (n=1706)			
0 (n=703)	Ref		
1 (n=303)	1.22 (0.80 – 1.85)	1.08 (0.76 – 1.53)	1.14 (0.74 – 1.75)
2 (n=415)	1.36 (0.87 – 2.12)	1.05 (0.73 – 1.50)	1.31 (0.82 – 2.10)
4-7 (n=94)	1.02 (0.49 – 2.11)	0.93 (0.52 – 1.64)	1.13 (0.52 – 2.45)
Deprivation (n=1755)			
1 (Least deprived) (n=263)	Ref		
2 (n=349)	1.43 (0.86 - 2.38)	1.27 (0.86 - 1.87)	1.14 (0.67 - 1.94)
3 (n=289)	1.44 (0.85 - 2.42)	1.03 (0.68 - 1.55)	1.42 (0.82 - 2.46)

Table 10 Continued

Characteristic	*Colposcopy Referral vs. Routine Recall*[A]	*Unresolved Cytology vs. Routine Recall*[B]	*Colposcopy Referral vs. Unresolved Cytology*[C]
	cOR (95% CI)	**cOR (95% CI)**	**cOR (95% CI)**
Deprivation (n=1755)			
4 (n=431)	1.22 (0.75 - 1.99)	1.11 (0.76 - 1.61)	1.13 (0.67 - 1.88)
5 (Most deprived) (n=423)	1.38 (0.85 - 2.25)	1.21 (0.83 - 1.77)	1.17 (0.71 - 1.94)
Marital status (n=1733)			
Single (n=478)	Ref		
Divorced/Separated/Widowed (n=240)	1.07 (0.64 - 1.81)	1.09 (0.71 - 1.67)	0.99 (0.58 – 1.69)
Married/Common-law (n=1015)	0.89 (0.62 - 1.30)	0.74 (0.54 - 1.02)	1.21 (0.83 - 1.77)
Physical activity (n=1722)			
<Once/week (n=721)	Ref		
1-3 times/week (n=422)	1.13 (0.79 - 1.61)	0.98 (0.73 - 1.31)	1.15 (0.79 - 1.67)
>3 times/week (n=579)	0.93 (0.67 - 1.29)	0.96 (0.74 - 1.26)	0.97 (0.69 - 1.36)

Notes

Ref: Reference category

Colposcopy Referral: eligible for a colposcopy referral; Routine Recall: Eligible for return to Routine Recall

***** (and bold font): Statistically significant (p-value <0.05)

A: cOR > 1 shows an increased odds of colposcopy referral compared to routine recall; and cOR <1 shows a reduced odds of colposcopy referral compared to routine recall.

B: cOR > 1 shows an increased odds of unresolved cytology compared to routine recall; and cOR <1 shows a reduced odds of unresolved cytology compared to routine recall.

C: cOR > 1 shows an increased odds of colposcopy referral compared to unresolved cytology; and cOR <1 shows a reduced odds of colposcopy referral compared to unresolved cytology.

Out of the 1755 observations, 1659 observations (94.5 %) were used due to missing values for the explanatory variables.

HPV infection at recruitment, smoking status, age group and trial centre were statistically significant beyond the 0.05 level

Deviance and Pearson Goodness-of-Fit Statistics: p-value: 0.85 and 0.33, respectively, suggesting that the data fitted the model well

3.4. Trajectories of Anxiety and Depression over Time and Among the Identified Management Pathways (Objective 3)

3.4.1 Descriptive Analysis

In the exploratory phase, the anxiety and depression assessments from the Hospital Anxiety and Depression Scale (HADS) data set were examined for missing values at each time point and across the three identified management pathways, as illustrated in Tables 11 and 12. This analysis was based on all women recruited to TOMBOLA from February 2001 onwards, the time at which the psychosocial assessments were introduced; thus, 1703 of the 2223 (76.6%) women in the study were eligible to complete the HADS questionnaire. Of the 1703 women, 1622 (95.2%) could be classified into one of the three identified management pathways because 81 women did not have at least one follow-up smear.

Although there were few missing data (4.7%) at baseline, almost half of the women (45.7%) did not complete the anxiety and depression subscale of the HADS questionnaire at the last follow-up. However, 1592 and 1590 of the 1622 women (98.2%, 98.0%) completed the anxiety and depression subscale of the HADS at some time point, including recruitment, within the three-year follow-up period, respectively. Women who had an unresolved test result at last follow-up had the highest proportion of missing data from both the anxiety and depression subscale of the HADS at the 30-month assessment after completing the baseline assessment, followed by women who were eligible for a colposcopy referral and return to routine recall.

Table 11. Frequency and % of eligible women who completed the anxiety subscale of the HADS questionnaire across the three identified management pathways at each time point

Time Point	1: Routine Recall (n=718)[1]	2:Colposcopy Referral (n=232)[1]	3:Unresolved Cytology (n=672)[1]	Total (n=1622)[1]
Baseline	690 (96.1)	223 (96.1)	633 (94.2)	1546 (95.3)
12 months	568 (79.1)	169 (72.8)	375 (55.8)	1112 (68.6)
18 months	541 (75.3)	145 (62.5)	311 (46.3)	997 (61.5)
24 months	510 (71.0)	138 (59.5)	305 (45.4)	953 (58.8)
30 months	475 (66.2)	135 (58.2)	271 (40.3)	881 (54.3)

Notes
[1]Proportion of 1622 women eligible to complete the HADS questionnaire (%)

Table 12. Frequency and % of eligible women who completed the depression subscale of the HADS questionnaire across the three identified management pathways at each time point

Time Point	1: Routine Recall (n=718)[1]	2:Colposcopy Referral (n=232)[1]	3:Unresolved Cytology (n=672)[1]	Total (1622)[1]
Baseline	690 (96.1)	222 (95.7)	633(94.2)	1545 (95.3)
12 months	575 (80.1)	168 (72.1)	375 (55.8)	1118 (68.9)
18 months	543 (75.5)	148 (63.8)	314 (46.7)	1005 (62.0)
24 months	512 (71.3)	138 (59.5)	305 (45.4)	955 (58.9)
30 months	474 (66.0)	136 (58.6)	271 (40.3)	881 (54.3)

Notes
[1]Proportion of women eligible to complete the HADS questionnaire (%)

When visualized (Figures 13 and 14 in Appendix F), the distribution of responses to the anxiety and depression subscales of the HADS were each positively skewed, but neither square root nor log transformations substantially improved these distributions. For this reason and due to the large sample size, we conducted the analyses on the original scale.

3.4.2 Differences in ANXIETY Scores (HADS) Among Management Pathways over Time

Figure 8 presents the observed mean anxiety profiles in the three management pathways, i.e. eligible for return to routine recall, eligible for a colposcopy referral, and unresolved cytology. Mean anxiety scores were similar at baseline among the management pathways, and there were no notable differences over time. Generally, there seemed to be a decrease in mean anxiety scores over time across the management pathways.

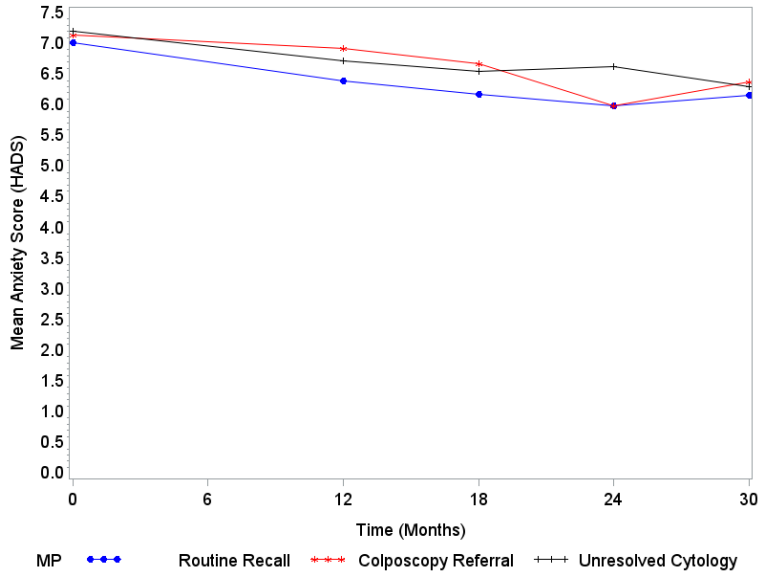


Figure 8. Mean anxiety score (increments of 0.5) over time by Management Pathway (MP)

An important step in longitudinal data analysis is to identify an appropriate covariance structure to account for correlation in repeated measures over time. Table 13 presents the information criteria and log-likelihood ratio tests that were used to identify a suitable covariance structure. The unstructured covariance minimized both the Akaike Information Criteria (AIC) and Schwarz's Bayesian Information Criteria (BIC), and was further identified by the likelihood ratio test as being a significantly better fit than other covariance structures. The unstructured covariance was therefore specified in all anxiety analyses.

Table 13. Information criteria comparing three covariance pattern models, anxiety subscale of the HADS

	Unstructured	Spatial Power	Compound Symmetry Heterogeneous
AICC[1]	27 330.2*	27 568.4	27 564.2
BIC	27 409.9*	27 579.0	27 596.1
-2 Res LL	27 300.1	27 564.4	27 552.2
Parameters	15	2	6

Notes
*Minimized Information Criteria
[1]AIC, adjusted for number of parameters in the model
Adjusted for HR-HPV infection, age group, smoking status, deprivation status, marital status, number of children, activity level, contraception prescribed by GP, and trial centre.

The primary research question for this portion of the analysis was whether the patterns of change from baseline in mean anxiety levels were significantly different between the identified management pathways, i.e. whether there was a management pathway by time interaction effect, and in particular, whether there were any pairwise differences at the thirty-month mark. Table 14 presents the results of the full multivariable regression analysis that includes the main effects for time (including at baseline), management pathway and the interaction between management pathway and time, as well as all covariates of interest. The p-value for the interaction was non-significant (p=0.29) indicating no significant difference in the longitudinal HADS mean anxiety responses among the management pathways over time. The overall tests of differences in least square mean anxiety responses among the management pathways at each time point are presented in Table 15. There were no statistically significant differences in mean anxiety scores observed among the three management pathways at any of the time points.

Table 14. Multivariable regression analysis–main effects for time, management pathway and the interaction between management pathways and time on mean anxiety scores

Effect	Estimate	Standard Error	p-value[1]	Overall p-value[2]
Intercept	5.60	0.46	**<0.0001***	
Management Pathway				0.28
Eligible for return to Routine Recall	**REF**			
Eligible for a Colposcopy Referral	-0.10	0.35	0.78	
Unresolved Cytology	0.05	0.25	0.85	
Time				**0.0009***
Baseline	**REF**			
12 months	-0.48	0.17	**0.004***	
18 months	-0.67	0.18	**0.0002***	
24 months	-0.85	0.18	**<0.0001***	
30 months	-0.72	0.19	**0.0002***	
Management Pathway*Time Interaction				0.29
Eligible for Return to Routine Recall	**REF**			
Colp[3], Baseline	**REF**			
Colp[3], 12 months	0.48	0.34	0.16	
Colp[3], 18 months	0.55	0.38	0.15	
Colp[3], 24 months	0.24	0.38	0.53	
Colp[3], 30 months	0.24	0.40	0.56	
Unresolved, Baseline	**REF**			
Unresolved, 12 months	0.39	0.26	0.13	
Unresolved, 18 months	0.37	0.28	0.19	
Unresolved, 24 months	0.64	0.29	**0.03***	
Unresolved, 30 months	0.17	0.31	0.59	
Covariates				
High-risk HPV infection				0.27
High-risk HPV negative	**REF**			
High-risk HPV positive	0.05	0.23	0.83	
High-risk HPV Inadequate/Missing	0.55	0.34	0.11	
Smoking status				**<.0001***
Never smoked	**REF**			
Current smoker	1.09	0.22	**<0.0001***	
Ex-smoker	0.43	0.27	0.11	
Age group				0.44
20-29 years	**REF**			
30-39 years	-0.17	0.29	0.55	
40-49 years	-0.54	0.34	0.11	
50-59 years	-0.41	0.43	0.34	
Trial Centre				0.06
A	**REF**			

Table 14 Continued

Effect	Estimate	Standard Error	p-value[1]	Overall p-value[2]
B	-0.48	0.23	**0.04***	
C	0.04	0.25	0.88	
Contraception prescribed by GP				0.29
No	**REF**			
Yes	-0.24	0.23	0.29	
Number of children				**0.001***
0	**REF**			
1	0.49	0.30	0.10	
2	0.79	0.30	**0.009***	
3	1.01	0.38	**0.009***	
4-7	1.89	0.47	**<0.0001***	
Deprivation quintile				0.06
1 (Least deprived)	**REF**			
2	0.06	0.33	0.86	
3	0.15	0.35	0.67	
4	0.46	0.32	0.14	
5 (Most deprived)	0.80	0.33	**0.01***	
Marital status				0.58
Single	**REF**			
Divorced/Separated/Widowed	0.35	0.37	0.34	
Married/Common-law	0.05	0.27	0.84	
Physical activity				**<0.0001***
<1 time/week	**REF**			
1-3 times/week	0.39	0.25	0.11	
>3 times/week	1.10	0.22	**<0.0001***	

Notes
[1]t-test of the beta coefficient; [2]Wald type 3 test of fixed effect (overall test of effects on anxiety)
[3]Colp: women eligible for a colposcopy referral; Ref: Reference
* (and bold font): Statistically Significant, p-value <0.05; 5202 of 7960 (65.4%) observations were used.

Table 15. Overall tests of differences in least square mean anxiety scores among the three management pathways at each time point

Time	Multivariable model* p-value
Baseline	0.91
12 months	0.25
18 months	0.25
24 months	0.06
30 months	0.78

Notes
*Adjusted for high-risk HPV status, age group, smoking status, deprivation, marital status, number of children, activity level, contraception prescribed by the GP, and trial centre.

Since the results demonstrated that there were no significant differences among the management pathways with respect to the time trend in mean anxiety levels, the interaction term was removed from the model. The final multivariable regression analysis results for the anxiety implications are presented in Table 16.

In this model, there were no statistically significant differences in mean anxiety scores among the three management pathways ($p=0.50$) in the full cohort, adjusted for the women's baseline characteristics. However, there was a significant reduction in mean anxiety levels over time ($p<0.0001$) in the full cohort, averaged across the management pathways and adjusted for the women's baseline characteristics. Smoking status, number of children and physical activity were significantly associated with repeated measures of anxiety, while deprivation quintile showed a trend towards a significant association with anxiety. Specifically, current smokers had significantly higher mean anxiety scores than non-smokers, while women with two or more children had significantly higher anxiety scores than women with no children. Women who reported that they exercised more than three times per week had higher anxiety scores relative to those who reported that they exercised less than once per week. Lastly, women who were from areas classified to be the most deprived had increased anxiety responses, on average, compared to those who were least deprived.

Table 16. Multivariable regression analysis–main effects for time and management pathway on mean anxiety scores

Effect	Estimate	Standard Error	p-value[1]	Overall p-value[2]
Intercept	5.48	0.45	**<0.0001***	
Management pathway				0.50
Eligible for return to Routine Recall	**REF**			
Eligible for a Colposcopy Referral	0.14	0.30	0.65	
Unresolved Cytology	0.26	0.22	0.24	
Time				**<0.0001***
Baseline	**REF**			
12 months	-0.27	0.12	**0.03***	
18 months	-0.45	0.13	**0.0004***	
24 months	-0.59	0.13	**<0.0001***	
30 months	-0.60	0.14	**<0.0001***	
Covariates				
High-risk HPV infection				0.27
High-risk HPV negative	**REF**			
High-risk HPV positive	0.05	0.23	0.83	
High-risk HPV Inadequate/Missing	0.55	0.34	0.11	
Smoking status				**<0.0001***
Never smoked	**REF**			
Current smoker	1.09	0.22	**<0.0001***	
Ex-smoker	0.43	0.27	0.11	
Age group				0.44
20-29 years	**REF**			
30-39 years	-0.17	0.29	0.56	
40-49 years	-0.54	0.34	0.12	
50-59 years	-0.41	0.43	0.34	
Trial centre				0.07
A	**REF**			
B	-0.48	0.23	**0.04***	
C	0.04	0.25	0.86	
Contraception prescribed by GP				0.30
No	**REF**			
Yes	-0.24	0.23	0.30	
Number of children				**0.001***
0	**REF**			
1	0.49	0.30	0.10	
2	0.79	0.30	**0.009***	
3	1.00	0.38	**0.009***	
4-7	1.89	0.47	**<0.0001***	
Deprivation quintile				
1 (Least deprived)	**REF**			0.06
2	0.06	0.33	0.87	
3	0.15	0.35	0.67	

Table 16 continued

Effect	Estimate	Standard Error	p-value[1]	Overall p-value[2]
4	0.46	0.32	0.15	
5 (Most deprived)	0.80	0.33	**0.01***	
Marital status				0.57
Single	**REF**			
Divorced/Separated/Widowed	0.35	0.37	0.34	
Married/Common-law	0.05	0.27	0.84	
Physical activity				**<0.0001***
<1 time/week	**REF**			
1-3 times/week	0.40	0.25	0.11	
>3 times/week	1.10	0.22	**<0.0001***	

Notes
[1]t-test of the beta coefficient; [2]Wald type 3 test of fixed effect (overall test of effects on anxiety); Ref: Reference
* (and bold font): Statistically Significant, p-value <0.05; 5202 of 7960 (65.4%) observations were used.

Table 17 presents the least square mean anxiety levels in the three management pathways over time for an "average woman". Since HADS scores of 0-7 indicate no anxiety, and scores of 8-11 indicate mild anxiety, the average profile for women in all three management pathways indicated high normal anxiety scores at baseline with slight decreases over time.

Table 17. Model-based mean anxiety profiles over time in each management pathway[1]

Time Point	Routine Recall1	Colposcopy Referral	Unresolved Cytology
Baseline	7.06	6.96	7.11
12 months	6.58	6.96	7.02
18 months	6.40	6.84	6.82
24 months	6.22	6.35	6.90
30 months	6.35	6.48	6.56

Notes
[1]Statistically significant mean anxiety at each time point, p-value <.0001

3.4.3 Sensitivity Analysis–Two Subgroups of the Unresolved Cytology Management Pathway (Anxiety Subscale of the HADS)

Sensitivity analysis was conducted to determine whether the patterns of change from baseline in the mean anxiety levels were significantly different between women in the unresolved cytology pathway who had some combination of (1) negative and low-grade or inadequate, versus (2) low-grade and inadequate, test results, regardless of the number of smears. Specifically, it was anticipated that there would be higher mean anxiety scores (and possibly depression) for women with at least one negative test result over the three-year period.

In the exploratory phase, the anxiety assessments from the HADS were examined for missing values in these two sub-groups of the unresolved cytology management pathway. Of the 672 women in the unresolved cytology pathway, 122 of these women had no negative test results (18.2%) and 550 women had at least one negative test result at last follow-up (81.8%). Trends over time by management pathway were visualized (Appendix G), and from the graph, there were no noteworthy differences in mean anxiety over time between those in the unresolved cytology management pathway who had no negative test results (Unresolved A) as compared to those who had at least one negative test result (Unresolved B).

