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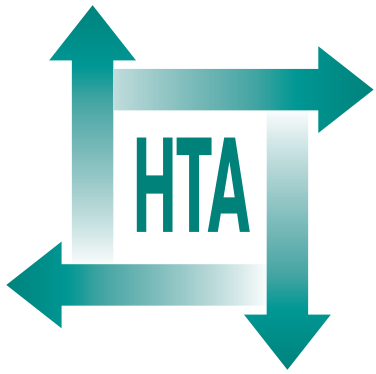

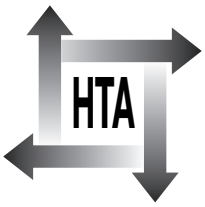

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Effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts. An economic decision model

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The research reported in this monograph was commissioned by the HTA Programme as project number 02/12/03. The contractual start date was in April 2003. The draft report began editorial review in August 2005 and was accepted for publication in January 2006. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts. An economic decision model

KS Thomas,[1*] MR Keogh-Brown,[2] JR Chalmers,[1] RJ Fordham,[2] RC Holland,[2] SJ Armstrong,[1] MO Bachmann,[2] AH Howe,[2] S Rodgers,[1] AJ Avery,[1] I Harvey[2] and HC Williams[1]

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Objectives: To estimate the costs of commonly used treatments for cutaneous warts, as well as their health benefits and risk. To create an economic decision model to evaluate the cost-effectiveness of these treatments, and, as a result, assess whether a randomised controlled trial (RCT) would be feasible and cost-effective.
Data sources: Focus groups, structured interviews and observation of practice. Postal survey sent to 723 patients. A recently updated Cochrane systematic review and published cost and prescribing data.
Review methods: Primary and secondary data collection methods were used to inform the development of an economic decision model. Data from the postal survey provided estimates of the effectiveness of wart treatments in a primary care setting. These estimates were compared with outcomes reported in the Cochrane review of wart treatment, which were largely obtained from RCTs conducted in secondary care. A decision model was developed including a variety of over-the-counter (OTC) and GP-prescribed treatments. The model simulated 10,000 patients and adopted a societal perspective.
Results: OTC treatments were used by a substantial number of patients (57%) before attending the GP surgery. By far the most commonly used OTC preparation was salicylic acid (SA). The results of the economic model suggested that of the treatments prescribed by a GP, the most cost-effective treatment was SA, with an incremental cost-effectiveness ratio (ICER) of 2.20 £/% cured. The ICERs for cryotherapy varied widely (from 1.95 to 7.06 £/% cured) depending on the frequency of applications and the mode of delivery. The most cost-effective mode of delivery was through nurse-led cryotherapy clinics (ICER = 1.95 £/% cured) and this could be a cost-effective alternative to GP-prescribed SA. Overall, the OTC therapies were the most cost-effective treatment options. ICERs ranged from 0.22 £/% cured for OTC duct tape and 0.76 £/% cured for OTC cryotherapy to 1.12 £/% cured for OTC SA. However, evidence in support of OTC duct tape and OTC cryotherapy is very limited. Side-effects were commonly reported for both SA and cryotherapy, particularly a burning sensation, pain and blistering.
Conclusions: Cryotherapy delivered by a doctor is an expensive option for the treatment of warts in primary care. Alternative options such as GP-prescribed SA and nurse-led cryotherapy clinics provide more cost-effective alternatives, but are still expensive compared with self-treatment. Given the minor nature of most cutaneous warts, coupled with the fact that the majority spontaneously resolve in time, it may be concluded that a shift towards self-treatment is warranted. Although both duct tape and OTC cryotherapy appear promising new self-treatment options from both a cost and an effectiveness perspective, more research is required to confirm the efficacy of these two methods of wart treatment. If these treatments are shown to be as cost-effective as or more cost-effective than conventional treatments, then a shift in service delivery away from primary care towards more OTC treatment is likely. A public awareness campaign would be useful to educate patients about the self-limiting nature of warts and the possible alternative OTC treatment options available. Two future RCTs are recommended for consideration: a trial of SA compared with nurse-led cryotherapy in primary care, and a trial of home treatments. Greater understanding of the efficacy of these home treatments will give doctors a wider choice of treatment options, and may help to reduce the overall demand for cryotherapy in primary care.

