PROTOCOL

PRINCess:
The Prediction of Regression in CIN2

A prospective multicentre trial of conservative management of CIN2 in women under the age of 25

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Introduction

Cervical cancers are usually preceded by a long phase of preinvasive disease. This is characterised microscopically as a spectrum of events progressing from cellular atypia to various grades of cervical intraepithelial neoplasia before progression to cervical cancer.

In 1968 the term cervical intraepithelial neoplasia (CIN) was introduced to denote the whole range of cellular atypia confined to the epithelium. CIN was divided into grades 1, 2 and 3. CIN 1 corresponded to mild dysplasia, CIN 2 to moderate dysplasia and CIN 3 corresponded to both severe dysplasia and carcinoma-in-situ. CIN 2 and 3 are considered high-grade lesions. It appears the mean interval for progression of cervical precursors to invasive cancer is 10-20 years.\(^1\)

A review of the literature on the natural history of cervical intraepithelial neoplasia since 1950\(^2\) showed that all women with histological evidence of CIN 2 have approximately a 43% likelihood of regression to CIN 1, a 35% likelihood of persistence of CIN 2, a probability of 20% of progression to CIN 3 and 1.5% likelihood of progression to invasive cancer.

Epidemiologic and laboratory data support the conclusion that human papillomavirus (HPV) is the etiologic agent for the vast majority of premalignant and malignant epithelial lesions of the cervical mucosa. In women under the age of 25, HPV infection rates have been reported to range from 28% to 46%. In the vast majority of cases, HPV infections are usually transient and do not necessarily lead to clinically significant lesions of the cervical mucosa.\(^3,4\)

The time to commence cervical screening is controversial with many different recommendations around the world. The New Zealand National Cervical Screening Programme recommends screening start at age 20 years, whilst in the United Kingdom screening commences at age 25.\(^5\) A case control study published in 2003 showed that smears under the age of 25 conferred no significant protective effect against cervical cancer.\(^6\)

Currently the routine management of CIN 2 on the cervix is a LLETZ biopsy (large loop excision of the transformation zone of the cervix). The LLETZ procedure has been associated with complications in future pregnancies. Studies have shown an increased risk of preterm rupture of membranes and preterm delivery.\(^11,12\) Repeat procedures significantly increase the risk for pregnancy complications. Recent American Society Colposcopy guidelines published in 2007 have advocated conservative management of CIN 2 in adolescents and young women.\(^13\) This is because of increasing evidence in studies of adolescents (up to age 21) showing higher rates of regression of CIN 2 in this age group than those quoted above.\(^7,8,9,10\)

In some studies of younger women, prolonged colposcopy follow-up was associated with a high loss to follow-up rate (24%).\(^13\)

Issues regarding fertility and other treatment related morbidities also are relevant in women from ages 20-25. A very large number of women in this age group are diagnosed with CIN2. In NZ alone 3-400 women a year in this age group have histologically diagnosed CIN2. Currently there are no guidelines that recommend conservative management in this age group. A summary of recent studies of conservative management is included in the table below, these normally single institution studies reveal regression rates of up to 70%. A larger study identified in the table below estimates the regression of CIN2 lesions to be at least 40% based on data from the alts study.\(^15,7,16,17,8,18,19\)
A recent, retrospective study of women under the age of 25 with CIN 2 in New Zealand demonstrated regression to CIN1 or less in 62% of women who were managed conservatively for more than 4 months. Ultimately 18% had CIN3 and none developed cancer. Only 3% were lost to follow up. In this study in the cohort of women with CIN 2 who were treated immediately 1 woman had a micro invasive tumour and 2 had AIS.  

It seems therefore if managed conservatively in most young women lesions diagnosed histologically as CIN2 will regress without the need for treatment. However some young women with a histological diagnosis of CIN2 have more significant lesions that require treatment. In addition there is a risk of loss to follow up with conservative regimes. While some practitioners already adopt a wait conservative approach to the management of CIN2 in young women and in the UK screening does not commence before the age of 25. There is a paucity of data that confirms the safety and success of conservative management. In order that patients and doctors can be properly informed it is essential that the regression rate and safety of a conservative management regime is documented in a large multicentre prospective study.