An overall test of differences in least square mean anxiety responses among the four management pathways at each time point was carried out. Table 18 shows that there were no significant differences in mean anxiety scores among the four management pathways at baseline, 12 months, 18 months, 24 months, and 30 months at the 5% level.

Table 18. Overall tests of differences in least square mean anxiety scores among the four management pathways at each time point–Sensitivity analysis

Time	Multivariable model* P-value
Baseline	0.89
12 months	0.39
18 months	0.40
24 months	0.11
30 months	0.87

Notes
*Adjusted for high-risk HPV status, age group, smoking status, deprivation, marital status, number of children, activity level, contraception prescribed by GP, and trial centre.

3.4.4 Sensitivity Analysis–Limit Heterogeneity within Unresolved Cytology Management Pathway (Anxiety Subscale of the HADS)

To limit the heterogeneity within the unresolved cytology management pathway, women who had less than three follow-up surveillance smears were excluded from the longitudinal analysis; it was possible that some of the differences observed in our analysis may be explained by factors associated with loss to follow-up.

After excluding women who had less than three follow-up surveillance smears, 403 of the 672 women (60.0%) in the unresolved cytology management pathway were eligible to have completed the HADS questionnaire; and 1592 out of the 1703 women (93.5%) recruited for the HADS questionnaire had at least one anxiety measurement at some point within the three-year follow-up period. In the exploratory phase, the anxiety assessments from the HADS data set were examined for missing values in the unresolved cytology management pathway at each time point. Even after excluding women who had less than three follow-up surveillance smears from the unresolved cytology management pathway, these women still had the highest proportion of

missing data at the 30-month assessment after completing the baseline assessment. To visualize mean anxiety profiles in women who were eligible for return to routine recall, eligible for a colposcopy referral and had continued unresolved status after three consecutive surveillance smears, we graphed this (Appendix G). Overall, the mean anxiety scores seemed to decrease over time, averaged across the management pathways.

In this sensitivity analysis, first, we sought to investigate whether the patterns of change from baseline in the mean anxiety levels were significantly different between the identified management pathways. Consistent with the original analysis, the overall tests of differences among the three overall management pathways at each time showed that there were no significant differences at baseline, 12 months, 18 months, 24 months, and 30 months, with a p-value >0.05 (Table 19).

Table 19. Overall tests of differences in least square mean anxiety scores among the three management pathways at each time point, excluding women with less than three follow-up surveillance smears in unresolved cytology–Sensitivity analysis

Time	Multivariable model* p-value
Baseline	0.78
12 months	0.33
18 months	0.35
24 months	0.17
30 months	0.89

*Adjusted for high-risk HPV status, age group, smoking status, deprivation, marital status, number of children, activity level, contraception prescribed by the GP, and trial centre.

For this reason, the interaction term of management pathway by time was excluded from the model (Appendix H). Consistent with the original analysis, the effect of the management pathway was not significant, and there was a significant reduction in mean anxiety levels over time ($p<0.0001$) in the full cohort, adjusted for the women's baseline characteristics. Smoking status, number of children and activity were still significantly associated with mean anxiety scores over time. The effect of deprivation quintile (based on the women's home postal code), was no longer close to statistical significance, and trial centre now had a significant effect on mean anxiety scores. Specifically, the average woman in trial centre B had reduced anxiety scores over time at baseline as compared to the average woman in trial centre A.

3.4.5 Differences in DEPRESSION Scores (HADS) Among Management Pathways over Time

Similar to the longitudinal analysis conducted for the anxiety subscale of the HADS, the mean depression profiles in the three management pathways were visualized (Figure 9). Mean depression scores were similar at baseline. In contrast to the anxiety profiles in which a slight decrease in mean anxiety scores over time over all management pathways was observed, there appears to be an increase in mean depression scores over time, except in women who were eligible for a colposcopy referral.

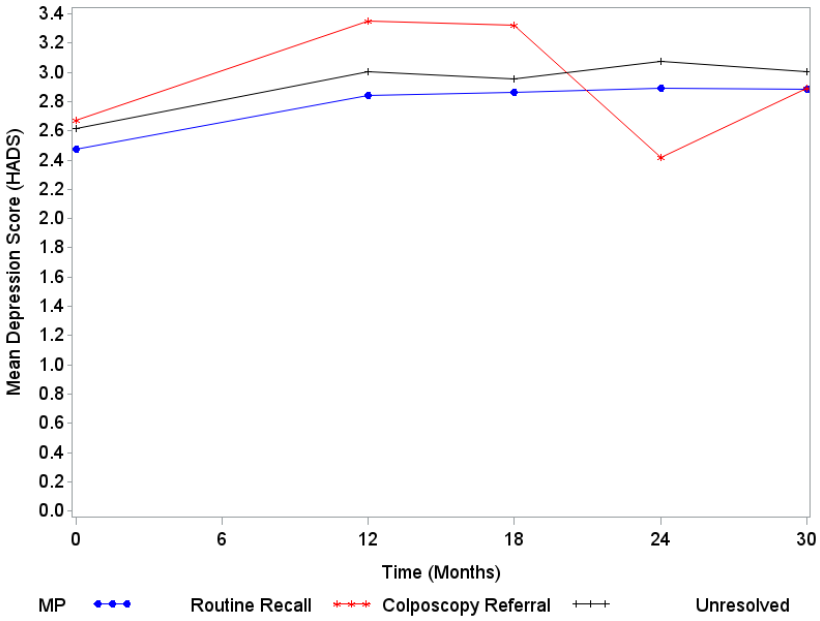


Figure 9. Mean depression score (increments of 0.2) over time by management pathway (MP)

As discussed for the anxiety longitudinal data analysis (section 3.4.2), an important step for this type of analysis is to identify an appropriate covariance structure to account for correlation in repeated measures over time. Information criteria and log-likelihood tests were used to identify a suitable covariance structure (Table 20). The unstructured covariance minimized both the AIC and the BIC, and was further identified by the likelihood ratio test as being a significantly better fit than other covariance structures. The unstructured covariance was therefore specified in all depression analyses.

Table 20. Information criteria comparing three covariance pattern models, depression subscale of the HADS

	Unstructured	Spatial Power	Compound Symmetry Heterogeneous
AICC[1]	24 808.7	25 048.0	25 012.6
BIC	24 888.4	25 058.6	25 044.5
-2 Res LL	24 778.6	25 044.0	25 000.6
Parameters	15	2	6

*Minimized Information Criteria

[1] AIC, adjusted for number of parameters in the model

Adjusted for high-risk HPV infection, age group, smoking status, deprivation status, marital status, number of children, activity level, contraception prescribed by GP, and trial centre.

With regard to whether the change in mean depression levels differed significantly among the management pathways over time, the results of the full multivariable regression analysis that includes the main effects for time, management pathway and the interaction between management pathway and time are presented in Table 21. There appear to be significant differences in the longitudinal HADS mean depression scores among the management pathways over time (p=0.02), adjusted for the baseline characteristics. For this reason, this interaction term was not removed from the model.

With respect to baseline covariates: smoking status, number of children, deprivation quintile and physical activity had a significant association with depression scores. Specifically, current smokers had a significantly higher mean depression score compared to never smokers; having more children was associated with heightened depression; and women who reported that they exercised more than three times per week had higher depression at baseline than those who reported that they exercised less than once per week.

Table 21. Multivariable regression analysis–main effects for time, management pathway and the interaction between management pathways and time on mean depression scores

Effect	Estimate	Standard Error	p-value[1]	Overall p-value[2]
Intercept	0.78	0.33	**0.02***	
Management Pathway				0.24
Eligible for return to Routine Recall	**REF**			
Eligible for a Colposcopy Referral	0.14	0.25	0.58	
Unresolved Cytology	0.21	0.18	0.25	
Time				**<0.0001***
Baseline	**REF**			
12 months	0.47	0.13	**0.0003***	
18 months	0.49	0.14	**0.0003***	
24 months	0.55	0.14	**<0.0001***	
30 months	0.53	0.15	**0.0003***	
Management Pathway*Time interaction				**0.02***
Eligible for Return to Routine Recall	**REF**			
Colp[3], Baseline	**REF**			
Colp[3], 12 months	0.36	0.27	0.17	
Colp[3], 18 months	0.43	0.29	0.14	
Colp[3], 24 months	-0.46	0.30	0.12	
Colp[3], 30 months	-0.17	0.31	0.59	
Unresolved, Baseline	**REF**			
Unresolved, 12 months	0.19	0.20	0.34	
Unresolved, 18 months	-0.002	0.22	0.99	
Unresolved, 24 months	0.13	0.22	0.55	
Unresolved, 30 months	0.08	0.24	0.73	
Covariates				
High-Risk HPV infection				0.86
High-risk HPV negative	**REF**			
High-risk HPV positive	0.002	0.16	0.99	
High-risk HPV Inadequate/Missing	0.13	0.25	0.59	
Smoking status				**<0.0001***
Never Smoked	**REF**			
Current smoker	0.89	0.16	**<0.0001***	
Ex-smoker	0.11	0.20	0.57	
Age group				0.53
20-29 years	**REF**			
30-39 years	0.18	0.21	0.38	
40-49 years	0.07	0.25	0.77	
50-59 years	0.41	0.32	0.20	

Table 21 Continued

Effect	Estimate	Standard Error	p-value[1]	Overall p-value[2]
Trial Centre				0.14
A	**REF**			
B	-0.16	0.17	0.36	
C	0.23	0.18	0.22	
Contraception prescribed by GP				0.55
No	**REF**			
Yes	-0.10	0.17	0.55	
Number of children				**<0.0001***
0	**REF**			
1	0.64	0.22	**0.003***	
2	0.92	0.22	**<0.0001***	
3	1.10	0.28	**<0.0001***	
4-7	1.68	0.35	**<0.0001***	
Deprivation quintile				**0.04***
1 (Least deprived)	**REF**			
2	0.31	0.24	0.20	
3	0.39	0.25	0.12	
4	0.46	0.23	**0.045***	
5 (Most deprived)	0.73	0.24	**0.002***	
Marital status				0.39
Single	**REF**			
Divorced/Separated/Widowed	0.22	0.27	0.42	
Married/Common-law	-0.08	0.19	0.67	
Physical activity				**0.0001***
<1 time/week	**REF**			
1-3 times/week	0.36	0.18	**0.05***	
>3 times/week	0.70	0.16	**<0.0001***	

Notes

[1]t-test of the beta coefficient; [2]Wald type 3 test of fixed effect (overall test of effects on anxiety); REF: Reference

[3]Colp: women eligible for a colposcopy referral

* (and bold font): Statistically Significant, p-value <0.05; 5217 of 7950 (65.6%) observations used.

The tests of specific differences in least square mean depression scores among the management pathways at each time showed that there were no statistically significant differences at any of the time points at alpha=0.05 (Table 22). Although the differences approached statistical significance at 12 and 24 months, these differences were in an unanticipated direction and not consistent over time, so they may be spurious (Figure 9). The model-based (predicted) mean depression responses at each time point for an "average" woman were computed from the

regression coefficients (Table 23). There was a statistically significant increase from baseline to thirty months in the unresolved cytology (p=0.0009) and routine recall (p=0.003) management pathways. Nevertheless, their depression scores were in the normal range (0-7) at all time points in each management pathway.

Table 22. Overall tests of differences in least square mean depression scores among the three management pathways at each time point

Time point	Multivariable model* p-value
Baseline	0.51
12 months	0.09
18 months	0.16
24 months	0.10
30 months	0.42

Notes
*Adjusted for high-risk HPV status, age group, smoking status, deprivation, marital status, number of children, activity level, contraception prescribed by GP, and trial centre.

Table 23. Model-based mean depression profiles over time in each management pathway[1]

Time	Routine Recall	Colposcopy Referral	Unresolved Cytology
Baseline	2.45	2.59	2.65
12 months	2.92	3.42	3.31
18 months	2.94	3.51	3.14
24 months	3.00	2.68	3.33
30 months	2.98	2.96	3.27

Notes
[1]Statistically significant mean depression at each time point, p-value <.0001

3.4.6 Sensitivity Analysis–Two Subgroups of the Unresolved Cytology Management Pathway (Depression Subscale of the HADS)

Further analysis was conducted to determine whether the change in mean depression levels were significantly different between women in the unresolved cytology pathway who had some combination of (1) negative and low-grade or inadequate, versus (2) low-grade and inadequate, test results, regardless of the number of smears. Table 24 confirms that there were no such significant differences over time.

Table 24: **Overall tests of differences in least square mean depression scores among the four management pathways at each time point–Sensitivity analysis**

Time	Multivariable model* p-value
Baseline	0.16
12 months	0.17
18 months	0.20
24 months	0.11
30 months	0.51

Notes
*Adjusted for high-risk HPV status, age group, smoking status, deprivation, marital status, number of children, activity level, contraception prescribed by GP, and trial centre

3.4.7 Sensitivity Analysis–Limit Heterogeneity within Unresolved Cytology Management Pathway (Depression Subscale of the HADS)

To limit the heterogeneity within the unresolved cytology management pathway, women who had less than three follow-up surveillance smears were excluded from the longitudinal analysis; it was possible that some of the differences observed in our analysis may be explained by factors associated with loss to follow-up.

Consistent with the original analysis, the multivariable regression analysis showed significant differences in the longitudinal HADS mean depression responses to the management pathways over time (p=0.02) in the full cohort, adjusted for the women's baseline characteristics (Appendix H). However, the overall tests of differences among the three overall management pathways at each time showed that, indeed, there were no significant differences at baseline, 12 months, 18 months, 24 months, and 30 months, with a p-value >0.05 (Table 25). Smoking status, number of children and physical activity were still significantly associated with mean depression; however, the deprivation quintile no longer a significant effect on mean depression (Appendix H).

Table 25: Overall tests of differences in least square mean depression scores among the three management pathways at each time point, excluding women with less than three follow-up surveillance smears in unresolved cytology–Sensitivity analysis

Time	Multivariable model* p-value
Baseline	0.55
12 months	0.15
18 months	0.16
24 months	0.14
30 months	0.49

Notes

*Adjusted for high-risk HPV status, age group, smoking status, deprivation, marital status, number of children, activity level, contraception prescribed by GP, and trial centre

4. DISCUSSION

4. DISCUSSION

In this chapter, the main results, and the strengths and limitations of this study are examined within the context of previously published work. The research implications of this study are discussed, and final conclusions are presented.

4.1 Summary of Main Results

Three mutually exclusive management pathways were identified for women with low-grade abnormal cervical smears over the three-year follow-up period within a cytological surveillance arm of a pragmatic trial: eligible for return to routine recall [41.3% (95% CI: 39.2 – 43.4)]; eligible for a colposcopy referral [16.0% (95 % CI: 14.4 – 17.5)], and unresolved cytology [42.7% (95% CI: 40.6 – 44.9)]. HPV infection at recruitment, smoking status, age group, and trial centre were significantly associated with these management pathways. Specifically, women with HR-HPV infection and current smokers had significantly increased odds of being eligible for a colposcopy referral rather than being eligible for return to routine recall and rather than being in the unresolved cytology pathway, as compared to their reference categories; whereas older women and women in trial centre B had reduced odds of being eligible for a colposcopy referral, as compared to their reference categories. In the sensitivity analysis, after excluding women who had less than three follow-up surveillance smears in the unresolved cytology management pathway, the results still indicated that HPV infection at recruitment, smoking status, age and trial centre were associated with the management pathways. However, the effect was attenuated for smokers

and older women since these characteristics were also associated with failure to attend for smears during surveillance [40].

Within our entire cohort of participants randomized to cytological surveillance, participants' anxiety scores significantly decreased over time. Contrarily, depression scores increased over time in the routine recall and unresolved cytology management pathway. (However, this is of questionable clinical significance). Smoking, having more children, lower socioeconomic status, and increased physical activity were associated with heightened mean anxiety and depression scores. There were no significant differences in anxiety and depression scores over time among the identified management pathways, even at thirty months of follow-up, although there was some evidence in support of a significant time and management pathway interaction for depression scores. These findings were consistent in our sensitivity analyses, whereby we (a) excluded women who had less than three follow-up surveillance smears, and (b) examined differences between women in the unresolved cytology management pathway who had some combination of negative and low-grade or inadequate, versus low-grade and inadequate, test results.

4.2 Interpretation of Key Results Related to Describing Management Pathways

In this study, we observed that more than 40% of the women were eligible for return to routine recall, and only 16% were eligible for a colposcopy referral over the three-year period after having low-grade abnormal cytology at recruitment. Of concern was the substantial proportion of participants who had ongoing unresolved cytology at last follow-up (43%). This raises questions

about whether it is efficient to follow women solely through cytological surveillance (i.e. repeat pap testing) over a number of years, after having a low-grade abnormal cervical smear. It has previously been reported that the time and travel costs associated with participation in the UK cervical screening programs are substantial[81]. Further, pain, bleeding and discharge are not uncommon in women having follow-up cervical cytology tests [82]. From a health service perspective, when a woman has a negative experience during screening, such as pain, this may have an impact on her future participation in routine screening, affecting her risk of developing underlying invasive cancer, and consequently impacting the effectiveness of the screening program[82]. Managing these after-effects and repeat pap testing also contribute to primary care providers' workloads [82]. Potential psychosocial costs to the patient as a result of undergoing screening over time and among the management pathways within a policy of cytological surveillance should also be taken into consideration (section 4.4). If faster resolution is desired perhaps a triage method for women with low-grade abnormal cervical smears (e.g. involving HPV testing) is needed–as reflected in current Canadian and UK cervical cancer screening guidelines [24].

In terms of deviations on the basis of describing these management pathways, most women who were eligible for return to routine recall followed the protocol, but some women (7.2%) received an additional smear after the first three consecutive negative smears. This did not merit sensitivity analysis for the psychosocial component of our analyses because we deemed having an extra surveillance smear was unlikely to change anxiety/depression scores; the bottom line was that these women achieved resolution. Furthermore, only 0.5% of women who were eligible for return to routine recall up to the third follow-up surveillance smear received a colposcopy referral.

More than 98% of women who were eligible for a colposcopy referral after the first three smears did indeed receive a colposcopy referral and subsequent colposcopy examination.

4.3 Interpretation of Key Results Related to Sociodemographic and Clinical Characteristics Associated with Management Pathways

The TOMBOLA trial tested for fourteen HR-HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 [28], and 70% of cervical cancer is caused by types 16 and 18 [42]. (Previous research has shown that cervical cancer screening should not include testing for low-risk HPV types [83]). As expected, HR-HPV was associated with these management pathways. Compared to women with a negative HR-HPV test result at recruitment, women with a positive HR-HPV test result had a four-fold increased odds of being eligible for a colposcopy referral rather than being eligible for return to routine recall; and a three-fold increased odds of being eligible for a colposcopy referral rather than being in the unresolved cytology management pathway. These women with a high-grade lesion will undergo a colposcopy examination, and a biopsy may be taken to confirm diagnosis of cervical cancer, graded as CIN grade I, II, or III. Although a single HPV test result at recruitment was associated with the overall identified management pathways, TOMBOLA data have indicated that a single HPV test alone cannot identify a sub-set of women with low-grade abnormal cervical cytology who should be referred to colposcopy. However, the authors suggested that a single HPV test could be useful as a guide to management in women aged 40 years or older [18].