Contents

List of abbreviations

CDLQI	Children's Dermatology Life Quality Index
CI	confidence interval
COMB	salicylic acid and cryotherapy used at the same time
CR	cryotherapy
CR1	one session of cryotherapy
CR2	two sessions of cryotherapy
CR2C	cryotherapy in secondary care
CR3	three sessions of cryotherapy
CRNurse	cryotherapy delivered by a nurse
CRSA	cryotherapy followed by salicylic acid
DLQI	Dermatology Life Quality Index
DMEP	dimethyl ether propane
DN	do nothing
EVPI	expected value of perfect information
GP SA	salicylic acid prescribed by a GP
ICER	incremental cost-effectiveness ratio
IQR	interquartile range
LA	lactic acid
NA	not applicable
OR	odds ratio
OTC	over the counter
OTC SA	salicylic acid bought over the counter
PCR	probability of cryotherapy cure
Pduct	probability of duct tape cure
PSA	probability of salicylic acid cure
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SA	salicylic acid
SACR	salicylic acid followed by cryotherapy
SD	standard deviation
UEA	University of East Anglia

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

This project was commissioned in response to a Cochrane systematic review of randomised controlled trials (RCTs), which found little evidence to suggest that cryotherapy was any more effective than salicylic acid (SA) for the treatment of warts. The aim of this study was to model the likely cost-effectiveness of these two commonly used treatments, and to explore whether commissioning an RCT comparing the two interventions was likely to be worthwhile. To do this, various data-gathering methods were used to inform an economic decision model, from which conclusions were drawn with regard to the cost-effectiveness of these and other commonly used wart treatments.

Objectives

The objectives of the study were:

- to estimate the costs of commonly used treatments for cutaneous warts
- to estimate the health benefits and risks associated with these treatments
- to create an economic decision model to evaluate the cost-effectiveness of these treatments
- to assess, in the light of the economic model, whether an RCT would be feasible and cost-effective, and if so, to comment on its design and conduct.

Methods

A variety of primary and secondary data collection methods was used to inform the development of an economic decision model. Primary data collection involved focus groups, structured interviews and observation of practice. These methods were used to capture the commonly used care pathways, and to identify issues of importance to patients and health professionals. The results were subsequently used to inform the design of a postal survey sent to 723 patients who had recently attended their GP's surgery for the treatment of warts. Data from the postal survey provided estimates of the effectiveness of wart treatments in a primary care setting. These estimates were compared with outcomes reported in the Cochrane review, which were largely obtained from RCTs conducted in secondary care.

Secondary data used to inform the decision model came from a variety of sources including the recently updated Cochrane systematic review and published cost and prescribing data. These primary and secondary data sources were used to develop a decision model including a variety of over-the-counter (OTC) and GP-prescribed treatments. The model simulated 10,000 patients and adopted a societal perspective. Data were analysed using TreeAge cost-effectiveness analysis and S-plus, using cohort simulation techniques.

Results

OTC treatments were used by a substantial number of patients (57%) before attending the GP surgery. By far the most commonly used OTC preparation was SA.

The results of the economic model suggested that of the treatments prescribed by a GP, the most cost-effective treatment was SA, with an incremental cost-effectiveness ratio (ICER) of 2.20 £/% cured. The ICERs for cryotherapy varied widely (from 1.95 to 7.06 £/% cured) depending on the frequency of applications and the mode of delivery. The most cost-effective mode of delivery was through nurse-led cryotherapy clinics (ICER = 1.95 £/% cured) and this could be a cost-effective alternative to GP-prescribed SA.

Overall, the OTC therapies were the most cost-effective treatment options. ICERs ranged from 0.22 £/% cured for OTC duct tape and 0.76 £/% cured for OTC cryotherapy to 1.12 £/% cured for OTC SA. However, evidence in support of OTC duct tape and OTC cryotherapy is very limited.

Side-effects were commonly reported for both SA and cryotherapy, particularly a burning sensation, pain and blistering.

Conclusions

Implications for healthcare

Many people suffer from warts. Incidence figures estimated from the fourth National Morbidity Survey (1991–2) suggest that almost 2 million people in England and Wales see their GP per year about this condition, at a cost of at least £40 million per annum. Cryotherapy delivered by a doctor is an expensive option for the treatment of warts in primary care. Alternative options such as GP-prescribed SA and nurse-led cryotherapy clinics provide more cost-effective alternatives, but are still expensive compared with self-treatment.

Given the minor nature of most cutaneous warts, coupled with the fact that the majority spontaneously resolve in time, it may be concluded that a shift towards self-treatment is warranted. Although both duct tape and OTC cryotherapy appear promising new self-treatment options from both a cost and an effectiveness perspective, more research is required to confirm the efficacy of these two methods of wart treatment. If these treatments are shown to be as cost-effective as or more cost-effective than conventional treatments, then a shift in service delivery away from primary care towards more OTC treatment is likely. A public awareness campaign would be useful to educate patients about the self-limiting nature of warts and the possible alternative OTC treatment options available.