There is currently little evidence to determine which lesions in which women will regress and which will persist. If we could identify the 2/3rds of women likely to regress at the first visit this would enable the doctor to safely advise patients to pursue conservative management and which should be treated immediately. There is evidence to suggest that HPV16/18 positive lesions are less likely to regress and that loss of HPV positivity may precede regression. There is also some evidence that certain immunohistochemical stains may predict regression and that some markers of immune response may be helpful. There are also newer liquid based sample tests that allow quantitative measures of DNA integration. Patient factors may also be helpful. A large multicentre prospective trial is the ideal opportunity to define histological cytological and patient predictors of regression.
1. Trial Objectives

Primary objectives
The trial objective is to provide clinically relevant information on the safety and practicality of conservative management of CIN2 from a prospective multicentre trial.

The primary aims of the trial are to document, for a cohort women under the age of 25 with a diagnosis of CIN 2;

- The safety of observational conservative management, and
- The spontaneous rate of regression.

We hypothesise that observational conservative management can be safely performed for women aged less than 25 years with CIN2 in a large multicentre trial, and that;

- No women will develop life threatening disease,
- Less than 5% of women will be lost to follow up,
- No more than half of women will require or request treatment,
- Approximately two thirds of women will undergo regression of their disease to CIN1 or less within 2 years.

Secondary objectives
A secondary objective of the trial is to identify clinical and biological markers that are predictive of outcome. Currently no such markers are reported, there is some evidence that HPV type expression has predictive value. Immunohistochemical markers in cytology and histology also have the potential to predict outcome and will be studied in this cohort of patients and reported separately.

The secondary aims are to identify;

- Predictors of regression and progression of CIN 2 in this cohort.

2. Methods

A multi-centre prospective trial.

The trial will be undertaken in large colposcopy centres in New Zealand and Australia. Participating centres will identify potential trial participants following initial colposcopy and biopsy. Cytology and biopsies from women who consent to the trial will be reviewed at a multidisciplinary review meeting. If inclusion criteria are met patients will be included in the trial.

Repeat colposcopy, cytology and cervical biopsy will be performed at 6 monthly intervals for 2 years. Patients with persistent CIN2 at 2 years will be treated by LLETZ biopsy. Women who develop CIN3 will be treated accordingly at any time in the trial as will patients with CIN2 who request treatment. Those women who regress require 2 consecutive colposcopy follow ups showing CIN1 or less (on cytology alone or cytology and histology) prior to discharge from colposcopy. These women will then undergo 12 monthly cytology follow up as per NCSP guidelines. In New Zealand women will return to
normal 3 yearly screening following 2 consecutive normal smears and negative HR-HPV tests at least 12 months apart.

The patients will be monitored by the local centre and data collated and analysed centrally in the Department of Obstetrics and Gynaecology, University of Otago - Christchurch.

Access to histological specimens and cytology vials for ancillary testing either in the local centre or centrally will be requested. Ancillary testing will include HPV typing and immunohistochemical staining and will be performed at no cost to the participating centre.

3. Statistical Considerations
In order to identify the rate of regression within 5% confidence intervals it is estimated that we require a cohort of about 550 women (see Appendix B Statistical Report). In addition, from our retrospective study of 452 young women with CIN2 we identified 1 woman who was treated immediately had a micro invasive carcinoma. Therefore to identify any safety issues a trial of this magnitude would be required. To ensure these confidence intervals we plan to recruit 600 women to the trial.

4. Ethical Considerations
It is apparent there is a very small risk of invasive carcinoma in this cohort of women and there is a risk of progressive disease in women who are lost to follow up. Safety considerations are therefore paramount and the patients will be carefully monitored. However the investigators believe with careful monitoring there is no significant risk of harm. In addition the actual benefit of avoiding treatment will outweigh any theoretical risk of harm. The trial has received ethics approval from the New Zealand Multi-region Ethics Committee.

5. Conduct
The conduct of the trial is summarised by the flow diagram (Appendix A).

Patient selection/consent
In participating centres all women under 25 referred for the assessment of an abnormal smear will be considered potential participants (excluding those with a possible invasive or atypical glandular smear).