Current cervical cancer screening guidelines in the UK and some provinces in Canada support HPV DNA testing in triage with cytology, although it is not currently funded by the Ontario Ministry of Health and Long-Term Care [24]. It has been consistently demonstrated through randomized and non-randomized trials that HPV DNA testing is much more sensitive than Pap in detecting high-grade precancerous lesions (95% versus 55%), and there is only a minor reduction in specificity as compared to Pap testing (94% versus 97%)[29]. In other settings, there is evidence to support HPV testing in triage of women with low-grade abnormal cytology [84, 85].

Our findings also showed an independent association of tobacco smoking with these management pathways. This was expected since there is sufficient evidence of carcinogenicity of tobacco smoking [43]. Specifically, current smokers had a two-fold increased odds of being eligible for a colposcopy referral rather than returning to routine recall as compared to never smokers. They also had a 40% increased odds of being eligible for a colposcopy referral rather than being in the unresolved group. A significant association was observed, despite evidence from a systematic review that found that that self-reports tend to underestimate smoking status (Gorber, 2009). There is also evidence that passive smoking significantly and independently increases the risk of cervical cancer [46], but we don't have this information in the TOMBOLA data.

Furthermore, an independent association of age group was found on the management pathways. Older women had reduced odds of being eligible for a colposcopy referral or being placed in the unresolved group, versus routine recall, as compared to women aged 20-29 years of age This was expected since young age at first intercourse may also be associated with a larger number of sex partners (a potential confounder), increasing risk for HPV infection [48].

Lastly, there was a significant, independent association between trial centre and the management pathways. For instance, it was found that women in trial centre B had reduced odds of being eligible for a colposcopy referral, and of having unresolved cytology versus routine recall, as compared to women in trial centre A. There are four possible explanations for this. First, there may be some unknown environmental exposures at one centre that may increase the risk of high-grade lesions and cervical cancer. Second, the women may be different in terms of their socio-demographic and lifestyle characteristics. Interactions with trial centre were not investigated for this analysis. Third, there may not be consistency in diagnosis and interpretation of cytology within and between centres, although quality assurance schemes were in place in TOMBOLA [28]. Fourth, information provision about the testing may have differed across centres. For example, perhaps more women in trial centre B were informed about potential after-effects associated with cytology, as compared to women in trial centre A. This may have better prepared them, minimizing non-participation with future screening [82], reflected in the number of women with unresolved cytology at last follow-up. Contraception prescribed by the GP, number of children, deprivation quintile as a marker for socioeconomic status, marital status and physical activity were not significantly associated with the management pathways.

A single high-risk HPV test result, smoking status, age and trial centre (location) may help predict the management pathways women follow within a policy of cytological surveillance. These baseline characteristics may also be important to consider when new policies for cervical cancer screening get implemented. For example, when the expected shift to HPV testing as a primary screening tool happens in Canada and the UK [13], these baseline characteristics could be used to help develop a clinical tool for managing these women. Additional biomarkers are now being

considered as triage tests such as HPV E6 and E7 messenger RNA testing, and cytologic methods that attempt to identify proliferating cells (for example, $p16^{INK4a}$ staining and Ki-67)

As a measure of accuracy, we computed the full model's discrimination ability using the c-statistic for each dichotomous comparison of management pathways. The c-statistic is by far the most commonly used index of discrimination ability, a measure of how well a model separates those who do and do not have the disease (or management pathway) of interest [86]. A c-statistic of 0.50 suggests no discrimination, < 0.70 suggests less than acceptable discrimination, 0.70 - 0.79 suggests acceptable discrimination, 0.80 - 0.89 suggests excellent discrimination, and at least 0.90 suggests outstanding discrimination [87]. Thus, our model had acceptable discrimination for women eligible for a colposcopy referral versus routine recall, but less than acceptable discrimination for the other two dichotomous comparisons of the management pathway, i.e. unresolved versus eligible for return to routine recall, and eligible for a colposcopy referral versus unresolved. The discrimination for these latter two dichotomous comparisons did not improve after excluding women who had less than three follow-up surveillance smears. Although three-way ROC curves are possible for the multinomial logistic regression model, they are not yet available in SAS [80, 88-92].

Clearly, this study may not be applicable in a jurisdiction that does not have at least a partially organized cervical screening program in place with reliance on a conservative management policy of cytological surveillance as the primary screening tool for cervical cancer. Few developing countries have organized and quality-assured cytology-based cervical cancer prevention programs due to the technical and financial constraints associated with having a robust

healthcare infrastructure. Two alternative screening tests that have been investigated are visual examination of the cervix with 3-5% acetic acid and HPV DNA testing [93].

4.4 Interpretation of Key Results Related to the Psychosocial Impact of Long-term Follow-up and Management Pathway

4.4.1 Differences among Management Pathways over Time

Our observation of no significant differences in mean anxiety and depression scores over time across the three management pathways in the full cohort of women managed through cytological surveillance is consistent with previous TOMBOLA findings. The authors observed no significant differences in thirty-month percentages of significant depression (OR=0.99, 95% CI 0.80-1.21) or anxiety (OR=0.97, 95% CI 0.81 - 1.16) between two alternative management polices of cytological surveillance and initial colposcopy [30]. However, it is important to recognize that each woman was classified into a management pathway based on her full trajectory of cytology testing observed over time; yet, management pathway was treated as a time-fixed or "baseline" variable in the analysis of the repeated psychological measures. Thus, any differences observed in anxiety and depression scores over time would not necessarily have been attributable to the management pathways. For this reason, significant interactions of time and management pathway on anxiety and depression would have been unlikely. However, we were especially interested in examining whether there were significant differences at the thirty-month mark (last HADS assessment) across management pathways. This was an appropriate comparison time as most women would have been classified into their respective management pathways prior to this time

point. Specifically, we hypothesized that women with unresolved cytology would have higher anxiety and depression scores at thirty months, compared to women who were eligible for return to routine recall; and have similar (or possibly higher) levels as compared to women eligible for a colposcopy referral. This hypothesis was not supported by our findings for anxiety nor for depression scores. Had significant differences been observed, it would also be important to recognize that the three groups of women may have differed in characteristics other than the management pathway, since the pathways were not randomly assigned. Nevertheless, in the analysis phase, we isolated the effect of the management pathway as much as possible by adjusting for all potential confounders on which we had information.

Previously published work has found that women with inadequate smear test results had higher state anxiety, were more concerned about their results, perceived themselves to be at higher risk of cervical cancer, and felt less satisfied with the information they had received about their test results, compared to women with normal test results after four weeks of follow-up [94]. After three months of follow-up, women who initially received inadequate smear test results were still more concerned about their test results and less satisfied with the information they had received about these initial test results, even after receiving normal results from repeat smear tests. This was strongly predicted by dissatisfaction with information provided about inadequate smear test results [95]. Therefore, our non-significant findings may firstly be explained by different amounts of information these women received or sourced for themselves based on their cytology test results and overall management pathways. For example, it may be that women with inadequate and high-grade test results in our study sought out or received more information, which may have served to minimize their anxiety and depression along their journey through screening, rendering it

comparable on average to participants with negative results. Secondly, in our study, women who were classified into any one of the management pathways may have had one or more inadequate test results. Therefore, the shorter and longer-term psychosocial impact of an inadequate test result may have been "diluted" across the management pathways. Thirdly, in these previous studies, comparisons were to women receiving negative results, whereas in our study everyone had at least one low-grade abnormal result as a criterion for entry into the study.

4.4.2 Significant Change over Time in Psychosocial Outcomes

Interestingly, we observed that anxiety scores decreased over time, whereas depression scores (i.e. reduced ability to experience pleasure) increased over time within our participant population of women undergoing cytological surveillance after at least one low-grade abnormal smear–regardless of when resolution was achieved. However, the minimum clinically important difference for the HADS has not been established [74]. For this reason, we cannot be certain that these differences are clinically relevant, particularly since the differences were very small. For example, the mean anxiety scores dropped at most by 0.60 at thirty months from baseline (Table 16) and mean depression scores increased at most by 0.55 at twenty-four months (with the interaction between management pathway and time included in the model), adjusted for management pathway, sociodemographic and clinical characteristics (Table 21).

Previous studies support our observation of a decrease or no impact of time on anxiety during the screening process. Although we found that mean depression scores slightly increased over time, previous studies suggest no longer-term impact on depression among those screened.

For example, in one meta-analysis related to screening in general, the authors revealed no significant impact of screening on longer term (>4 weeks) anxiety, depression or quality of life subscales. There weren't enough studies that assessed psychosocial outcomes before four weeks for the authors of this study to comment on the shorter term emotional impact of screening[96]. It is also important to note that in this meta-analysis, only six of the twelve studies involved screening for cancer, and none were specific to cervical cancer. A two-year follow-up study, specific to cervical cancer screening, also found that referral for colposcopy after an abnormal cervical smear did not seem to result in long-lasting anxiety and depression, based on the State-Trait Anxiety Inventory (STAI) and the Montgomery-Asberg Depression Rating Scale—self-rate. However, a subgroup of women, with the initially highest depression scores, still had anxiety and depressions scores that were significantly higher than normal [64]. Another study assessed generic health quality of life and anxiety based on the STAI in a cohort of women with abnormal Pap test results who were referred for a colposcopy referral. Although the colposcopy group reported more anxiety than the reference group, with differences being clinically relevant, overall health quality of life improved and anxiety scores decreased over time, irrespective of CIN-grade. This may indicate that management had a reassuring effect and led to decreased anxiety levels [65]. Similarly, although receiving an abnormal cytology result significantly increased anxiety (STAI mean difference between both groups = 8.3), this negative impact subsided after 12 weeks for the majority of the women [63].

4.4.3 Sociodemographic and Clinical Characteristics of Women Associated with Anxiety and Depression scores

In this study, we also observed that smoking, having more children and being physically active (as compared to their respective reference categories) were associated with heightened anxiety and depression scores. There was a borderline statistically significant association between deprivation quintile and mean anxiety scores (P=0.06), and a statistically significant association with mean depression scores (P=0.04). Educational tools to target this vulnerable population may be warranted. This includes ensuring clear communication about the meaning of low-grade abnormal cytology (which may be a false-positive test result) for women who are screened, and of high-grade abnormal cervical cytology test results [65].

The effect of deprivation quintile, a marker for socioeconomic status, on anxiety and depression is consistent with other studies. For example, 35% of women who had clinically meaningful anxiety (based on the STAI) at 12 weeks after receiving an abnormal cervical smear result reported a lower socioeconomic level [63]. It was particularly surprising that women who were more physically active would have heightened anxiety and depression. Regular physical activity has been demonstrated to have a beneficial effect on mental health [97], but perhaps women who exercise the most are overly concerned about their health–which may increase anxiety and depression upon receipt of a low-grade abnormal cervical cytology test result. These results are also consistent with a previous study that assessed anxiety at recruitment for all women within TOMBOLA. The authors found that women at highest risk of anxiety were current smokers, had children, had highest levels of physical activity, and were also younger [68].

Another TOMBOLA article investigated the association between HPV infection and anxiety in women who were unaware they had been tested specifically for HPV. They found no association between HPV status and anxiety among white women. Among non-white women, however, anxiety was less common among HPV-positive than HPV-negative women. Among non-smokers, cancer worry was more common in HPV-positive than HPV-negative women; the opposite association was observed among ex-smokers [69]. The authors concluded that sociodemographic and lifestyle factors other than knowledge of HPV test results may explain the occurrence of anxiety in this population[69]. In our analyses, we did not adjust for ethnicity, and we examined sociodemographic and clinical characteristics as main effects only.

4.5 Challenges and Limitations

There were challenges related to how best to summarize the experiences of the women in the trial. On the basis of published screening guidelines, it was expected that some women would return to routine recall, some would receive a colposcopy, and some would have unresolved cytology at last follow-up during surveillance [24]. However, operationalizing these definitions within the TOMBOLA context was complicated primarily due to the longitudinal nature of this study as described in Chapter 3. Specifically, there was substantial heterogeneity of cytology test results, varying number of smears, and substantial loss to follow-up. Nevertheless, we identified three overarching management pathways that served to describe women's overall experiences and impacts on the health system. An important limitation to note is that the proportions of women identified in each of these management pathways may also be biased (non-differential

misclassification bias), as there may be errors in the interpretation of the cytology test results- especially if the cytopathologists were not blinded to the previous smear test results.

A second important limitation of this study was the high rate of attrition with respect to the psychological variables. Although at baseline there was almost complete data (95.3%), only half of the women (54.3%) completed the anxiety and depression subscale of the HADS questionnaire at last follow-up. There are several possible approaches for dealing with missing data, including analyzing only the subset of participants with complete data at all time points; analyzing all available data at all time points; single imputation using, for example, last observation carried forward (LOCF); and multiple imputation [98]. Excluding participants from analysis is not a reasonable option as the remaining subset may no longer be representative of the population and there may be specific sociodemographic characteristics associated with loss to follow-up [40]. Single imputation is not recommended as it would tend to lead to under-estimated standard errors due to artificially increasing the sample size; likewise, LOCF is not recommended as it makes the implausible assumption that that there was no change in the response over time. Multiple imputation under an assumption of MAR is the gold standard imputation procedure, but in a regression analysis, imputation for missing data on the dependent variable is analogous to conducting an analysis of all available data with the variables used in the imputation process included as covariates. Both the analysis of all available data and multiple imputation assume the missing data mechanism is MAR. It is impossible to distinguish between "Missing Not At Random" and MAR using only the data at hand because the variable needed to verify it is missing. However, under MAR, including as many covariates potentially associated with the missing data

mechanism makes the assumption of MAR more plausible. When there are substantial missing data, regardless of the strategy used to manage this, the results need to be interpreted with caution.

Third, by involvement in the TOMBOLA trial, these women may have heightened awareness of the importance of cervical cancer screening, and may have received or sought information from their primary care provider irrespective of management, which in turn, may have mitigated the effects of anxiety and depression.

Fourth, the majority of the women (95%) classified their ethnic group as white. Although this may be representative of the UK population in Tayside, Grampian and Nottingham, this may not be representative of the Canadian or US population. For example, more than 200 ethnic origins were reported in the 2011 National Health Survey in Canada, and 19.1% of the total population identified themselves as a member of a visible minority group [99]. First Nations communities in Canada continue to have a higher incidence of invasive cervical cancer compared to the rest of the population[5], highlighting the need for improved support to ensure their equal access to screening and HPV vaccination. Similarly, in the US, almost a quarter of the population reported their race and ethnicity as something other than non-Hispanic white alone in 2013 [100]. Black or Hispanic US populations continue to have the highest incidence of invasive cervical cancer compared to Non-Hispanic/White [59]. In our analysis, we did not examine the association between ethnicity and management pathway or anxiety/depression due to the homogeneity of the study population. However previous TOMBOLA work has found that the association between HPV status and anxiety varied by ethnicity [69]. If a study were conducted in Canada, and we were able to recruit a sufficient number of women who classified their ethnic group as non-white (including First

Nations women), we would expect a higher proportion of women in the unresolved cytology management pathway due to losses from follow-up.

Fifth, the recruitment rate for the TOMBOLA trial was 52% through hospital-based recruitment clinics, and this remained static, despite strenuous efforts to increase it. In the ALTS trial, which achieved a participation rate of 75%, women with a low-grade abnormal cervical smear were expected to attend a hospital appointment with a gynaecologist (funded privately) which may partially explain the higher recruitment rate. Further, women were only eligible for the ALTS trial if they were likely to participate for the full duration of the trial and "modest financial incentives" were provided to help retain women in the ALTS trial. This was not true for TOMBOLA [28]. Nevertheless, non-adherence (deviations) to the protocol and non-adherence to continued cervical cancer screening participation (reflected in the unresolved management pathway) are likely to be underestimated in TOMBOLA. Common reasons for non-participation included preference of follow-up from their own GP, inconvenient clinic appointment times, arranging time off work or child care, and cost of travelling and child care. Also, in a survey of a sub-sample of potentially eligible women, 14% reported they were too frightened to participate; this was unrelated to the grade of the cervical cytology abnormality [101]. This would also underestimate the true prevalence of anxiety and depression in the population.

4.6 Strengths

TOMBOLA was a large, population-based pragmatic study, with the participants drawn from the cervical screening programmes; thus, representative of the UK screening population as a whole. There was very little unknown and missing information (3%) on socio-demographic and lifestyle characteristics, and baseline psychosocial information. The three-year follow up period enabled us to identify management pathways and psychosocial impact within a policy of cytological surveillance. We assessed the potential value of HPV testing, and other sociodemographic and lifestyle characteristics, as a guide to understanding overall management pathways. Further, our psychosocial instrument (HADS) has been extensively validated. Additionally, our study had increased power to detect a difference by modeling anxiety and depression scores on a continuous scale. Therefore, there was no uncertainty with respect to the thresholds used for the definitions of clinically significant anxiety and depression. Although a recent study has established normative HADS data for the UK population [76], the HADS authors have stated that ideally thresholds should be validated in each setting [74]. Lastly, our sensitivity analyses confirmed that our findings were robust to the decisions made about identifying the management pathways, both in terms of associations with sociodemographic and clinical characteristics, and longer term psychological implications.

4.7 Conclusions

Cervical cancer is the fourth most common cancer among women worldwide, in terms of incidence and mortality [1]. Clearly, organized cervical screening programs must be designed in such a way to maximize the benefit for all women within available resources, but also to minimize the harms for the entire population that is undergoing screening within available resources [21]. This research has helped create insight about the management of women with low-grade cervical abnormalities. It has implications for both the health care system in terms of coverage and cytological performance, and for women themselves in terms of their overall well-being and mental health.

This is the first study, as far as we are aware, to examine the longitudinal nature of the sequence of test results and related interventions for women with low-grade abnormal cervical cytology who were managed through repeat pap testing. The possible relationship between management pathways and characteristics of cancer screening participants had not been previously investigated. Although others have investigated the immediate psychosocial impact of follow-up among those undergoing cervical cancer screening, this study examines the long-term impact of screening in terms of both anxiety and depression as it relates to the different management pathways within a policy of cytological surveillance. This is also the first study to our knowledge that aims to address the psychosocial impact of persistent inadequate/normal test results without resolution. Further, sociodemographic and clinical characteristics associated with anxiety and depression, specifically for women who are managed through repeat pap testing after receipt of low-grade abnormal cervical cytology had not been previously examined.