Recommendations for research

Two future RCTs are recommended for consideration. First, a head-to-head trial of SA compared with nurse-led cryotherapy in primary care is an obvious gap in the current evidence base. Such a trial would have the benefit of providing efficacy data for these two most commonly used treatments, while also providing a measure of the cost-effectiveness of nurse-led clinics.

Second, further research would be valuable to provide a more reliable evidence base for the available OTC treatments. Nevertheless, by investing in a trial of home treatments, it may be possible to encourage more patients to self-treat their warts and verrucae, thus reducing the overall burden on the NHS. In some cases this will mean greater cost falling on individual patients. A three-arm trial comparing OTC SA, duct tape and OTC cryotherapy (Wartner®) is recommended. Greater understanding of the efficacy of these home treatments will give doctors a wider choice of treatment options, and may help to reduce the overall demand for cryotherapy in primary care.

It is recommended that the above trials be conducted in a primary care setting, be of sufficient duration to capture long-term recurrence data, and have sufficient sample size to allow for planned subgroup analysis. Before conducting an RCT of OTC therapies, further work is required to assess the optimum dosage and duration of these treatments.

Chapter 1
Introduction

Rationale for this study

This project was commissioned in response to a Cochrane systematic review in which a dilemma for the treatment of cutaneous warts was highlighted. This review found little or no evidence to suggest that cryotherapy was any more effective than salicylic acid (SA) for the treatment of warts, despite the wide use of cryotherapy by the medical profession.

The aim of the current study was to model the likely cost-effectiveness of these two commonly used treatments, and to explore whether commissioning a randomised controlled trial (RCT) was likely to be a worthwhile investment. To do this, various data-gathering methods were used to inform an economic decision model, from which conclusions were drawn with regard to the cost-effectiveness of these and other commonly used wart treatments. This model was then used as the basis to identify the most cost-effective options for further study.

Background

Epidemiological background

Cutaneous viral warts are caused by the human papilloma virus. They are an extremely common form of morbidity experienced by most people at some time during their lives. Warts can be painful, and cause disfigurement and stigma for those affected. Various studies have examined the prevalence of warts and have produced a wide range of estimates. Three population-based all-age studies reported point prevalences ranging from 0.84% (USA)[1] to 3.3% (UK)[2] and up to 12.9% (Russia).[3] Studies of school-age populations have reported prevalence of 3.9–4.7% in the 11–16-year-old age group,[4] and 12% in 4–6-year-olds and 24% in 16–18-year-olds.[5]

Rationale for treatment

Estimates of the rate of natural resolution of warts also vary widely. Massing[6] found that two-thirds resolved within 2 years, but the resolution rates reported in the placebo arms of trials recently reviewed in a Cochrane systematic review suggest more rapid spontaneous resolution.[7] This has led some to suggest that warts should not be treated at all.[8] However, some viral warts may persist for many years and there is no reliable means of predicting which ones will resolve spontaneously. Many people find warts unsightly and socially stigmatising (having connotations of ugliness from childhood literature).[9] Warts on the plantar surface of the feet and near the nails can be painful, and multiple warts on the hand may serve as a barrier to employment (e.g. in the catering trade). Warts are spread through direct contact and by contact with infected dead skin in areas such as swimming pools and communal showers.[10] As a result, many people present to GPs and dermatologists seeking treatment for this problem.

Commonly used treatments

Numerous treatments have been attempted to cure warts, with varying degrees of evidence to support their use. The commissioning brief for this study was to concentrate on the two main treatments recommended by GPs: SA and cryotherapy. The authors also chose to include an evaluation of two more recently introduced treatments, duct tape (Gaffa tape) and a self-treatment cryotherapy kit using dimethyl ether propane (DMEP; Wartner®), because they are available over the counter (OTC) and there is some evidence to support their use. Details of these commonly used treatments are provided in *Table 1*.

Current evidence base for SA, cryotherapy, OTC cryotherapy and duct tape

The majority of published studies pertain to cryotherapy and SA.

The recently updated Cochrane systematic review[11] reviewed the findings of 52 RCTs that provide evidence concerning the effectiveness of various treatments for cutaneous warts. Although the studies were of generally poor quality (only three trials were judged to be of high quality), several findings emerged.