Inclusion Criteria
- Age under 25 at enrolment.
- Attending colposcopy clinic as a result of an abnormal smear but without a history of prior high grade abnormality.
- Biopsy proven CIN 2.
- Entire lesion accessible to colposcopy.
Participants in trial agree to six monthly colposcopy and cervical smear and biopsy for a total of two years.

- Cytology and pathology reviewed and CIN2 confirmed at a multidisciplinary meeting and no other clinical factor was identified that would exclude them from the trial.
- Signed informed consent.

**Exclusion Criteria**

- High grade cytological or histological abnormality prior to this referral.
- Unsatisfactory colposcopy.
- Large complex colposcopic abnormality where adequate histological sampling difficult.
- Cytology suspicious of invasion or glandular abnormality.
- Histology suspicious of CIN3 or worse.
- Patients unwilling or unable to attend follow up.
- Patients whose cytology and histology have not been reviewed at MDM.
- Clinical suspicion of invasion or AIS.
- Any glandular histological or cytological abnormality.
- Concern on behalf of treating doctor that patient is unlikely to attend follow up.
- Immunosuppression.
- Pregnancy

**Initial Colposcopy visit**

Initial colposcopy will be performed as per routine practice. Attention should be paid to ensuring the clinical details are completed on the database and notes. It is requested that where clinically reasonable a liquid based cytology sample is taken. Attention should be paid to ensure the entire lesion is colposcopically visualised, any features suspicious of invasion or glandular abnormality are recorded and that adequate biopsy sampling is undertaken. It is recommended that at least 2 biopsies are taken and in larger lesions a biopsy from each effected quadrant is taken. It is requested that a careful diagram of the cervical abnormality is drawn or a photo is taken. If CIN2 is considered a likely diagnosis the patient should be made aware of the trial and the information sheet given to them.

Histology results will be reviewed and the patient informed of the results as per routine practice. If the biopsy is reported as CIN2 the inclusion and exclusion criteria should be reviewed. If a potential participant the patient should discuss the result with the colposcopist and the option of immediate treatment or entry into the trial considered. If informed consent is given, the patient is entered into the trial by completing the **Eligibility Form** and the **Baseline Study Data Form**. The cytology and pathology should then be reviewed at an MDM. If there is evidence of CIN3 on cytology or histology or concern regarding a higher grade abnormality the patient should be excluded from the trial and offered immediate treatment. Similarly, if the diagnosis on review is only CIN1 or less, the patient is then excluded from the trial. A trial **Completion form** should be completed and the patient subsequently managed as per routine practice.

**Histology/ Cytology review**

In each centre an experienced gynae pathologist or pathologists will be nominated to be responsible for review of the pathology and cytology specimens at a multidisciplinary meeting attended by
colposcopists. To remain eligible for the trial patients must have their histology and cytology reviewed at an MDM **within 4 weeks.** This should at least be by gynae pathologist in conjunction with colposcopist.

The patients should be excluded from the trial if on review the worst biopsy is considered CIN1 or less or there is reasonable suspicion of CIN 3 or any suspicion of invasion or glandular abnormality. Where considered clinically appropriate ancillary tests such as HRHPV or p16 can be utilised.

**Following the MDM review**

If the woman is **ineligible**, this should be recorded in patients’ clinical notes, on the Baseline Biopsy Data Form and a trial Completion form should be completed. The patient should be managed at the discretion of the colposcopist.

If the woman is **eligible**, the patient should undergo follow-up colposcopy in 6 months. This should be recorded in patients’ clinical notes and on the Baseline Biopsy Data Form.

**Follow up colposcopy visits**

For participating patients follow up colposcopy should be performed at 6 monthly intervals. This should be performed in a routine manner by an experienced colposcopist. Routine follow up information should be recorded on the specific trial Follow up form. Liquid based cytology sample taken, as per primary colposcopy attention should be paid as to whether the whole transformation zone and lesion are seen and any colposcopic evidence of glandular or invasive disease. If a lesion persists representative biopsies must be taken, two if possible and one from each quadrant in larger lesions. If the colposcopy is normal we encourage the taking of a biopsy from the transformation zone in the previously effected area.