A policy of following women solely through cytological surveillance (i.e. repeat pap testing) to manage women with low-grade cervical abnormalities may be inefficient, as there was a high prevalence of women with unresolved cytology at last follow-up. This includes 21% of women who were lost to follow-up before having at least three consecutive smears or a high-grade test result, which increases this group's risk of developing invasive cancer. Also, the substantial heterogeneous sequence of smear test results following a low-grade abnormal cervical smear shows that the pathophysiology of low-grade abnormalities may not be well-understood. While there were some limitations, our results were reassuring with respect to this group of women with ongoing unresolved cytology, since there were no differences in anxiety and depression scores across the management pathways–even after thirty months of follow-up. While depression scores increased somewhat over time for women with unresolved cytology and those who returned to routine recall, anxiety scores decreased for the entire cohort, and on average, both scores were well below cut-offs indicating clinically important mental illness. Nevertheless, if faster resolution is desired, a triage method involving HR-HPV testing, smoking status, and other important predictors is needed for women with a low-grade abnormal cervical smear. These baseline characteristics may also be important to consider as new policies for cervical cancer screening get implemented.

Thus, this descriptive study enhanced our understanding of the trajectory of women with low-grade abnormal cervical cytology within a policy of cytological surveillance, and has created further knowledge about the psychosocial journey through cervical cancer screening follow-up. The challenge to provide high-quality evidence of the effectiveness of current screening and/or emerging screening modalities to ensure that cervical cancer prevention and screening is safe, efficient, timely, effective, accessible, equitable and of course, patient-centered remains [102].

5. REFERENCES

1. International Agency for Research on Cancer. Press release - latest world cancer statistics. http://www.iarc.fr/en/media-centre/pr/2013/pdfs/pr223_E.pdf. Updated 2013. Accessed June 18th, 2015.

2. Singh G, Azuine R, and Siahpush M. Global inequalities in cervical cancer incidence and mortality are linked to deprivation, low socioeconomic status, and human development. *International Journal of MCH and AIDS*. 2012;1(1):17.

3. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian cancer statistics 2015 - special topic: Predictions of the future burden of cancer in Canada. May 2015.

4. Navaneelan T. Health at a glance - trends in the incidence and mortality of female reproductive system cancers. 2015;82-624-X.

5. Maar M, Burchell A, Little J, et al. A qualitative study of provider perspectives of structural barriers to cervical cancer screening among first nations women. *Womens Health Issues*. 2013;23(5):e319-25.

6. Pottie K, Greenaway C, Feightner J, et al. Evidence-based clinical guidelines for immigrants and refugees. *CMAJ*. 2011;183(12):E824-925.

7. Jeudin P, Liveright E, Del Carmen MG, Perkins RB. Race, ethnicity, and income factors impacting human papillomavirus vaccination rates. *Clin Ther*. 2014;36(1):24-37.

8. Tsui J, Gee GC, Rodriguez H, et al. Exploring the role of neighborhood socio-demographic factors on HPV vaccine initiation among low-income, ethnic minority girls. *J Immigr Minor Health*. 2013;15(4):732-740.

9. Canadian Cancer Society. Risk factors for cervical cancer. http://www.cancer.ca/en/cancer-information/cancer-type/cervical/risks/?region=on. Updated 2015. Accessed May 4, 2015.

10. Kripke C. Pap smear vs. HPV screening tests for cervical cancer. *American Family Physician*. 2008;77(12):1740.

11. Canadian Partnership Against Cancer (CPAC). Cervical cancer screening in Canada: Monitoring program performance 2009-2011. http://www.cancerview.ca/idc/groups/public/documents/webcontent/cervical_cancer_report.pdf. Updated 2013.

12. Lee JK, So KA, Piyathilake CJ, Kim MK. Mild obesity, physical activity, calorie intake, and the risks of cervical intraepithelial neoplasia and cervical cancer. *PLoS One*. 2013;8(6):e66555.

13. Tota J, Mahmud SM, Ferenczy A, Coutlee F, Franco EL. Promising strategies for cervical cancer screening in the post-human papillomavirus vaccination era. *Sex Health*. 2010;7(3):376-382.

14. Public Health Agency of Canada. Performance monitoring for cervical cancer screening programs in Canada. 2009. http://www.phac-aspc.gc.ca/cd-mc/cancer/pmccspc-srpdccuc/pdf/cervical-eng.pdf.

15. Dickinson J, Stankiewicz A, Popadiuk C, Pogany L, Onysko J, Miller A. Reduced cervical cancer incidence and mortality in Canada: National data from 1932 to 2006. *BMC Public Health*. 2012;12:992.

16. Office for National Statistics. Cervical cancer is the most common cancer for women aged 15-34 (cancer statistics registrations, England (series MB1) , no. 42, 2011). http://www.ons.gov.uk/ons/rel/vsob1/cancer-statistics-registrations--england--series-mb1-/no--42--2011/sty-cervical-cancer.html. Updated January 30 2014. Accessed June 20, 2015.

17. NHS Cancer Screening Programmes. Achievable standards, benchmarks for reporting, and criteria for evaluating cervical cytopathology. 2013;1. http://www.cancerscreening.nhs.uk/cervical/publications/nhscsp01.pdf.

18. Cotton S, Sharp L, Little J, et al. The role of human papillomavirus testing in the management of women with low-grade abnormalities: Multicentre randomised controlled trial. *BJOG*. 2010;117(6):645-59.

19. Canadian Cancer Society. Precancerous conditions of the cervix. http://www.cancer.ca/en/cancer-information/cancer-type/cervical/cervical-cancer/precancerous-conditions/?region=bc. Updated 2015. Accessed August 23, 2015.

20. Canadian Cancer Society. Abnormal cervical biopsy results. http://www.cancer.ca/en/cancer-information/cancer-type/cervical/diagnosis/abnormal-cervical-biopsy-results/?region=on. Updated 2015. Accessed June 22, 2015.

21. Miles A, Cockburn J, Smith RA, Wardle J. A perspective from countries using organized screening programs. *Cancer*. 2004;101(5 Suppl):1201-1213.

22. Williams JH, Carter SM, Rychetnik L. 'Organised' cervical screening 45 years on: How consistent are organised screening practices? *Eur J Cancer*. 2014;50(17):3029-3038.

23. Mayrand MH, Franco S. Integrating novel primary- and secondary-prevention strategies: The next challenge for cervical cancer control. *Future Oncology*. 2010;6(11):1725-1733.

24. Cancer Care Ontario. Recommendations for follow-up of abnormal cytology. https://www.cancercare.on.ca/pcs/screening/cervscreening/abnormal_followup/. Updated March 10, 20152015.

25. Smith JH. ABC3 part I: A review of the guidelines for terminology, classification and management of cervical cytology in England. *Cytopathology*. 2012;23(6):353-359.

26. The British Society for Colposcopy and Cervical Pathology. HPV testing Introduced to the NHSCSPs. https://www.bsccp.org.uk/healthcare-professionals/professional-news/hpv-testing-introduced-to-the-nhscsp-1/. Updated 2015. Accessed July 20, 2015.

27. Raffle A, Gray M. *Screening: Evidence and practice.* Oxford: Oxford University Press; 2007.

28. Cotton SC, Sharp L, Little J, et al. Trial of management of borderline and other low-grade abnormal smears (TOMBOLA): Trial design. *Contemp Clin Trials*. 2006;27(5):449-471.

29. Tota JE, Ramana-Kumar AV, El-Khatib Z, Franco EL. The road ahead for cervical cancer prevention and control. *Curr Oncol*. 2014;21(2):e255-64.

30. Sharp L, Cotton S, Little J, et al. Psychosocial impact of alternative management policies for low-grade cervical abnormalities: Results from the TOMBOLA randomised controlled trial. *PLoS One*. 2013;8(12):e80092.

31. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, et al. Management of minor cervical cytological abnormalities: A systematic review and a meta-analysis of the literature. *Cancer Treat Rev*. 2007;33(6):514-520.

32. TOMBOLA Group. Cytological surveillance compared with immediate referral for colposcopy in management of women with low grade cervical abnormalities: Multicentre randomised controlled trial. *BMJ*. 2009;339:b2546.

33. ASCUS-LSIL Triage Study (ALTS) Group. Results of a randomized trial on the management of cytology interpretations of atypical squamous cells of undetermined significance. *Am J Obstet Gynecol*. 2003;188(6):1383-1392.

34. ASCUS-LSIL Triage Study (ALTS) Group. A randomized trial on the management of low-grade squamous intraepithelial lesion cytology interpretations. *Am J Obstet Gynecol*. 2003;188(6):1393-1400.

35. Isaoglu U, Yilmaz M, Delibas IB, Bilici AE, Kabalar ME. Evaluation of 37,438 consecutive cervical smear results in the Turkish population. *Arch Med Sci*. 2015;11(2):402-405.

36. Filipi K, Xhani A. Assessment of cervical cytological data in Albanian females. *Asian Pac J Cancer Prev*. 2014;15(5):2129-2132.

37. Landy R, Castanon A, Hamilton W, et al. Evaluating cytology for the detection of invasive cervical cancer. *Cytopathology*. 2015.

38. Persson M, Elfstrom KM, Olsson SE, Dillner J, Andersson S. Minor cytological abnormalities and up to 7-year risk for subsequent high-grade lesions by HPV type. *PLoS One*. 2015;10(6):e0127444.

39. Cruickshank ME, Cotton SC, Sharp L, et al. Management of women with low grade cytology: How reassuring is a normal colposcopy examination? *BJOG*. 2015;122(3):380-386.

40. Sharp L, Cotton S, Thornton A, et al. Which women default from follow-up cervical cytology tests? A cohort study within the TOMBOLA trial. *Cytopathology*. 2012;23(3):150-160.

41. Bosch FX, Lorincz A, Munoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol*. 2002;55(4):244-265.

42. Kapeu AS, Luostarinen T, Jellum E, et al. Is smoking an independent risk factor for invasive cervical cancer? A nested case-control study within Nordic biobanks. *Am J Epidemiol*. 2009;169(4):480-488.

43. IARC: International Agency for Research on Cancer. Tobacco smoking. In: *A Review of Human Carcinogens: Personal Habits and Indoor Combustions.* IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 100E, pp. 43-212, WHO Press, Geneva, 2012.

44. Roura E, Castellsague X, Pawlita M, et al. Smoking as a major risk factor for cervical cancer and pre-cancer: Results from the EPIC cohort. *Int J Cancer*. 2014;135(2):453-466.

45. IARC: International Agency for Research on Cancer. Second-hand tobacco smoke. In: *A Review of Human Carcinogens: Personal Habits and Indoor Combustions.* IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 100E, pp. 213-264. WHO Press, Geneva, 2012.

46. Zeng XT, Xiong PA, Wang F, Li CY, Yao J, Guo Y. Passive smoking and cervical cancer risk: A meta-analysis based on 3,230 cases and 2,982 controls. *Asian Pac J Cancer Prev*. 2012;13(6):2687-2693.

47. Cancer Research UK. Cervical cancer incidence statistics. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/cervical-cancer/incidence. Updated 2014. Accessed May 4, 2015.

48. Shepherd JP, Frampton GK, Harris P. Interventions for encouraging sexual behaviours intended to prevent cervical cancer. *Cochrane Database Syst Rev*. 2011;(4):CD001035. doi(4):CD001035.

49. Smith J, Green J, de Gonzalez A, et al. Cervical cancer and use of hormonal contraceptives: A systematic review. *Lancet (London, England)*. 2003;361(9364):1159-1167.

50. Gierisch JM, Coeytaux RR, Urrutia RP, et al. Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: A systematic review. *Cancer Epidemiol Biomarkers Prev*. 2013;22(11):1931-1943.

51. La Vecchia C, Boccia S. Oral contraceptives, human papillomavirus and cervical cancer. *Eur J Cancer Prev*. 2014;23(2):110-112.

52. Canadian Cancer Society. Socio-economic status. http://www.cancer.ca/en/cancer-information/cancer-101/what-is-a-risk-factor/socio-economic-status/?region=on. Updated 2015. Accessed June 22, 2015.

53. Tao L, Han L, Li X, et al. Prevalence and risk factors for cervical neoplasia: A cervical cancer screening program in Beijing. *BMC Public Health*. 2014;14:1185-2458-14-1185.

54. International Collaboration of Epidemiological Studies of Cervical Cancer. Cervical carcinoma and reproductive factors: Collaborative reanalysis of individual data on 16,563 women with cervical carcinoma and 33,542 women without cervical carcinoma from 25 epidemiological studies. *Int J Cancer*. 2006;119(5):1108-1124.

55. Munoz N, Franceschi S, Bosetti C, et al. Role of parity and human papillomavirus in cervical cancer: The IARC multicentric case-control study. *Lancet*. 2002;359(9312):1093-1101.

56. Jensen KE, Schmiedel S, Norrild B, Frederiksen K, Iftner T, Kjaer SK. Parity as a cofactor for high-grade cervical disease among women with persistent human papillomavirus infection: A 13-year follow-up. *Br J Cancer*. 2013;108(1):234-239.

57. Alberta Health Services. Factors associated with breast, cervical, and colorectal cancer screening. 2010.

58. Cust A. Physical activity and gynecologic cancer prevention. *Recent Results Cancer Res*. 2011;186:159-85.

59. Barnholtz-Sloan J, Patel N, Rollison D, Kortepeter K, MacKinnon J, Giuliano A. Incidence trends of invasive cervical cancer in the United States by combined race and ethnicity. *Cancer Causes Control*. 2009;20(7):1129-1138.

60. Rogstad KE. The psychological impact of abnormal cytology and colposcopy. *BJOG: An International Journal of Obstetrics and Gynaecology*. 2002;109(4):364-368.

61. Sharp L, Cotton S, Cruickshank M, et al. The unintended consequences of cervical screening: Distress in women undergoing cytologic surveillance. *J Low Genit Tract Dis*. 2014;18(2):142-150.

62. Jerachotechueantaveechai T, Charoenkwan K, Wongpakaran N. Prevalence and predicting factors for anxiety in Thai women with abnormal cervical cytology undergoing colposcopy. *Asian Pac J Cancer Prev*. 2015;16(4):1427-1430.

63. Drolet M, Brisson M, Maunsell E, et al. The psychosocial impact of an abnormal cervical smear result. *Psychooncology*. 2012;21(10):1071-1081.

64. Hellsten C, Sjostrom K, Lindqvist PG. A 2-year follow-up study of anxiety and depression in women referred for colposcopy after an abnormal cervical smear. *BJOG*. 2008;115(2):212-218.

65. Korfage IJ, Essink-Bot ML, Westenberg SM, Helmerhorst T, Habbema JD, van Ballegooijen M. How distressing is referral to colposcopy in cervical cancer screening?: A prospective quality of life study. *Gynecol Oncol*. 2014;132(1):142-148.

66. Collins RE, Lopez LM, Marteau TM. Emotional impact of screening: A systematic review and meta-analysis. *BMC Public Health*. 2011;11:603-2458-11-603.

67. Cotton SC, Sharp L, Little J, et al. A normal colposcopy examination fails to provide psychological reassurance for women who have had low-grade abnormal cervical cytology. *Cytopathology*. 2014.

68. Gray NM, Sharp L, Cotton SC, et al. Psychological effects of a low-grade abnormal cervical smear test result: Anxiety and associated factors. *Br J Cancer*. 2006;94(9):1253-1262.

69. Johnson CY, Sharp L, Cotton SC, et al. Human papillomavirus infection and anxiety: Analyses in women with low-grade cervical cytological abnormalities unaware of their infection status. *PLoS One*. 2011;6(6):e21046.

70. Hirschfeld RM. The comorbidity of major depression and anxiety disorders: Recognition and management in primary care. *Prim Care Companion J Clin Psychiatry*. 2001;3(6):244-254.

71. von Elm E, Altman D, Egger M, Pocock S, Gøtzsche P, Vandenbroucke J. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Int J Surg*. 2014;12(12):1495-9.

72. Little J. Human papillomavirus testing. effectiveness of testing for high risk HPV for triage of low grade abnormal smears is being assessed in TOMBOLA trial. *BMJ*. 2001;323(7304):109.

73. Jacobs MV, Snijders PJ, van den Brule AJ, Helmerhorst TJ, Meijer CJ, Walboomers JM. A general primer GP5+/GP6(+)-mediated PCR-enzyme immunoassay method for rapid detection of 14 high-risk and 6 low-risk human papillomavirus genotypes in cervical scrapings. *J Clin Microbiol*. 1997;35(3):791-795.

74. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica*. 1983;67(6):361 - 370.

75. Snaith RP. The hospital anxiety and depression scale. *Health Qual Life Outcomes*. 2003;1:29.

76. Breeman S, Cotton S, Fielding S, Jones GT. Normative data for the hospital anxiety and depression scale. *Qual Life Res*. 2015;24(2):391-398.

77. Herrmann C. International experiences with the hospital anxiety and depression scale--a review of validation data and clinical results. *J Psychosom Res*. 1997;42(1):17-41.

78. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the hospital anxiety and depression scale. an updated literature review. *J Psychosom Res*. 2002;52(2):69-77.

79. Harrell F. 4.5 shrinkage. In: *Regression modeling strategies: With applications to linear models, logistic regression, and survival analysis (google eBook).* Nashville, TN: Springer-Verlag New York, Inc.; 2001:61.

80. Allison PD. *Logistic regression using SAS theory and application, second edition.* 2nd ed. Cary, N.C.: Cary, N.C. : SAS Institute, 2012; 2012.

81. Woolley C, Philips Z, Whynes DK, et al. United Kingdom cervical cancer screening and the costs of time and travel. *Int J Technol Assess Health Care*. 2007;23(2):232-239.

82. Cotton S, Sharp L, Cochran C, et al. After-effects reported by women having follow-up cervical cytology tests in primary care: A cohort study within the TOMBOLA trial. *Br J Gen Pract*. 2011;61(587):e333-9.

83. Thomsen LT, Frederiksen K, Munk C, et al. High-risk and low-risk human papillomavirus and the absolute risk of cervical intraepithelial neoplasia or cancer. *Obstet Gynecol*. 2014;123(1):57-64.

84. Arbyn M, Ronco G, Anttila A, et al. Evidence regarding human papillomavirus testing in secondary prevention of cervical cancer. *Vaccine*. 2012;30 Suppl 5:F88-99.

85. Arbyn M, Roelens J, Simoens C, et al. Human papillomavirus testing versus repeat cytology for triage of minor cytological cervical lesions. *Cochrane Database Syst Rev*. 2013;3:CD008054.

86. Wu Y, Lee W. Alternative performance measures for prediction models. *PLoS ONE*. 2014;9(3):e91249.

87. Ambrosius W. 6.4.3 assessing predictive accuracy. In: *Topics in biostatistics.* Totawa, New Jersey: Humana Press Inc.; 2007:295.

88. Mossman D. Three-way ROCs. *Med Decis Making*. 1999;19(1):78-89.

89. Kapasny J, Reze M. Three-way ROC analysis using SAS software. *Acta Universitatis Agriculturae Et Silviculturae Mendelianae Brunensis*. 2013;LXI(7):2269-2275.

90. SAS Institute Inc. Chapter 58: The LOGISTIC procedure. In: *SAS/STAT 13.1 user's guide.* SAS Institute Inc.; 2013:4485.

