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ScienceDirect
Contemporary Clinical Trials 27 (2006) 449–471
Contemporary Clinical Trials
www.elsevier.com/locate/conclintrial

# Trial of management of borderline and other low-grade abnormal smears (TOMBOLA): Trial design ☆

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Received 1 October 2004; accepted 21 April 2006

**Abstract**

Cervical screening reduces the risk of cervical cancer by detecting and treating cervical intraepithelial neoplasia (CIN). The management of women with low-grade cervical abnormalities is controversial. Two management policies exist: repeat smears in primary care and colposcopy examination. It is not clear which of these is the more effective and efficient. There is also uncertainty as to the most effective and efficient management of women at colposcopy when an area of abnormality is seen on the cervix — immediate treatment or biopsy and selective recall for treatment if the biopsy result suggests this is necessary. The result of a human papillomavirus (HPV) test might assist in deciding the appropriate management of women with low-grade abnormalities. TOMBOLA, a pragmatic randomised-controlled trial set within the cervical screening programmes in Scotland and England, addresses these three areas of uncertainty. Almost four and a half thousand women aged 20–59 with a low-grade cervical abnormality have been recruited and randomised to either repeat smears or colposcopy examination. Women in the colposcopy arm of the trial are further randomised to a policy of either immediate treatment or biopsy and selective recall for treatment if they have an abnormal transformation zone. Women are followed up to an exit examination at 3 years. HPV testing is undertaken at recruitment and at the exit examination. The primary endpoint is cumulative incidence of CIN2/3. A range of other clinical, psychosocial and economic outcomes is being considered. This paper describes the design of the trial, and discusses the rationale underlying aspects of the design and the challenges faced in designing and implementing the trial.


*Keywords:* Randomised-controlled trial; Cervical screening; Colposcopy; Cytological surveillance; Management; Low-grade abnormalities; Cervix uteri; Mild dyskaryosis

☆ TOMBOLA is funded by the Medical Research Council, the NHS in Scotland and the NHS in England.
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doi:10.1016/j.cct.2006.04.001

## 1. Introduction

By detecting and treating cervical intraepithelial neoplasia (CIN), cervical screening has reduced the incidence of, and mortality due to, cervical cancer. In the UK, screening is based on 3–5 yearly cytological smear tests for women aged 20 or 25 to 60 or 65. Smears are classified as "unsatisfactory", "normal", "borderline nuclear abnormalities" (BNA), "mild", "moderate" or "severe dyskaryosis" or "indicating invasive cancer". Most clinicians consider smears showing BNA or mild dyskaryosis as "low-grade" and those showing moderate or severe dyskaryosis as "high-grade". There are well-established guidelines for management of women with high-grade abnormalities but the management of women with low-grade abnormalities is controversial. Each year in the UK, more than 250,000 cytological smears show low-grade abnormalities [1,2], so this uncertainty regarding management has important implications for both women and the National Health Service.

Two methods of management for women with low-grade abnormalities are routinely employed — repeat smears in primary care at regular intervals (cytological surveillance) or colposcopic examination in a hospital outpatient clinic, with biopsy if an abnormal area is seen on the cervix. It is not clear which of these is the more effective or efficient management policy. Revised guidelines on colposcopy and programme management for the NHS Cervical Screening Programme in England reflect this uncertainty, suggesting that "women should be referred for colposcopy after one test reported as mild dyskaryosis, but it is acceptable to recommend a repeat test" [3]. Referral to colposcopy after a single mild smear will increase the number of referrals to colposcopy, which may increase waiting times. In Scotland, there has been reluctance to deviate from the previous guidelines which applied to the whole of the UK, deferring colposcopy until two smears showing mild dyskaryosis or three smears showing BNA had been reported [4]. In addition, there is considerable heterogeneity in management across the UK. Furthermore, over time and without treatment, some low-grade lesions will progress to higher-grade lesions, others will remain stable, and others will regress spontaneously; follow-up and treatment may therefore be of no benefit to the group of women who have a low-grade lesion that is going to regress. At the moment, however, it is not possible to identify which abnormalities will regress, and which will progress.

Human papillomavirus (HPV) has been shown to have a role in the aetiology of cervical cancer and pre-cancer, with certain types leading to a particularly high risk [5,6]. This has led to suggestions that HPV testing would be of potential value in the triage of women with low-grade abnormalities [7,8]. If HPV testing could be used to discriminate between women with a low-grade smear who are likely to have underlying high-grade CIN and those who are unlikely to have high-grade disease, then it might be possible to manage the two groups of women in different ways. For example, those likely to have underlying disease might be referred straight to colposcopy, while those unlikely to have underlying disease could be kept under cytological surveillance, thus reducing the burden on colposcopy clinics in terms of new referrals.

There is also uncertainty as to the most effective and efficient method of managing women with a low-grade smear when an area of abnormality is seen on the cervix during colposcopy. There are two main methods — biopsy followed by recall for treatment if the histological result confirms CIN or immediate treatment [9]. The recent English guidelines discourage immediate treatment for women with low-grade smears, because of the potential for over-treatment [3]. However, trial evidence is lacking on whether immediate treatment or biopsy and recall is the most effective and efficient policy.

In 1995 the Medical Research Council and Department of Health issued a joint commissioning brief for a randomised-controlled trial of alternative referral and management policies for women with low-grade smears, to include a HPV component (BMJ, 10 June 1995, vol 310). TOMBOLA (Trial Of Management of Borderline and Other Low-grade Abnormal smears) is the result of that call.

This paper describes the design of TOMBOLA, the outcomes being considered, and discusses some of the issues arising in the design and implementation of this pragmatic trial nested within the NHS Cervical Screening Programmes in England and Scotland.

## 2. Aims

The aims of TOMBOLA are, in women with a low-grade smear:

- To determine whether cytological surveillance or a colposcopic examination is the more effective and efficient management policy;