Treatment is indicated if the patient becomes symptomatic, there is colposcopic or cytological suspicion of invasive or glandular disease, the colposcopy is unsatisfactory and abnormal cytology persists, the histology is reported as CIN3 or worse, the patient requests treatment or is unable to attend further follow up and the lesion persists. If treatment is performed a trial Completion Form is filled in and the patient subsequently managed as per normal practice.

If CIN 2 persists, or cytology is reported as ASCH or HSIL colposcopy should be repeated at 6 monthly intervals to 2 years. If CIN2, or ASCH or HSIL cytology persists at this point the patient should be treated. At this point a trial Completion form is filled in.

**Regression**

Regression is defined as return to normal/ low grade cytology and biopsy as defined below, and persistent regression is defined as regression on two or more successive 6 monthly visits.

Regression is:

- normal colposcopy , normal / low grade cytology, normal or no histology
- normal colposcopy, cytology normal or low grade, low grade biopsy
- low grade colposcopy, low grade cytology and low grade/normal biopsy
- CIN 2 colposcopy but low grade/ normal cytology and low grade/normal biopsy
Regression is not confirmed:
- if a lesion is present and a biopsy not taken
- if smear is ASCH or worse or
- a smear is not taken or unsatisfactory

If regression is documented women must have a follow-up at 6 months with;
- a repeat colposcopy and smear and
- a biopsy if a lesion is present

If following the repeat colposcopy criteria for regression is again met, the lesion has demonstrated persistent regression.

Following persistent regression and after discussion between the colposcopist and the woman, the patient may be discharged from the colposcopy clinic. If this is the case, a trial Completion Form is filled and follow-up is then as per NCSP guidelines following high grade abnormality (see long term follow up) with a smear in 6 months (by primary smear taker). If the woman is not discharged from colposcopy clinic a repeat colposcopy occurs at 6-12 months and completion form is filled at follow-up visit 24 months following initial biopsy. Management should be based on the NCSP guidelines.

If regression is demonstrated at the 24 month follow up for the first time the colposcopist will discuss either immediate treatment or follow up at 6 months. However at this point, a trial Completion form will be filled in, and the patient subsequent management should be based on the results of this colposcopy and the NCSP guidelines.

If following apparent regression, at the next follow up CIN2 is seen or smear is reported as ASCH or worse 6 monthly follow up must continue unless the woman elects to be treated or continues on the trial protocol

**Long term follow-up**

Following completion of the trial protocol all participating women should be followed up in accordance with NCSP guidelines. As CIN 2 was initially confirmed, all women following treatment or regression should have an initial follow up at 6-12 months and then annually unless they have had two consecutive negative cytology and HRHPV tests 12 months apart in which case they can return to 3 yearly screening. [http://www.nsu.govt.nz/files/NCSP/NCSP_Guidelines_ALL_small(1).pdf](http://www.nsu.govt.nz/files/NCSP/NCSP_Guidelines_ALL_small(1).pdf) (30/5/12)

**Pregnancy**

Women who are pregnant should not be enrolled on the trial. However, if a woman becomes pregnant once enrolled they should not be taken off the trial. It is important that 6 monthly follow-up is continued. As per NCSP guidelines, we recommend colposcopy is performed by an experienced colposcopist, and cytology is recommended. In this instance, biopsy and treatment if required may be deferred. These treatment decisions are considered to be according to the clinical judgement of the colposcopist. Once the pregnancy is completed follow-up colposcopy, cytology and biopsy should be as per trial protocol.
Treatment

Treatment where indicated should be performed by an experienced colposcopist using an excisional technique (LLETZ or cone) the indication must be recorded and data recorded on the trial Completion form.

Follow up of women who do not attend appointments

The greatest safety risk to patients in the trial is loss to follow up without treatment. Due to this risk it is important that special attention is paid to ensure these women get their appointments on time and that every reasonable attempt is made to ensure they attend their appointments. This is the responsibility of the principal investigator in each site. Non attending patients should be followed up by telephone and mail on at least 3 attempts.

It is strongly recommended that a second contact address (e.g. parent) is filled in on the space provided on the consent form. If the patient is lost to follow up the NCSP, the GP and primary smear taker should be informed and consulted in order to obtain other possible contacts. If non-attendance is greater than 9 months from last follow up a Serious Adverse Event (SAE) form should be completed. A trial Completion form filled in and the patient should be recommended treatment if they can be contacted. It is considered too much of a risk for these patients to continue on the trial.