91. Inácio V, Turkman A, Nakas C, Alonzo T. Nonparametric Bayesian estimation of the three-way receiver operating characteristic surface. *Biom J*. 2011;53(6):1011-24.

92. Dreiseitl S, Ohno Machado L, Binder M. Comparing three-class diagnostic tests by three-way ROC analysis. *Med Decis Making*. 2000;20(3):323-31.

93. Wright TC,Jr, Kuhn L. Alternative approaches to cervical cancer screening for developing countries. *Best Pract Res Clin Obstet Gynaecol*. 2012;26(2):197-208.

94. French DP, Maissi E, Marteau TM. Psychological costs of inadequate cervical smear test results. *Br J Cancer*. 2004;91(11):1887-1892.

95. French DP, Maissi E, Marteau TM. The psychological costs of inadequate cervical smear test results: Three-month follow-up. *Psychooncology*. 2006;15(6):498-508.

96. Collins RE, Lopez LM, Marteau TM. Emotional impact of screening: A systematic review and meta-analysis. *BMC Public Health*. 2011;11:603-2458-11-603.

97. Anderson E, Shivakumar G. Effects of exercise and physical activity on anxiety. *Front Psychiatry*. 2013;4:27.

98. Friedman L, Furbery C, DeMets D. Chapter 17: Issues in data analysis. In: *Fundamentals of clinical trials.* 4th ed. New York, USA: Springer Science+Business Media; 2010:345. 10.1007/978-1-4419-1586-3.

99. Statistics Canada. Immigration and ethnocultural diversity in Canada - national household survey, 2011. 2013;99-010-X2011001. http://www12.statcan.gc.ca/nhs-enm/2011/as-sa/99-010-x/99-010-x2011001-eng.pdf.

100. U.S. Department of Commerce. US Census Bureau: State and county quick facts. http://quickfacts.census.gov/qfd/states/00000.html. Updated 2015. Accessed July 31, 2015.

101. Sharp L, Cotton SC, Alexander L, et al. Reasons for participation and non-participation in a randomized controlled trial: Postal questionnaire surveys of women eligible for TOMBOLA (Trial of management of borderline and other low-grade abnormal smears). *Clin Trials.* 2006;3(5):431-442.

102. Cancer Care Ontario. Ontario Cancer Plan 2011-2015. https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=84204. Updated 2015. Accessed August 3, 2015.

6. APPENDICES

Appendix A. Hospital Anxiety and Depression Scale

The participants should underline the reply which comes closest to describing how they have been feeling in the past week. They should give an immediate response and should not think too long about their answers. The questions relating to anxiety are marked "A", and to depression "D".

A	**I feel tense or 'wound up':**
3	Most of the time
2	A lot of the time
1	From time to time, occasionally
0	Not at all
D	**I still enjoy the things I used to enjoy:**
0	Definitely as much
1	Not quite so much
2	Only a little
3	Hardly at all
A	**I get a sort of frightened feeling as if something awful is about the happen:**
3	Very definitely and quite badly
2	Yes, but not too badly
1	A little, but it doesn't worry me
0	Not at all
D	**I can laugh and see the funny side of things:**
0	As much as I always could
1	Not quite so much now
2	Definitely not so much now
3	Not at all
A	**Worrying thoughts go through my mind:**
3	A great deal of the time
2	A lot of the time
1	From time to time but not too often
0	Only occasionally
D	**I feel cheerful:**
3	Not at all
2	Not often
1	Sometimes
0	Most of the time
A	**I can sit at ease and feel relaxed:**
0	Definitely
1	Usually
2	Not often
3	Not at all

Appendix A Continued

D	I feel as if I am slowed down:
3	Nearly all the time
2	Very often
1	Sometimes
0	Not at all
A	**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0	Not at all
1	Occasionally
2	Quite often
3	Very often
D	**I have lost interest in my appearance:**
3	Definitely
2	I don't take so much care as I should
1	I may not take quite as much care
0	I just take as much care as ever
A	**I feel restless as if I have to be on the move:**
3	Very much indeed
2	Quite a lot
1	Not very much
0	Not at all
D	**I look forward with enjoyment to things:**
0	As much as ever I did
1	Rather less than I used to
2	Definitely less than I used to
3	Hardly at all
A	**I get sudden feelings of panic:**
3	Very often indeed
2	Quite often
1	Not very often
0	Not at all
D	**I can enjoy a good book or radio or TV programme:**
0	Often
1	Sometimes
2	Not often
3	Very seldom

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica*. 1983; 67(6):361 - 370.

Appendix B. Ethics Documents

Ottawa Hospital Research Institute
Institut de recherche de l'Hôpital d'Ottawa

uOttawa

University of Ottawa Heart Institute
Institut de cardiologie de l'Université d'Ottawa

Ottawa Health Science Network Research Ethics Board/ Conseil d'éthique de la recherche du Réseau de science de la santé d'Ottawa

Civic Box 411 725 Parkdale Avenue, Ottawa, Ontario K1Y 4E9 613-798-5555 ext. 14902 Fax : 613-761-4311
http://www.ohri.ca/ohsn-reb

Tuesday, November 25, 2014

Dr. Julian Little
University of Ottawa
Faculty of Medicine
Department of Epidemiology and Community Medicine
451 Smyth Road, Room [redacted]
Ottawa, ON K1H 8M5

Dear Dr. Little:

Re: Protocol # 20140662-01H — **Cytological Surveillance Patterns for Women with a Low-Grade Abnormal Cervical Smear by HPV Test Results: Findings from TOMBOLA**

Protocol approval valid until - Tuesday, November 24, 2015

I am pleased to inform you that this protocol underwent delegated review by the Ottawa Health Science Network Research Ethics Board (OHSN-REB) and is approved. No changes, amendments or addenda may be made to the protocol without the OHSN-REB's review and approval.

Approval is for the following:
- Protocol dated August 12, 2014

If the study is to continue beyond the expiry date noted above, a Renewal Form should be submitted to the REB approximately six weeks prior to the current expiry date. If the study has been completed by this date, a Termination Report should be submitted.

The Ottawa Health Science Network Research Ethics Board (OHSN-REB) was created by the merger of both the Ottawa Hospital Research Ethics Board (OHREB) and the Human Research Ethics Board (HREB) for meetings held at the University of Ottawa Heart Institute.

OHSN-REB complies with the membership requirements and operates in compliance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; the International Conference on Harmonization - Good Clinical Practice: Consolidated Guideline and the provisions of the Personal Health Information Protection Act 2004.

Yours sincerely,

[redacted]

Raphael Saginur, M.D.
Chairperson
Ottawa Health Science Network Research Ethics Board

RS/kd

Appendix B Continued (2)

University of Aberdeen
Aberdeen Maternity Hospital
Cornhill Road
Aberdeen
AB25 2ZL

21 November 2014

Research Proposal:	**Cytological Surveillance Patterns for Women with a Low-Grade Abnormal Cervical Smear by HPV Test Results: Findings from TOMBOLA**
Research Student:	**Abhi Bhandari**
Supervisors:	**Julian Little and Beth Potter**

The TOMBOLA trial was funded by the UK Medical Research Council, who have a policy on data sharing to maximise the life-time value of research data assets for human health.

The proposed project is in-keeping with the original aims of TOMBOLA, and will further our understanding of patterns of abnormal cytology within a policy of surveillance.

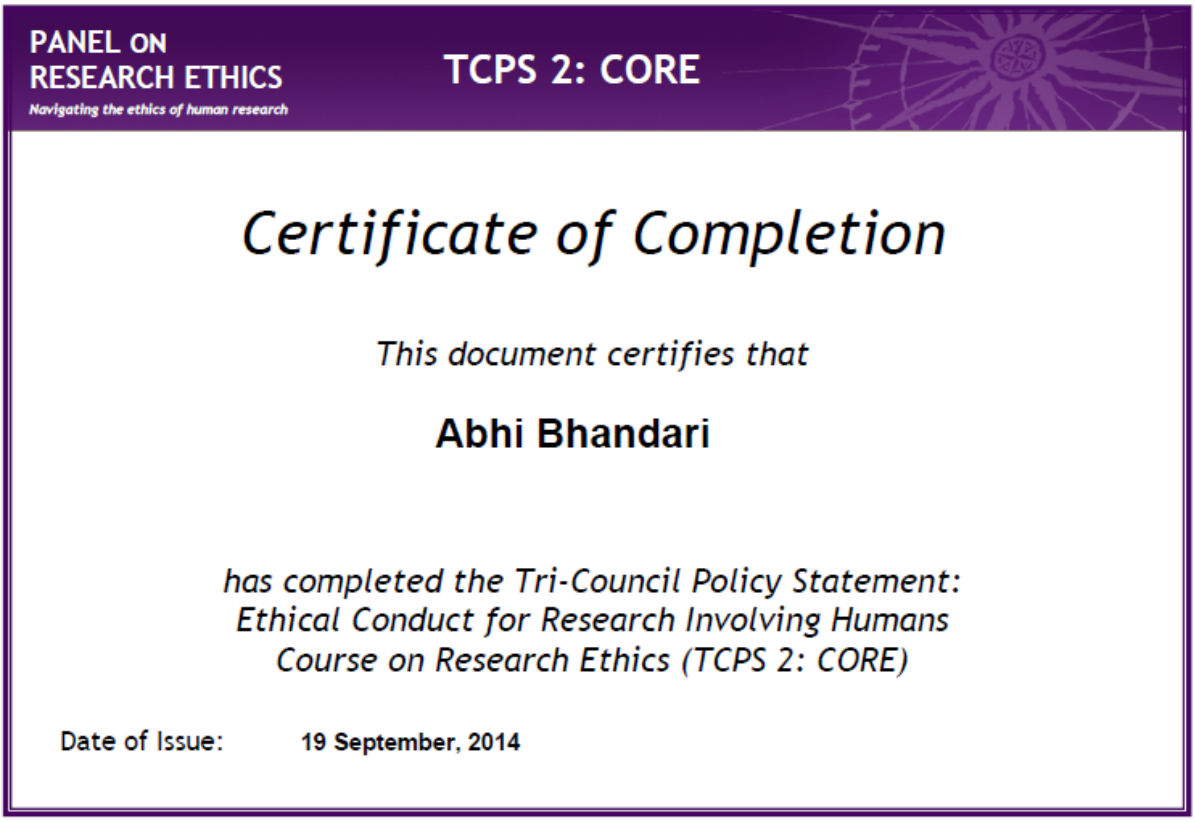
The data to be used in the proposed project is non-identifiable.

As custodian of data from the original TOMBOLA study, I am supportive of its use in the proposed project, and hereby give permission for its use.

[redacted]

Professor Maggie Cruickshank
TOMBOLA Chief Investigator

Appendix B Continued (3)



PANEL ON RESEARCH ETHICS
Navigating the ethics of human research

TCPS 2: CORE

Certificate of Completion

This document certifies that

Abhi Bhandari

has completed the Tri-Council Policy Statement:
Ethical Conduct for Research Involving Humans
Course on Research Ethics (TCPS 2: CORE)

Date of Issue: **19 September, 2014**

Appendix C: Flow Charts

Figure 10a. Follow-up Smear 1

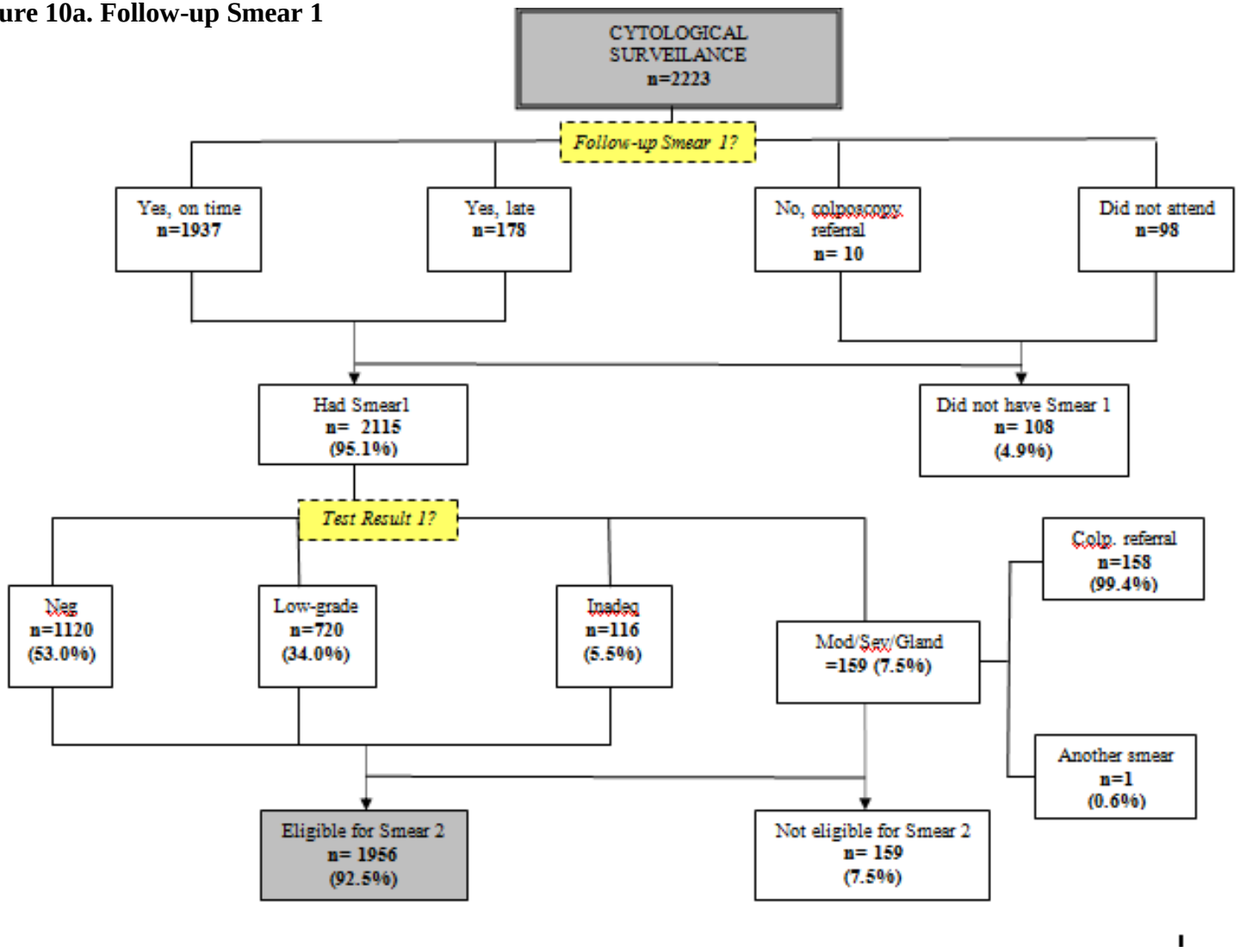


Figure 10b. Follow-up Smear 2

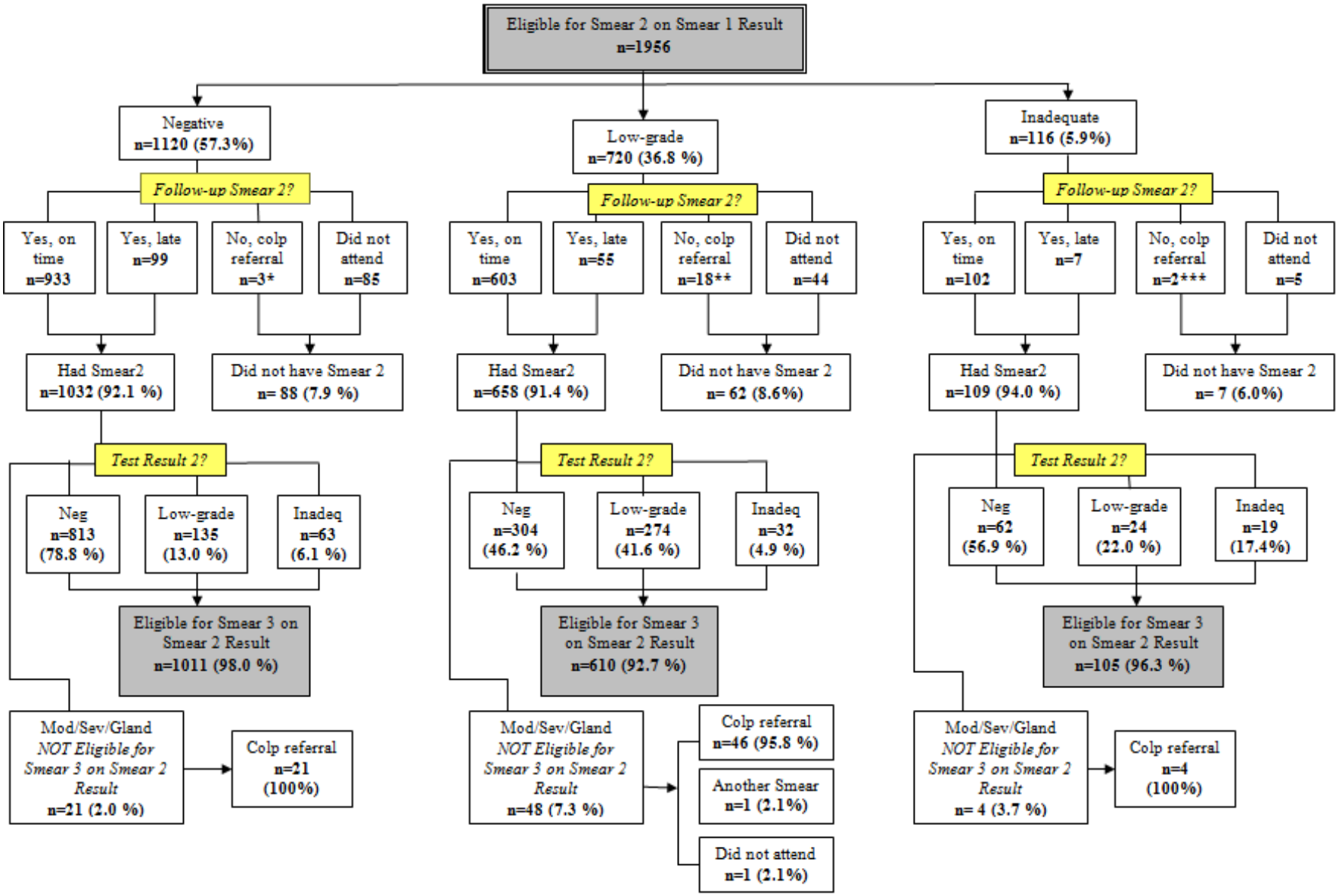


Figure 10c. Follow-up Smear 3, Cytology Test 1 Negative

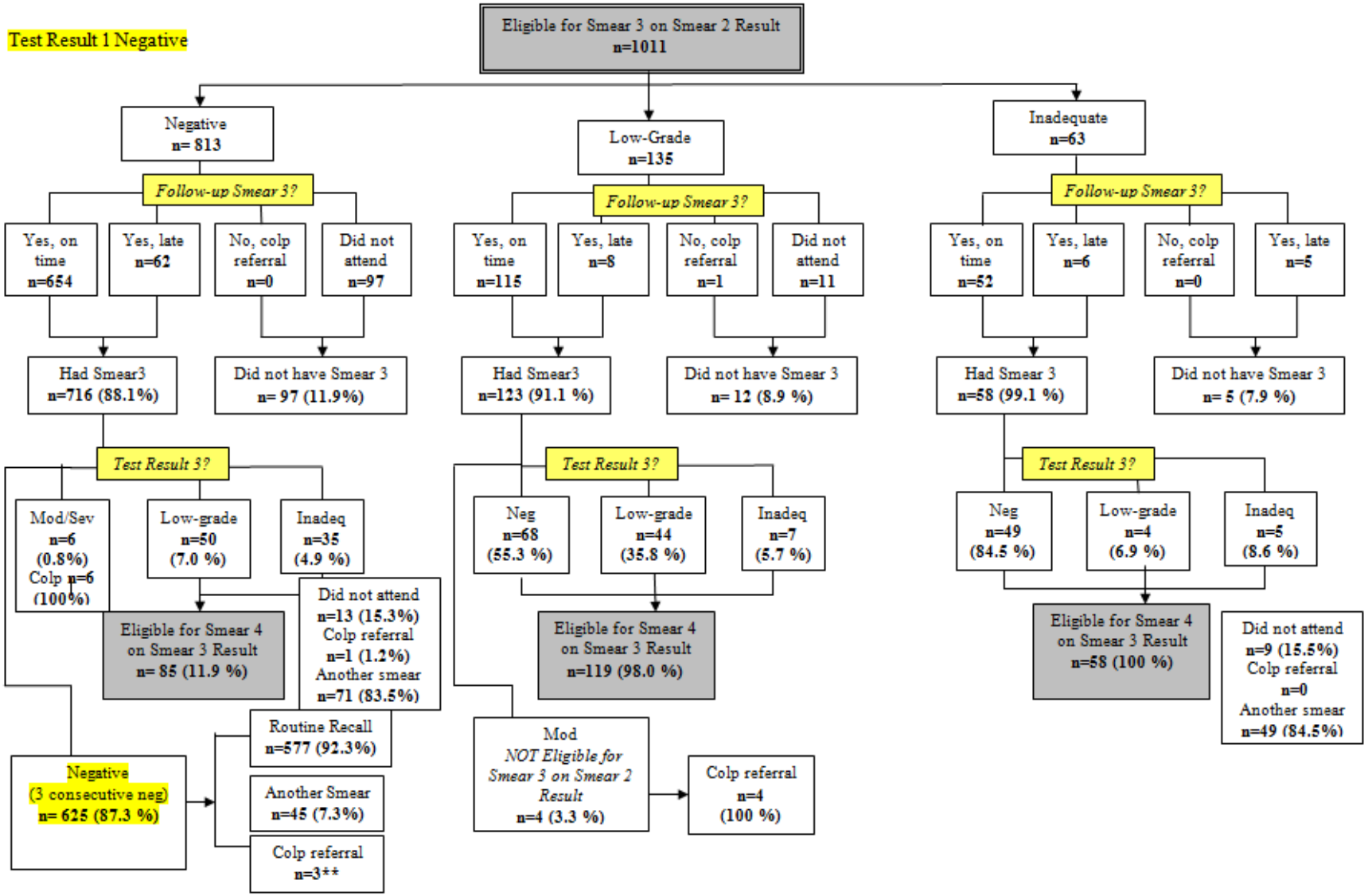


Figure 10d. Follow-up Smear 3, Cytology Test 1 Low-Grade

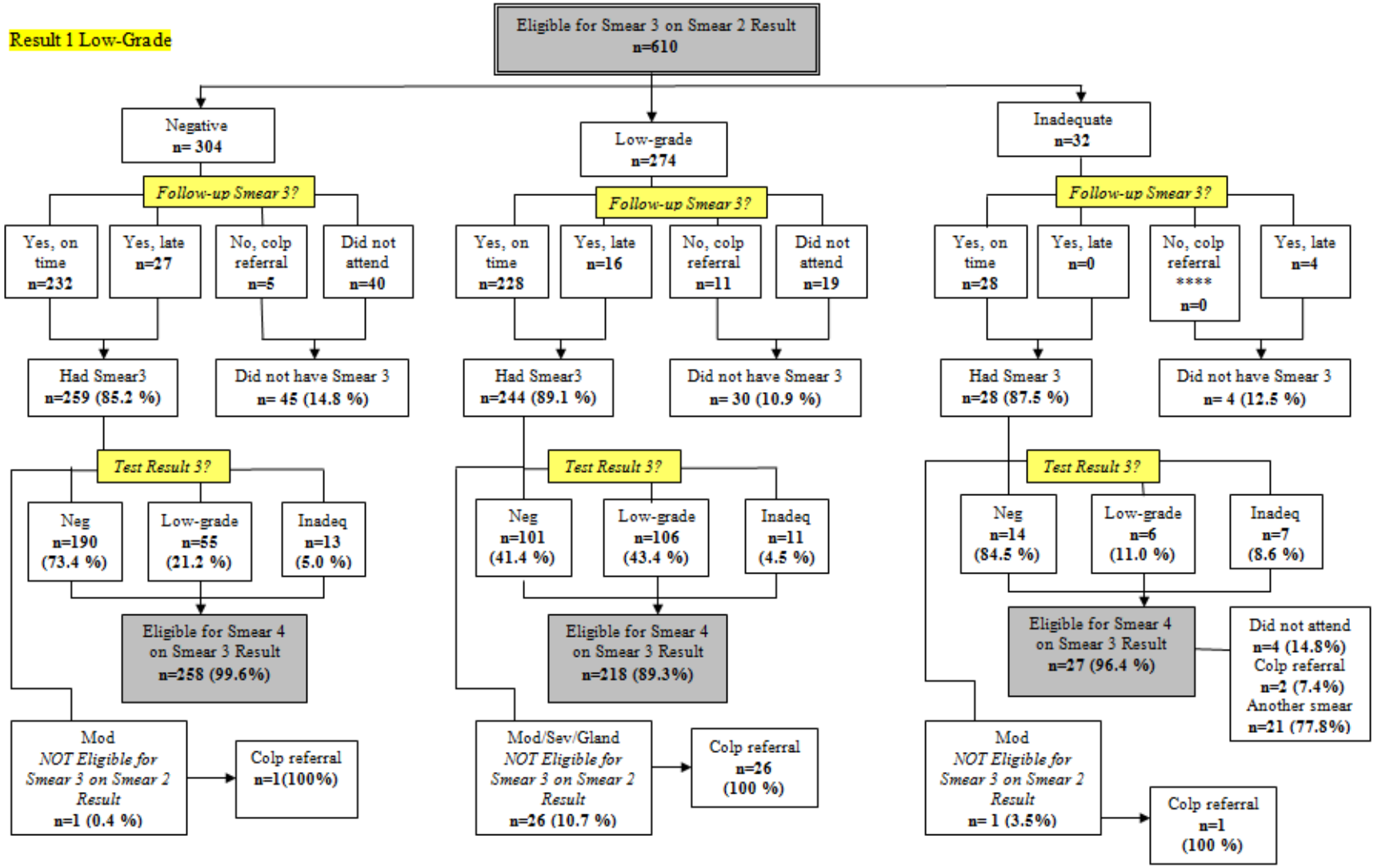


Figure 10e. Follow-up Smear 3, Cytology Test 1 Inadequate

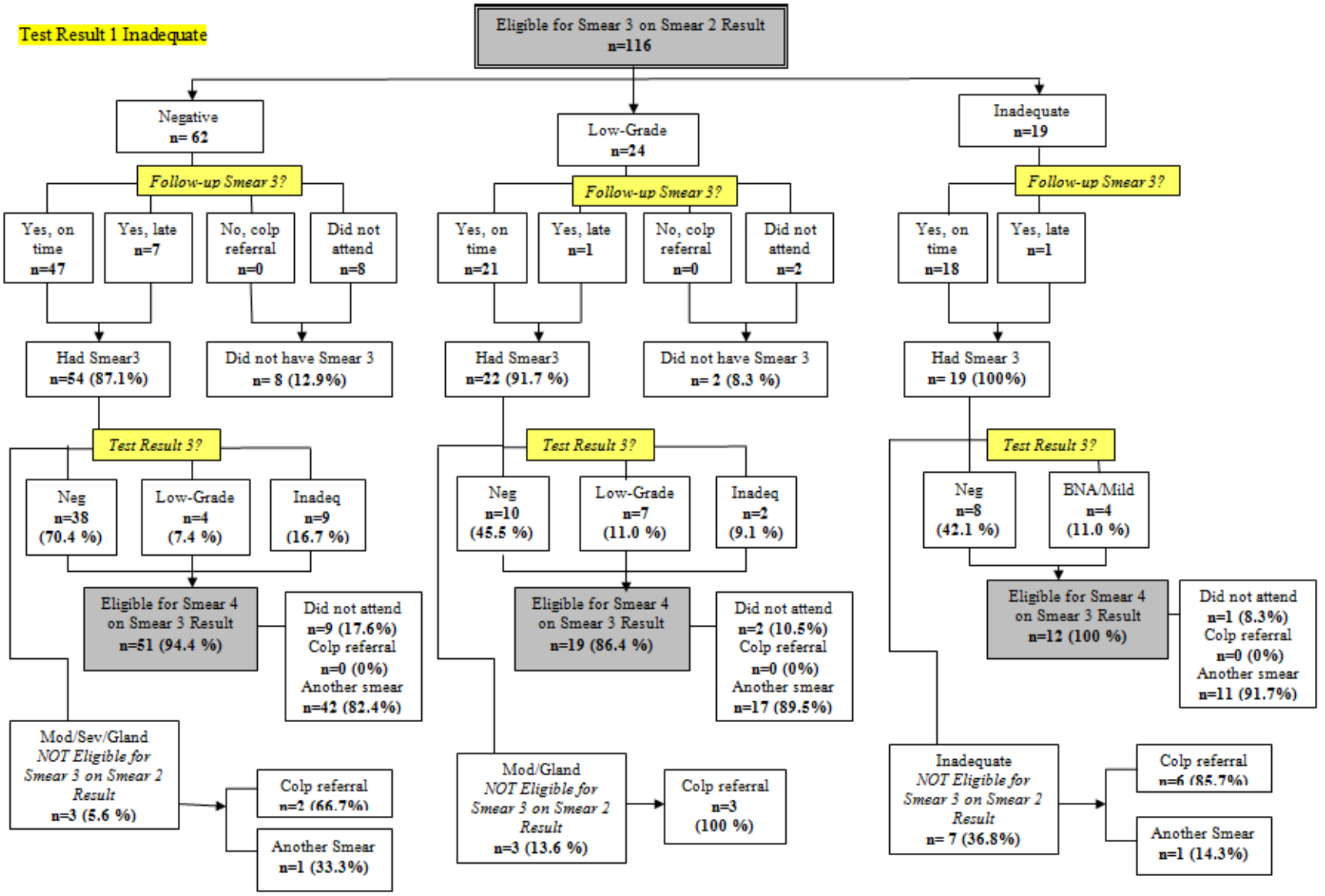


Figure 10f. Follow-up Smear 3; Cytology Test 1 Negative, Test 2 Low-Grade

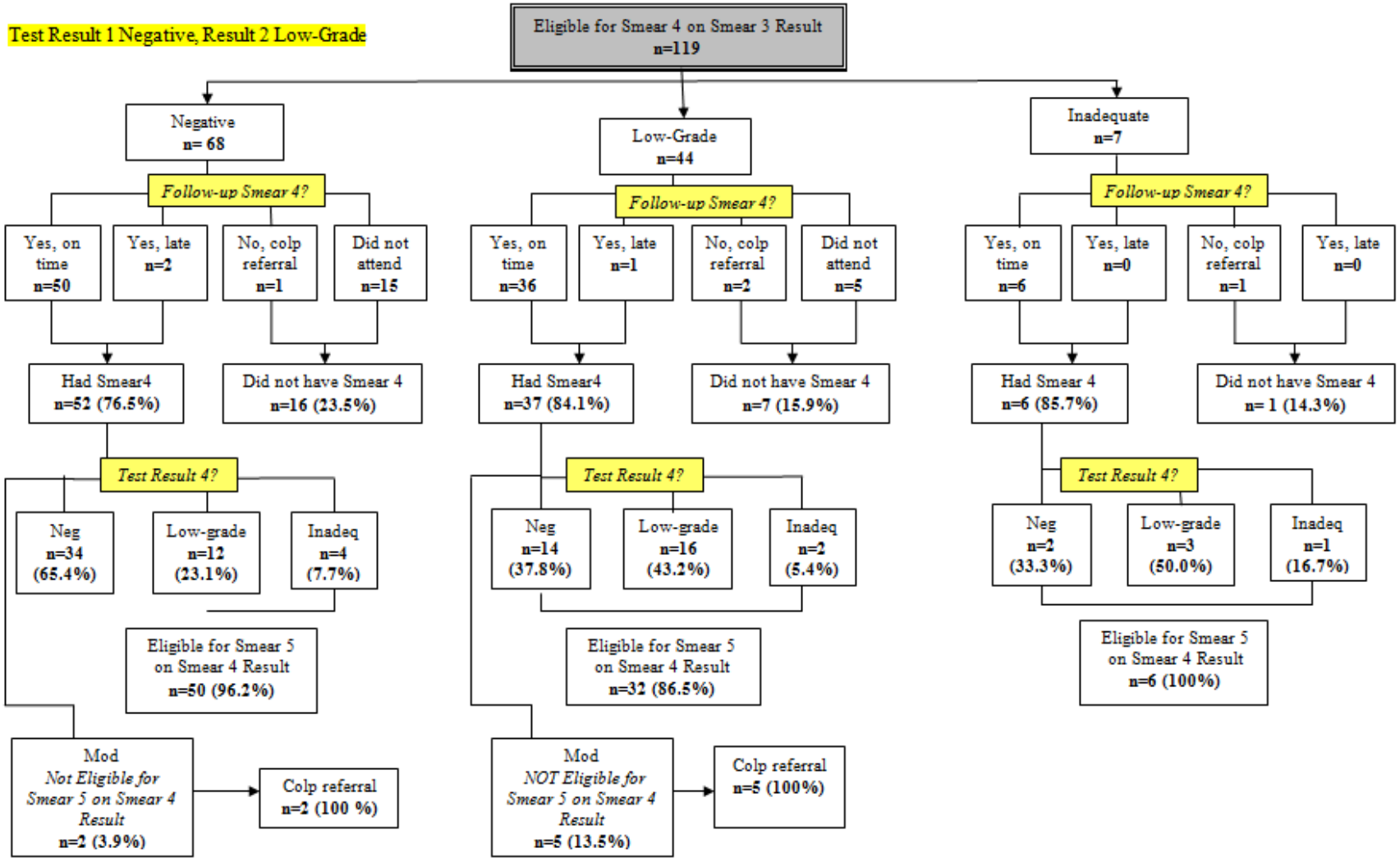


Figure 10g. Follow-up Smear 3; Cytology Test 1 Low-Grade, Test 2 Negative

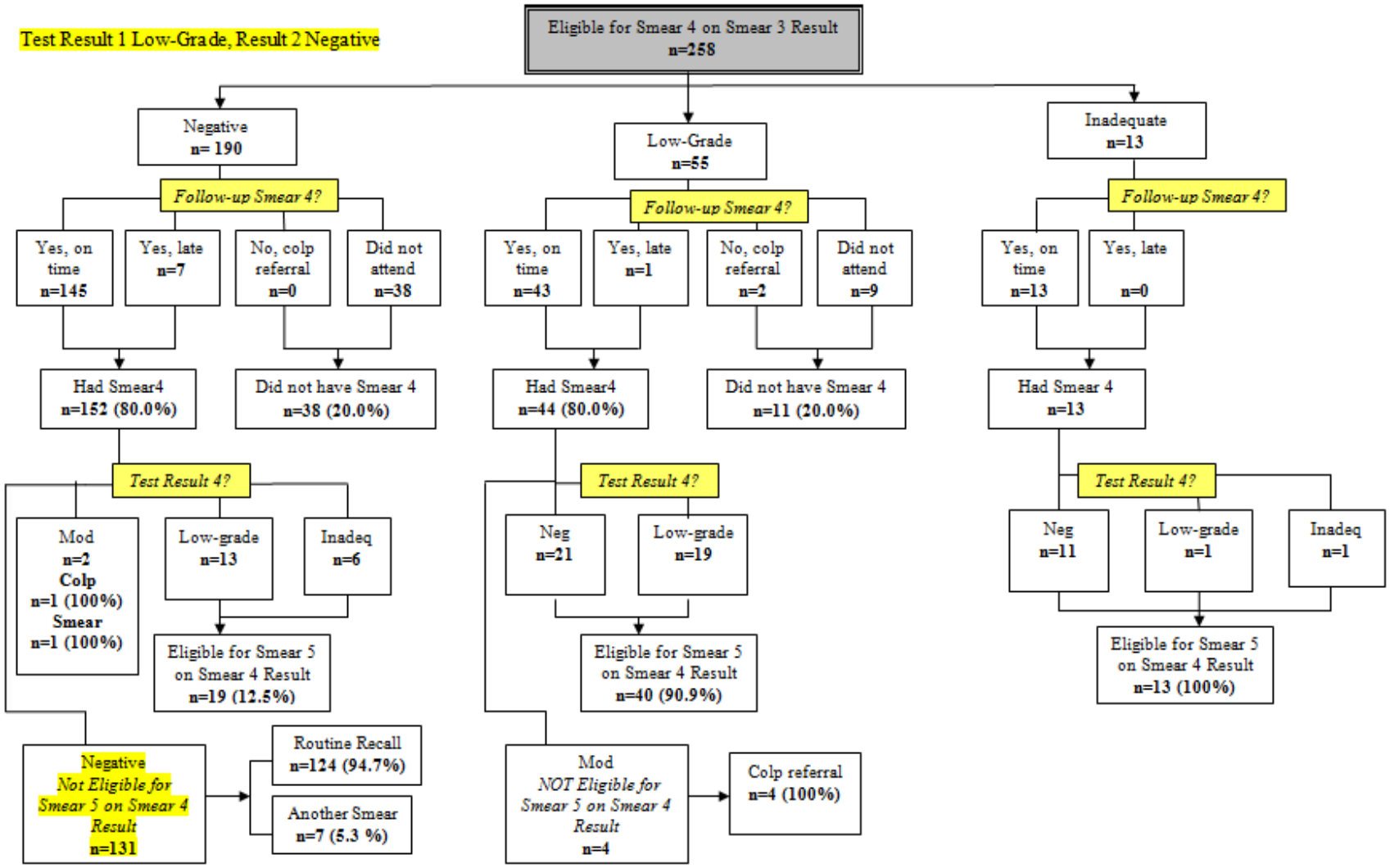
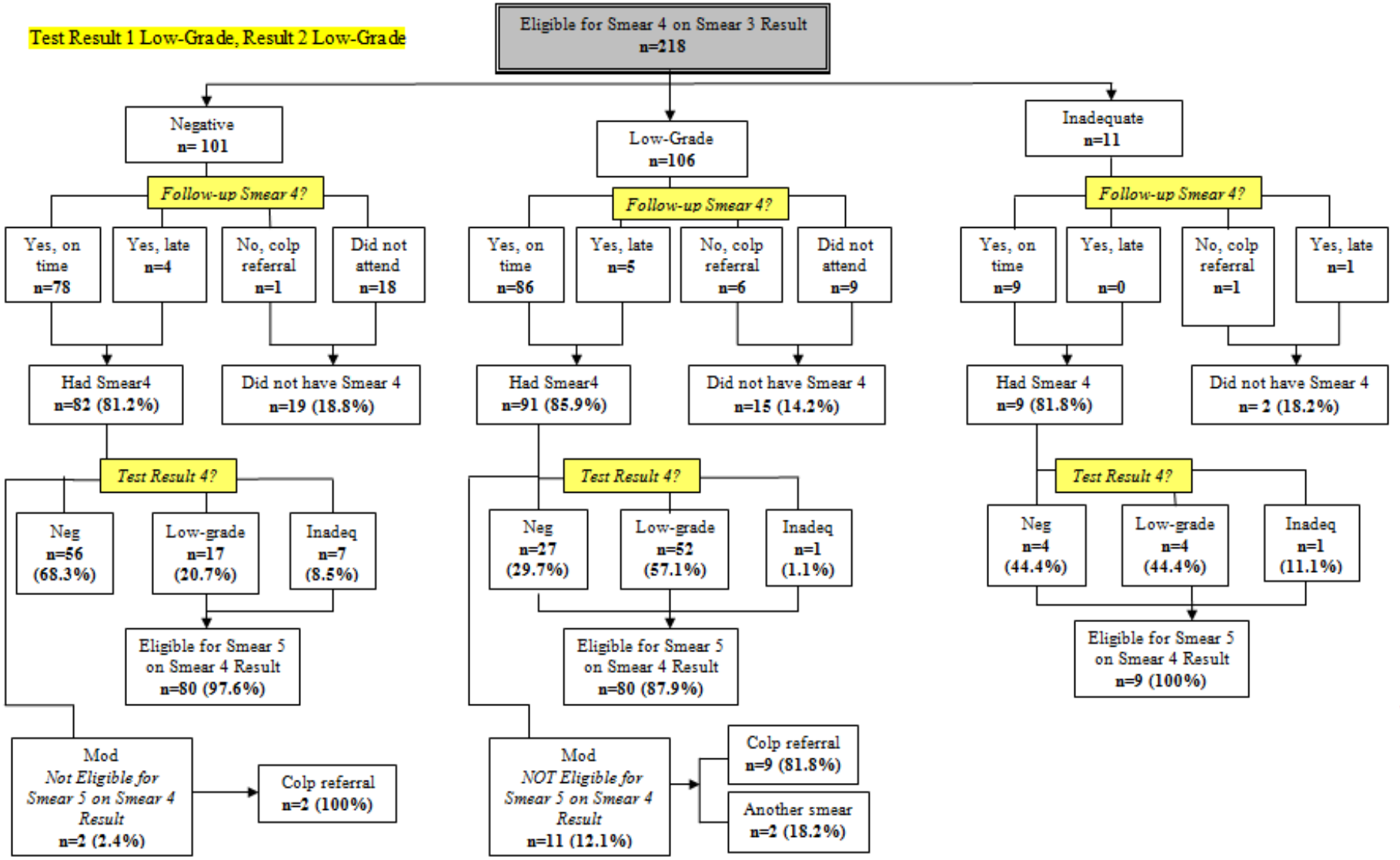


Figure 10h. Follow-up Smear 3; Cytology Test 1 Low-Grade, Test 2 Low-Grade



Appendix D. Objective 1-Breakdown of the Identified Management Pathways

MANAGEMENT PATHWAY ONE: Women who were eligible to be returned to "routine recall" on the basis of three consecutive negative cytology test results **(n=873)**

a) Three consecutive negative test results (n=625)

b) One low-grade/inadequate test results --> three consecutive negative test results (n=156)

c) One low-grade/inadequate/negative test result -> one low-grade/inadequate test result -> three consecutive negative test results (n=68)

d) Two low-grade/inadequate/negative test results -> one low-grade/inadequate test result -> three consecutive negative test results (n=22)

- Excluded women who had three consecutive inadequate test results as they should have received a colposcopy referral (outcome 2).

e) Three low-grade/inadequate/negative test results-> one low-grade/inadequate test result --> three consecutive negative test results (n=2)

- Excluded women who had three consecutive inadequate test results
- Excluded women who had three consecutive negative test results (management pathway 1a)

MANAGEMENT PATHWAY TWO: Women who were eligible to be referred for colposcopy on the basis of a "high-grade" cytology test result or three consecutive inadequate test results **(n=338)**

A: High-grade test result (n=321):

a) High-grade test result at smear one (n=159)

b) High-grade test result at smear two (n=73)

c) High-grade test result at smear three (n=44)

d) High-grade test result at smear four (n=28)

e) High-grade test result at smear five (n=13)

f) High-grade test result at smear six (n=4)

Appendix D Continued (2)

B: Three consecutive inadequate test results (**n=17**)

a) Three consecutive inadequate test results (n=7)

b) One negative/low-grade test result -> three consecutive inadequate test results (n=4)

c) One negative/low-grade/inadequate test result, one negative/low-grade test result, followed by three consecutive inadequate test results (n=3)

d) Two negative/low-grade/inadequate test results, one negative/low-grade test result, followed by three consecutive inadequate test results (n=2)

- Excluded women who had three consecutive negative test results (Management Pathway 1)
- Excluded women who had three consecutive inadequate test results (Management Pathway 2B.a)

e) Five negative/low-grade/inadequate test results, one negative/low-grade test result, followed by three consecutive inadequate test results (n=1)

- Excluded women who had three consecutive negative test results (Management Pathway 1)
- Excluded women who had three consecutive inadequate test results (Management Pathway 2B.a, 2B.b, 2B.c and 2B.d

MANAGEMENT PATHWAY THREE: Continued "uncertainty", with no definitive outcome as per protocol (i.e. return to routine recall, referral for colposcopy) (**n=904**)