Women leaving the study area

If women enrolled in the trial advise that they are planning to leave the area there are two options. Firstly, if the woman is planning to move to an area where the trial is underway and wishes to continue conservative management, the Principal Investigator in that area and the central study coordinator should be notified and if possible the woman remains on the trial. A referral letter would be written as part of standard clinical practice. If the patient is moving to a centre not participating in the trial we strongly recommend patients are treated and a trial completion form is filled.

Ancillary testing

Ancillary testing should be performed as requested by pathologist or colposcopist as per routine practice. These investigations and their results should be recorded in patients’ clinical notes and on trial visit Case Report Form (CRF).

HPV testing

It is anticipated that HPV expression will be strongly correlated with regression of CIN2. It is therefore of great importance that we have the potential to perform HPV typing on cytology samples from each visit. For the purposes of the trial we request that (from NZ sites) all smear vials are stored or forwarded to the central study centre once diagnostic testing is completed. We also request access to histology blocks for immunohistochemical staining. Costs for transport will be met by the central study centre. It is planned that type specific HPV DNA testing and E6 and E7 RNA testing as well as a yet as undetermined panel of immunohistochemistry histology stains will be performed, however preliminary investigations are underway. The aim is to determine a test or tests that predict regression of CIN2 in women under 25.
We request that Liquid Based Cytology is performed on all index specimens (i.e. samples taken at first colposcopy visit) and subsequent follow up visits. We will request and pay for further tests including HPV testing. **PLEASE use** the PINK labels provided by the study coordinator to label the request form with “likely PRINCess participant” or “PRINCess Follow up 1 or 2 or 3 or 4”.

HR HPV testing should be requested at 12 months after regression or treatment as per NCSP guidelines. We recommend HPV testing is performed on the final visit for a patient with regression or greater than 6 months following treatment.

**National Cervical Screening Programme (NCSP) Policy and Standards and Guidelines**

We wish to emphasise that although conservative management of young women is not recommended in the NCSP guidelines, for all other aspects of histology, cytology and colposcopy NCSP policies and standards and guidelines should be followed. Refer to: [www.nsu.govt.nz](http://www.nsu.govt.nz)

**6. Data Collection**

Data should be collected prospectively on Case Report Forms and forwarded to the central study centre in at least monthly intervals. Each participating study site will be given selected study numbers to allocate to eligible women once informed consent is obtained.

**Case Report Form (CRF) Schedule:**

- **Eligibility Form** – to be completed prior to entry into the trial.
- **Baseline Data Form** – to be completed at the visit when trial confirmation biopsy is performed.
- **Baseline Biopsy Data Form** – to be completed at the visit when trial confirmation biopsy is performed and discussion visit when result given to woman.
- **Follow-up 1 Form (6 month)** – to be completed at 6 month visit after first confirmed CIN2 biopsy
- **Follow-up 2 Form (12 month)** - to be completed at 12 month visit after first confirmed CIN2 biopsy
- **Follow-up Form 3 (18 month)** - to be completed at 18 month visit after first confirmed CIN2 biopsy
- **Follow-up 4 Form (24 month)** - to be completed at 24 month visit after first confirmed CIN2 biopsy
- **Completion Form** - to be completed:
  - If progression occurs
  - If treatment occurs
  - If regression occurs on 2 consecutive follow-up visits
  - At completion of trial protocol
  - If non-attendance is greater than 9 months
  - If woman moves away from the area
7. Data Safety Monitoring and Serious Adverse Events

Data Monitoring Committee
At six monthly intervals a statistical report will be prepared and independently reviewed for data integrity and safety. Prior to HRC funding, independent data monitoring was undertaken under the supervision of Dr Lynn Sadler (Auckland Hospital). With the acquisition of HRC funding, the HRC data safety monitoring committee has taken over the role of 6-monthly data monitoring.

Serious Adverse Events
The diagnosis of micro invasive or invasive carcinoma of the cervix and loss to follow up for greater than 9 months will be considered serious adverse events. If any of these occur then a Serious Adverse Event form will be completed and returned to the study centre within 2 weeks.