A: Persistent low-grade/inadequate test results, no negative test result (n=169)

- Excluded women in management pathway one and two

a) Only had one smear; one-low-grade inadequate test result (n=69)

b) Only had two smears; two consecutive low-grade inadequate test results (n=36)

c) Only had three smears; three consecutive low-grade/inadequate test results (n=21)

d) Only had four smears; four consecutive low-grade/inadequate test results (n=22)

e) One had five smears; five consecutive low-grade/inadequate test results (n=16)

Appendix D Continued (3)

f) Only had six smears; six consecutive low-grade/inadequate test results (n=4)

g) Only had seven smears; seven consecutive low-grade/inadequate test results (n=1)

B: Persistent low-grade/inadequate test results, with at least one negative test result (n=735)

- Excluded women in pattern one and two

a) Only had one smear; negative test result (n=88)

b) Only had two smears; at least one negative test result (n=167)

c) Only had three smears; at least one negative test result (n=130)

d) Only had four smears; at least one negative test result (n=175)

e) Only had five smears; at least one negative test result (n=118)

f) Only had six smears; at least one negative test result (n=52)

g) Only had seven smears, at least one negative test result (n=3)

h) Only had eight smears; at least one negative test result (n=2)

Appendix E. Deviations from TOMBOLA Protocol

Table 26. Characteristics of the women whose management deviated from the TOMBOLA protocol

Characteristic ***(n for whom data available)***	**Frequency**	**%[1]**
HPV Infection at Recruitment ***(50)***		
High-risk HPV Negative	23	46.0%
High-risk HPV Positive	25	50.0%
Inadequate/Missing	2	4.0%
Smoking Status ***(50)***		
Never smoked	23	46.0%
Current Smoker	21	42.0%
Ex-Smoker	6	12.0%
Age Group ***(50)***		
20-29 years	31	62.0%
30-39 years	11	22.0%
40-49 years	7	14.0%
50-59 years	1	2.0%
Contraception prescribed by GP ***(50)***		
No	23	46.0%
Yes	27	54.0%
Marital Status ***(50)***		
Single	18	37.5%
Divorced/Separate/Widowed	9	18.8%
Married/Common-law	21	43.8%
Ever had children ***(48)***		
No	21	43.8%
Yes	27	56.3%
Number of Children ***(46)***		
0	21	45.7%
1	10	21.7%
2	9	19.6%
3	4	8.7%
4-7	2	4.4%
Deprivation ***(50)***		
1 (Least Deprived)	6	12.0%
2	7	14.0%
3	5	10.0%
4	16	32.0%
5 (Most Deprived)	16	32.0%
Activity ***(49)***		
<Once/week	14	28.6%
1-3 times/week	11	22.4%
>3 times/week	24	49.0%
Trial Centre ***(50)***		
A	23	46.0%
B	13	26.0%
C	14	28.0%

[1]Calculated with missing data excluded

Appendix F. Objective 3-Histograms

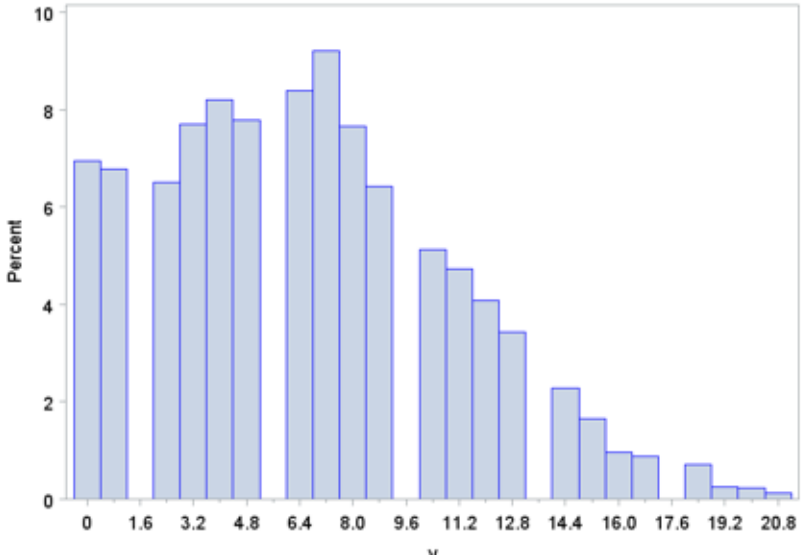


Figure 11a. Anxiety scores on the original scale (y) across all time points

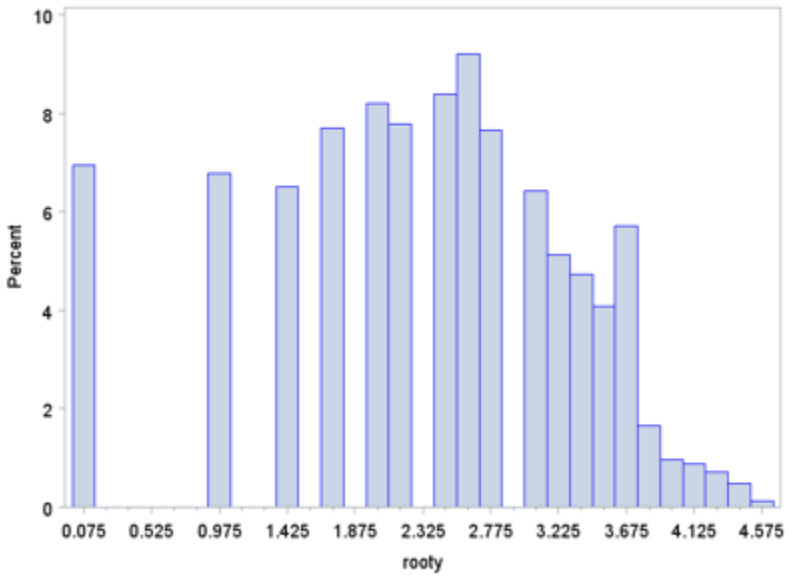


Figure 11b. Square root transformation of anxiety scores (rooty) across all time points

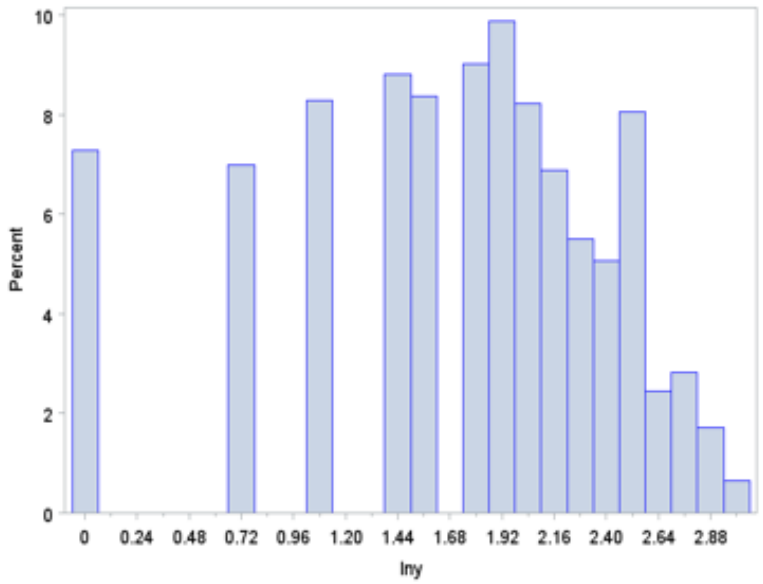


Figure 11c. Log transformation of anxiety scores (lny) across all time points

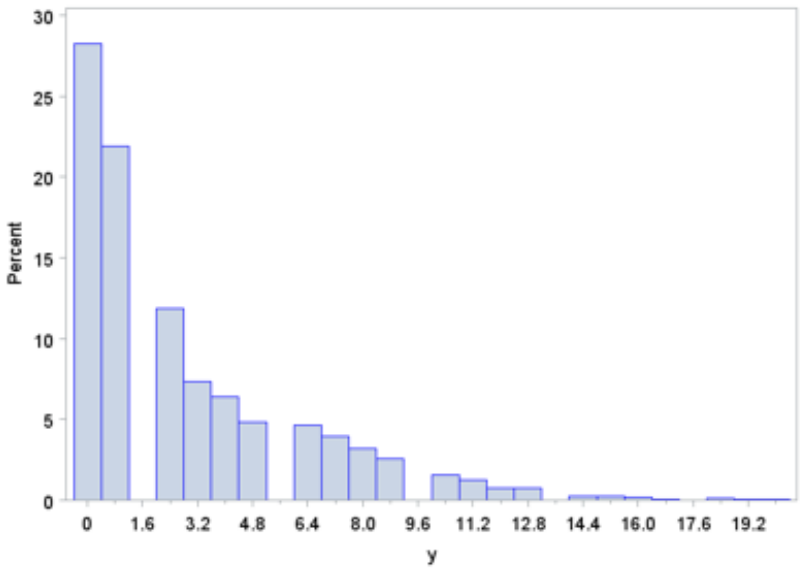


Figure 12a. Depression scores on the original scale (y) across all time points

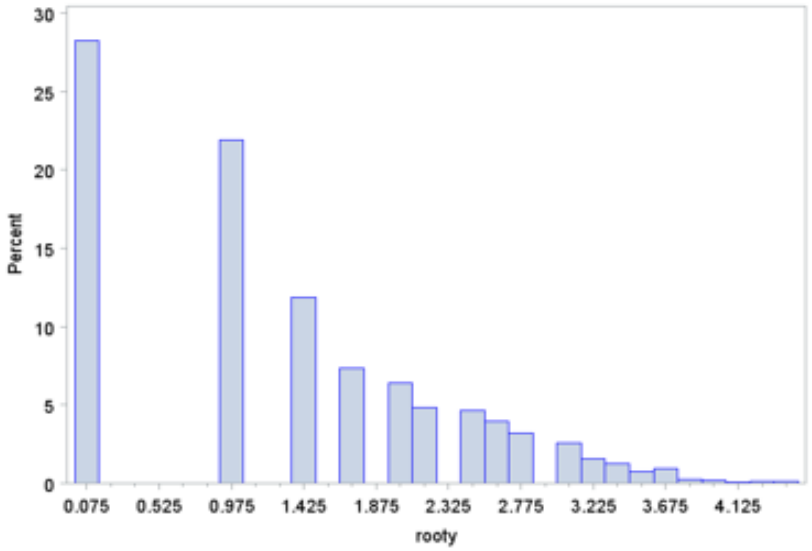


Figure 12b. Square root transformation of depression scores (rooty) across all time points

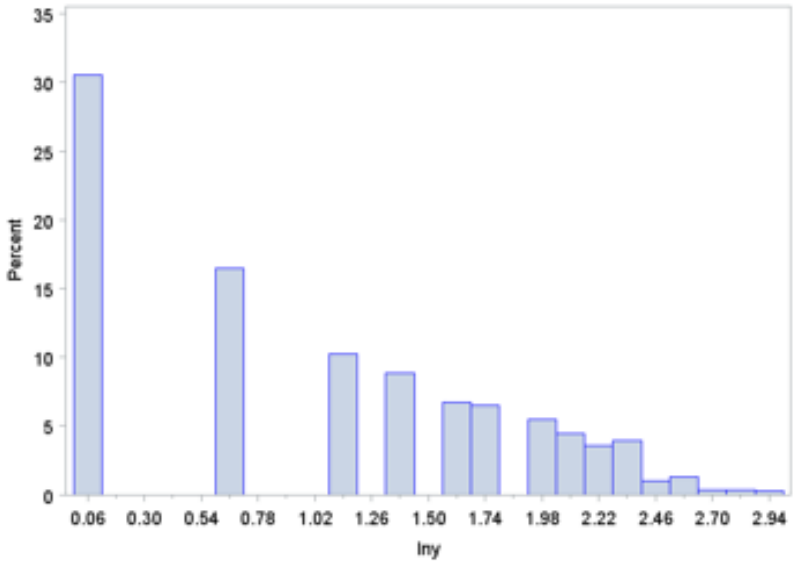


Figure 12c. Log transformation of anxiety scores (lny) across all time points

Appendix G. Additional Figures

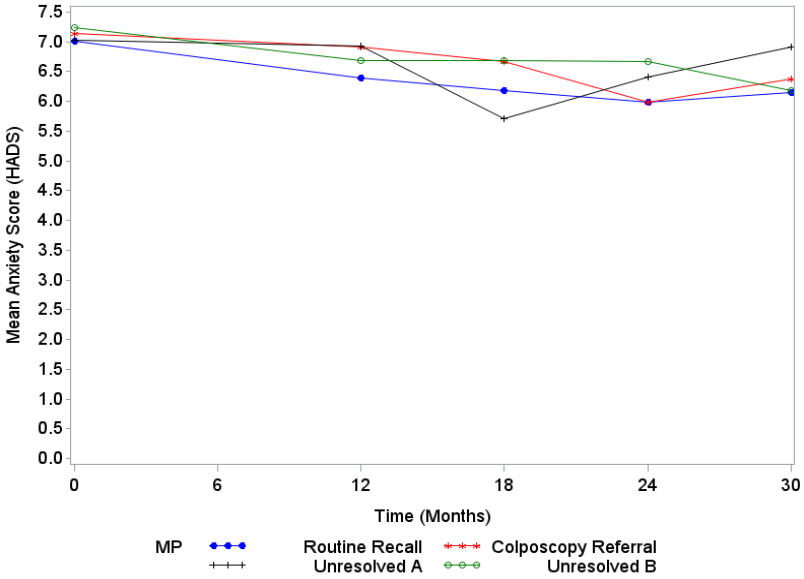


Figure 13. Mean anxiety score (increments of 0.5) over time by Management Pathway (MP) in women who had no negative test results (Unresolved A) as compared to those with at least one negative test result (Unresolved B)