Stopping Rules
The trial will be terminated prematurely if;

- Invasive carcinoma of the cervix (>1a) is diagnosed in any patient undergoing conservative management,
- Micro invasive squamous carcinomas are diagnosed in more than 2% of women undergoing conservative management.

Further, if the proportion of women with delayed follow up is greater than 10% in any site the site will be formally reviewed and could be closed. If more than 10% of sites need to be closed (due to greater than 10% delayed follow up) then the overall trial will be formally reviewed and may need to be terminated prematurely.

8. Data analysis
Data analysis will be completed centrally once all patients have completed 24 months follow up.

Primary outcome measures
- Proportion of women under the age of 25 (trial participants) with CIN 2 whose lesions regress to CIN1 and normal within 24 months of follow up.
- Proportion of trial participants who are lost to follow up (greater than 9 months) during the trial.

These outcomes will be compared with the trial hypotheses;
- That less than 5% of participants will be lost to follow up.
- That approximately two thirds of women will undergo regression of their disease to CIN1 or less within 2 years.
- That no women will develop life threatening disease.

Secondary outcome measures
- Proportion of trial participants who require treatment during 24 month period
- The reason treatment is required.
- The proportion of the eligible women included in the trial and reasons for exclusion
• Correlation of clinical factors with regression of CIN2, including age, smoking, gravidity, ethnicity, colposcopic impression, lesion size.
• Correlation of cytology/pathology factors with regression, including referral cytology, cytology at first visit, cytology at first follow up, HPV type at first visit, HPV type at first follow up, immunohistochemistry at first visit.
• Correlation of above factors and requirement for treatment (for CIN3 or worse).

Descriptive statistics, life table analysis, univariate and multivariate regression analysis will be performed.

The second of these outcomes will be compared with the trial hypothesis;
  • That no more than half will require or request treatment

**Correlation analysis**
A secondary outcome of this trial is to identify clinical histological, cytology, or biological factors that are predictive of outcome.

• Correlation of clinical factors with regression of CIN2, including age, smoking, gravidity, ethnicity, colposcopic impression, lesion size.
• Correlation of cytology/pathology factors with regression, including referral cytology, cytology at first visit, cytology at first follow up, HPV type at first visit, HPV type at follow up, immunohistochemistry at first visit.
• Correlation of above factors and requirement for treatment (for CIN3 or worse).
• Descriptive statistics, life table analysis, univariate and multivariate regression analysis will be performed.

**9. Funding arrangements**
To date we have received small grants from NZ Cancer Society - Canterbury West Coast Division, Genesis Oncology Trust, and Department of O & G University of Otago – Christchurch to assist with ethics and central data collection. Currently for the clinical aspects of the trial other centres are required to take part within their own clinical resources.

All trial directed ancillary testing will be performed at the study centre at no cost to individual sites. The study centre will also take responsibility for reasonable transport costs of specimens to the study centre.

A New Zealand Cancer Society grant has now been received for funding to cover some of the costs of ancillary tests, transport, and administrative support to the study sites and study centre.
10. References


5. NHS Cancer Screening Programmes. NHS Cancer Screening Programmes; 2004.


12. Appendices

Appendix A. Trial Flow Chart

Appendix B. Initial statistical report 2008 (available on request)
Appendix A.  Trial Flow Chart

PRINCeSS: The prediction of regression in CIN2 Flowchart

INITIAL VISIT - Pre-study
Potential Participants
Under 25 at time of enrolment
Referral to colposcopy for abnormal cytology
Colposcopy, REPEAT cytology, biopsy
Please use provided PINK labels
Possible CIN2 = study information given to woman

Biopsy = C I N 2

? Eligible patient
Check inclusion/exclusion criteria
Results discussed
Offer study entry

Criteria not met
- not eligible

Study Participant
Consent form signed
CRF ELIGIBILITY FORM & BASELINE DATA FORM
To be completed

MDM review within 4 weeks
Review of cytology & histology
Send cytology vial to Christchurch

CIN1 or less
CIN3 or worse suspected
Exclude & complete CRF COMPLETION FORM

29/05/2014