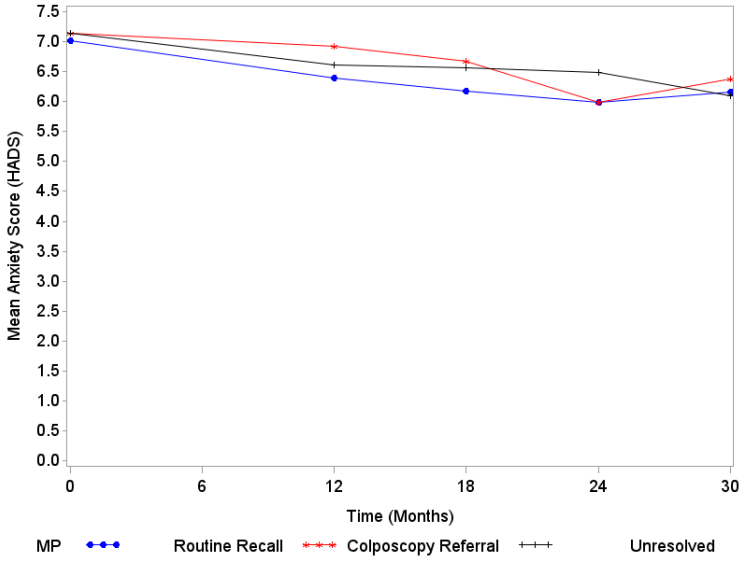


Figure 14. Mean anxiety score (increments of 0.5) over time by Management Pathway (MP), excluding women who had less than three follow-up surveillance smears in unresolved cytology

Appendix H. Additional Tables

Table 27. Multivariable regression analysis–main effects for time and management pathway on mean anxiety scores, excluding women with less than three follow-up surveillance smears in unresolved cytology–Sensitivity analysis

Effect	Estimate	Standard Error	p-value[1]	Overall p-value[2]
Intercept	5.47	0.48	**<0.0001***	
Management Pathway				0.53
Eligible for return to Routine Recall	**REF**			
Eligible for a Colposcopy Referral	0.17	0.30	0.57	
Unresolved Cytology	0.27	0.24	0.27	
Time				**<0.0001***
Baseline	**REF**			
12 months	-0.34	0.12	**0.006***	
18 months	-0.53	0.13	**<0.0001***	
24 months	-0.69	0.14	**<0.0001***	
30 months	-0.69	0.15	**<0.0001***	
Covariates				
High-risk HPV infection				0.07
High-risk HPV negative	**REF**			
High-risk HPV positive	0.06	0.24	0.81	
High-risk HPV inadequate/missing	0.83	0.37	**0.02***	
Smoking Status				**0.0002***
Never smoked	**REF**			
Current smoker	0.98	0.24	**<0.0001***	
Ex-smoker	0.46	0.28	0.10	
Age group				0.58
20-29 years	**REF**			
30-39 years	-0.13	0.31	0.69	
40-49 years	-0.45	0.37	0.23	
50-59 years	-0.48	0.46	0.29	
Trial Centre				**0.01***
A	**REF**			
B	-0.52	0.25	**0.04***	
C	0.29	0.27	0.29	
Contraception prescribed by GP				0.56
No	**REF**			
Yes	-0.14	0.25	0.56	
Number of children				**0.0001***
0	**REF**			
1	0.82	0.32	**0.01***	

Table 27 Continued

Effect	Estimate	Standard Error	p-value[1]	Overall p-value[2]
2	1.03	0.32	**0.001***	
3	1.35	0.40	**0.0009***	
4-7	2.17	0.51	**<0.0001***	
Deprivation quintile				0.36
1 (Least deprived)	**REF**			
2	-0.08	0.35	0.83	
3	-0.04	0.37	0.92	
4	0.32	0.34	0.35	
5 (Most deprived)	0.47	0.35	0.17	
Marital status				0.57
Single	**REF**			
Divorced/Separated/Widowed	0.27	0.39	0.49	
Married/Common-law	-0.06	0.29	0.84	
Physical activity				**<0.0001***
<1 time/week	**REF**			
1-3 times/week	0.32	0.26	0.22	
>3 times/week	1.15	0.24	**<0.0001***	

Notes

[1]t-test of the beta coefficient; [2]Wald type 3 test of fixed effect (overall test of effects on anxiety); REF: Reference
* (and bold font): Statistically Significant, p-value <0.05; 4717 of 7960 observations used

Table 28. Multivariable regression analysis–main effects for time, management pathway and the interaction between management pathways and time on mean depression scores, excluding women with less than three follow-up surveillance smears in unresolved cytology– Sensitivity analysis

Effect	Estimate	Standard Error	p-value[1]	Overall p-value[2]
Intercept	0.64	0.35	0.07	
Management Pathway				0.35
Eligible for return to Routine Recall	**REF**			
Eligible for a Colposcopy Referral	0.15	0.25	0.55	
Unresolved Cytology	0.23	0.20	0.24	
Time				**<0.0001***
Baseline	**REF**			
12 months	0.47	0.13	**0.0002***	
18 months	0.49	0.14	**0.0003***	
24 months	0.55	0.14	**0.0001***	
30 months	0.53	0.15	**0.0004***	
Management Pathway*Time interaction				**0.02***
Eligible for Return to Routine Recall	**REF**			
Colp[3], Baseline	**REF**			
Colp[3], 12 months	0.36	0.26	0.17	
Colp[3], 18 months	0.43	0.29	0.14	
Colp[3], 24 months	-0.45	0.30	0.13	
Colp[3], 30 months	-0.16	0.31	0.61	
Unresolved, Baseline	**REF**			
Unresolved, 12 months	0.09	0.22	0.68	
Unresolved, 18 months	-0.06	0.24	0.79	
Unresolved, 24 months	0.10	0.24	0.69	
Unresolved, 30 months	0.03	0.26	0.91	
Covariates				
High-Risk HPV infection				0.45
High-risk HPV negative	**REF**			
High-risk HPV positive	0.02	0.18	0.90	
High-risk HPV Inadequate/Missing	0.33	0.27	0.22	
Smoking status				**<0.0001***
Never Smoked	**REF**			
Current smoker	0.81	0.17	**<0.0001**	
Ex-smoker	-0.02	0.21	0.94	
Age group				0.46

Table 28 Continued

Effect	Estimate	Standard Error	p-value[1]	Overall p-value[2]
20-29 years	**REF**			
30-39 years	0.24	0.23	0.29	
40-49 years	0.12	0.27	0.67	
50-59 years	0.46	0.33	0.17	
Trial Centre				**0.008***
A	**REF**			
B	0.50	0.20	**0.01***	
C	-0.13	0.18	0.49	
Contraception prescribed by GP				0.80
No	**REF**			
Yes	-0.05	0.18	0.80	
Number of children				**<0.0001***
0	**REF**			
1	0.88	0.23	**0.0002***	
2	1.02	0.23	**<0.0001***	
3	1.22	0.30	**<0.0001***	
4-7	1.78	0.37	**<0.0001***	
Deprivation quintile				0.26
1 (Least deprived)	**REF**			
2	0.17	0.25	0.51	
3	0.26	0.27	0.34	
4	0.41	0.25	0.10	
5 (Most deprived)	0.52	0.25	**0.04***	
Marital status				0.31
Single	**REF**			
Divorced/Separated/Widowed	0.25	0.29	0.39	
Married/Common-law	-0.10	0.21	0.63	
Physical activity				**<0.0001***
<1 time/week	**REF**			
1-3 times/week	0.34	0.19	0.08	
>3 times/week	0.84	0.18	**<0.0001***	

Notes

[1]t-test of the beta coefficient; [2]Wald type 3 test of fixed effect (overall test of effects on anxiety); REF: Reference

[3]Colp: women eligible for a colposcopy referral

* (and bold font): Statistically Significant, p-value <0.05

Appendix I. Poster Presentation at Canadian Society for Epidemiology and Biostatistics Conference, June 2015

What Happens to Women after they Have a Low-Grade Abnormal Cervical Smear?

Abhi Bhandari, BHSc, MSc Candidate; Beth Potter, PhD; Monica Taljaard, PhD; Seonaidh Cotton, PhD; Susan McFaul, MD; Julian Little, PhD

uOttawa

Background

•Worldwide, cervical cancer ranks as the fourth most common cancer in terms of incidence and mortality (1).
•Papinacolaou (Pap) testing remains the primary screening test for cervical cancer in many jurisdictions around the world.
•Organized programs that identify and treat cervical intraepithelial neoplasia (CIN) through screening using the Pap test, i.e. cytological surveillance, results in very large numbers of women having to be followed up; this may result in over-treatment and psychological distress.
•We seek to understand how different management strategies for women with a low-grade abnormal smear may affect patient and health system outcomes over time.

Specific Objectives

(1) To identify and describe specific management pathways based on test results of women with low-grade abnormal cervical cytology;
(2) To identify the participant characteristics of women in each management pathway and;
(3) To conduct a longitudinal analysis of the effects of anxiety and depression over time, and associations with management policy.

Methods

•This study was a secondary data analysis from TOMBOLA (Trial of Management of Borderline and Other Low-grade Abnormal smears), a pragmatic randomized-controlled trial nested within the Cervical Screening Programmes in the United Kingdom. These women were assigned to have follow-up Pap tests in primary care for up to three years.

•The trajectories of testing and test results were examined to classify women into one of 4 mutually exclusive management pathways (Figure 1) .

• Multinomial logistic regression was used to examine differences among management pathways based on the participant characteristics.

• Longitudinal analysis was conducted to examine differences in the Hospital Anxiety and Depression Scale (HADS) over time and between the outcomes, adjusting for baseline participant characteristics.

• Information criteria and likelihood ratio tests were used to identify an appropriate covariance structure to account for correlation over time.

• Pair-wise mean differences and 95% confidence intervals (CIs) were computed to describe differences over time; and overall test of differences and 95% CIs were computed to describe differences between management pathways over time.

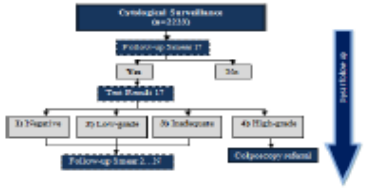


Figure 1: Flow charts to visualize the trajectory of testing and sequence of test results

Results

(1) Three main characteristics of the observed test result and trajectory of testing are:
1) Substantial heterogeneity in patterns of test results.
2) Varying number of smears (Figure 2).
3) Substantial loss to follow-up; approximately 21% (n=468) dropped out before having at least three consecutive smears, a high-grade test result or completing three-years of follow-up.

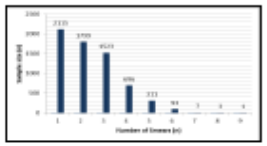


Figure 2: Number of Smears Women had in the Cytological Surveillance Arm over the Three-Year Follow-Up Period

Figure 3: Visual Diagram of the Management Pathways Identified in the Cytological Surveillance Arm

(2) In the multinomial logistic regression analysis, HPV status at recruitment, smoking status, age group and trial centre were identified as independent factors associated with classification into one of the three relevant management pathways. Details are illustrated (Table 1).

(3) There was a significant effect of time on both anxiety and depression scores; mean anxiety scores decreased at each time point from baseline (Figure 4), while mean depression scores increased for these women (Figure 6).
•There were no significant effects of the management pathways on repeated measures of anxiety and depression over the 30-month period, adjusted for sociodemographic and lifestyle characteristics. This is illustrated in Figures 5 and 7.

Table 1: Adjusted model cORs and 95% CIs for management pathways Colposcopy Referral vs. Routine Recall, Unresolved vs. Routine Recall, and Colposcopy Referral vs. Unresolved (Multinomial response)

Characteristic	Colposcopy Referral vs. Routine Recall*	Unresolved vs. Routine Recall*	Colposcopy Referral vs. Unresolved*
HPV Infection at Recruitment			
High-risk HPV negative	Ref	Ref	Ref
High-risk HPV positive	0.60 (0.23 - 0.99)*	1.14 (0.54 - 1.90)*	3.09 (2.27 - 4.21)*
Unknown status	1.72 (1.00 - 2.69)*	0.99 (0.48 - 1.41)	1.73 (1.20 - 2.46)*
Smoking Status			
Non-smoker	Ref	Ref	Ref
Current smoker	1.39 (1.04 - 2.03)*	1.21 (0.93 - 1.67)*	1.41 (1.09 - 1.89)*
Ex-smoker	1.16 (0.79 - 1.77)	0.93 (0.72 - 1.24)	1.24 (0.86 - 1.80)
Age group			
20-29	Ref	Ref	Ref
30-39	0.56 (0.37 - 0.83)*	0.51 (0.38 - 0.70)*	1.14 (0.78 - 1.67)
40-49	0.35 (0.20 - 0.59)*	0.21 (0.17 - 0.71)*	0.63 (0.38 - 1.00)
50-59	0.27 (0.13 - 0.53)*	0.19 (0.15 - 0.46)*	1.13 (0.56 - 2.26)
Trial Centre			
A	Ref	Ref	Ref
B	0.40 (0.24 - 0.67)*	0.71 (0.56 - 0.90)*	0.57 (0.42 - 1.25)
C	1.00 (0.74 - 1.34)	0.64 (0.49 - 0.83)*	1.60 (1.18 - 2.16)*
Contraception prescribed by GP			
Yes	Ref	Ref	Ref
No	0.82 (0.67 - 1.24)	0.84 (0.71 - 1.21)	0.98 (0.76 - 1.32)
Number of children			
0	Ref	Ref	Ref
1	1.29 (0.79 - 1.81)	1.00 (0.74 - 1.34)	1.28 (0.91 - 1.77)
2	1.72 (1.07 - 2.58)	0.91 (0.71 - 1.31)	1.89 (1.30 - 2.74)
3	1.58 (0.90 - 2.91)	1.18 (0.88 - 1.77)	1.42 (0.92 - 2.48)
4+	1.53 (0.77 - 2.92)	1.63 (1.10 - 2.61)	1.38 (0.74 - 2.74)
Deprivation			
1 (Least Deprived)	Ref	Ref	Ref
2	1.47 (0.89 - 2.41)	1.25 (0.89 - 1.79)	1.18 (0.73 - 1.94)
3	1.34 (0.82 - 2.18)	1.15 (0.80 - 1.65)	1.16 (0.80 - 2.04)
4	1.26 (0.77 - 1.94)	1.15 (0.84 - 1.64)	0.95 (0.74 - 1.72)
5 (Most Deprived)	1.18 (0.81 - 2.24)	1.28 (0.91 - 1.79)	1.08 (0.67 - 1.74)
Marital Status			
Single	Ref	Ref	Ref
Divorced/Separated/Widowed	1.10 (0.67 - 1.84)	1.07 (0.73 - 1.57)	1.02 (0.62 - 1.68)
Married/Cohabiting	0.93 (0.64 - 1.34)	0.79 (0.60 - 1.04)	1.18 (0.83 - 1.66)
Ethnicity			
Other/mixed	Ref	Ref	Ref
1-2 times/week	1.09 (0.72 - 1.65)	1.04 (0.78 - 1.41)	1.06 (0.73 - 1.56)
>2 times/week	0.91 (0.66 - 1.27)	1.07 (0.83 - 1.41)	0.85 (0.61 - 1.19)
Ethnicity			
White	Ref	Ref	Ref
Non-white	1.22 (0.61 - 2.61)	1.14 (0.71 - 1.85)	1.00 (0.54 - 2.02)

Figure 4: Mean Anxiety Score (increments of 1.0) over Time, and p-values for pair-wise mean comparisons from baseline*

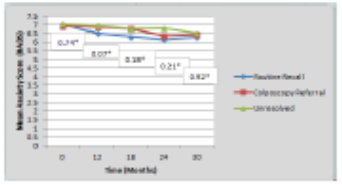


Figure 5: Mean Anxiety Score over Time (increments of 0.5) by Pathway Management, and p-values for overall test of differences*

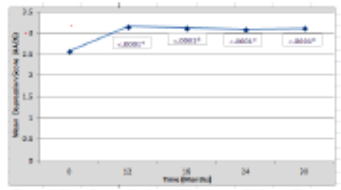


Figure 6: Mean Depression Score (increments of 0.5) over Time, and p-values for pair-wise mean comparisons from baseline*

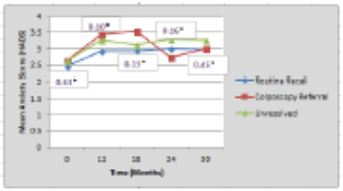


Figure 7: Mean Depression Score (increments of 0.5) over Time by Pathway Management, and p-values for overall test of differences*

Conclusion

•There were three management pathways identified for women with a low-grade abnormal cervical smear test result: eligible for return to routine recall, eligible for colposcopy referral and unresolved.
•Although a large proportion of these women became eligible for return to routine recall over the three-year follow-up period, a similar proportion of women remained unresolved.
•HPV status at recruitment, age, smoking status and trial centre were associated with these three management pathways.
•Women who did not achieve resolution, i.e. remain unresolved, is of high concern. However, even at the thirty-month mark there were no significant effects of anxiety and depression scores between the management pathways.
•Interestingly, while the anxiety scores decreased from the baseline assessment, the depression scores increased.

Acknowledgements/ Additional Information

The TOMBOLA trial was supported by the Medical Research Council (G9718008) and the NHS in England and Scotland. We acknowledge the TOMBOLA group who were involved in the design, co-ordination, clinical aspects and analysis of the study, and NHS staff in the co-ordinating centres and clinical sites for their co-operation and assistance. We thank the women who participated in TOMBOLA.

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References: International Agency for Research on Cancer. Press release - latest world cancer statistics. http://www.iarc.fr/en/media-centre/pr/2013/pdfs/pr223_E.pdf. Updated December 12, 2013.

. TOMBOLA Group. Cytological surveillance compared with immediate referral for colposcopy in management of women with low grade cervical abnormalities: Multicentre randomised controlled trial. BMJ. 2009;339:b2548.