First, it was evident from a meta-analysis of six trials that compared topical agents containing SA and/or lactic acid (LA) with placebo that these agents were superior to placebo (75% cure versus 48% cure over a period of 6–12 weeks).

TABLE 1 *Commonly used treatments for warts*

Treatment	Comments
Salicylic acid (SA)	Usually used as first-line treatment Cheap and readily available OTC Requires daily application for approximately 12 weeks Can be messy, time-consuming and painful if applied to healthy skin around the wart
Cryotherapy	May be a first-line treatment, but often used as second-line therapy Involves freezing wart with liquid nitrogen or dimethyl ether propane Treatment applied every 2–4 weeks Several treatments usually required Usually applied by a doctor, but some surgeries run wart clinics run by practice nurses Side-effects include pain, soreness, blistering and swelling
OTC cryotherapy (Wartner®)	Uses DMEP to freeze the wart (which has a higher freezing temperature than liquid nitrogen) Home-use version of similar product used by GPs (Histofreezer®)
Duct tape (Gaffa tape)	Not widely used in the UK Subject of recent RCT comparing duct tape with cryotherapy RCT suggested similar efficacy to cryotherapy Involves application of a piece of tape to wart Tape left in place for periods of 6 days at a time Requires treatment for approximately 8 weeks Cheap and more simple to use than SA

Second, the evidence concerning the effectiveness of cryotherapy (in all cases using liquid nitrogen) was mixed and to some extent conflicting.

Two small and low-quality older trials compared cryotherapy with placebo topical treatment[12] or no intervention[13] and found, surprisingly, no statistically significant advantage for cryotherapy [odds ratio (OR) 0.82, 95% confidence interval (CI) 0.16 to 4.24], although the confidence limits were very wide. However, four further trials compared more aggressive with more gentle cryotherapy[14–17] and found a significant benefit associated with aggressive treatment (OR 3.69, 95% CI 1.45 to 9.41), suggesting that there is a differential effect across different 'doses' of cryotherapy. This would appear to contradict the findings of the lack of clear difference in the cryotherapy versus placebo comparison.

Two relatively poor-quality trials directly compared cryotherapy with topical SA/LA preparations in a total of 320 patients.[18,19] There was no statistically significant difference with relatively narrow confidence limits (OR 1.15, 95% CI 0.72 to 1.82). There was some evidence however, that the two therapies combined might be more effective than either singly (cryotherapy + SA/LA versus SA/LA alone, OR 2.08, 95% CI 1.26 to 3.43; and cryotherapy + SA/LA versus cryotherapy alone, OR 1.82, 95% CI 0.86 to 3.84).

In addition to the more common treatments of cryotherapy and SA, the use of duct tape as a treatment for warts is considered in the RCT performed by Focht.[20] Of the 51 patients completing the study, 26 (51%) were treated with duct tape and 25 (49%) were treated with cryotherapy. Twenty-two patients (85%) in the duct tape arm, versus 15 patients (60%) enrolled in the cryotherapy arm, had complete resolution of their warts.

There are currently no RCTs of home cryotherapy using DMEP. Nevertheless, two RCTs have been reported for the same product used by GPs (Histofreezer) compared with traditional cryotherapy.[21,22] These RCTs yielded conflicting results. One RCT suggested that both cryotherapy and DMEP have cure rates in excess of 90%, which would seem to be unrealistically high. The other suggested that there was no significant difference between DMEP and cryotherapy in terms of the number of warts that responded, but that only 28% of patients exhibited a cure. Since this is below expected cure rates on the basis of spontaneous resolution it is difficult to assess the relevance of this result. In the absence of a believable estimate for DMEP cure, but some evidence to suggest similarity between DMEP and cryotherapy, the model was based on the assumption that the two treatments have similar cure rates.

In summary, the superiority of SA to placebo is reasonably well demonstrated, while the relative

efficacy of cryotherapy versus SA remains unclear. In light of the very different cost implications of these two treatments, cost-effectiveness analysis within the range of clinical uncertainty would be informative. Although one might argue that the only way to establish the relative efficacy of cryotherapy versus SA is by means of an RCT, such trials are expensive. An economic analysis based on existing RCT data and high-quality additional data on costs and outcomes could help to inform the NHS HTA as to whether an RCT is justified. If a further trial were to be recommended, the economic model could then help to inform its design in terms of sample size and data to be collected.[23]

Specific objectives of this study

- To estimate the costs of commonly used treatments for cutaneous warts.
- To estimate the health risks and benefits associated with these treatments.
- To create an economic decision model using the above data that will evaluate the cost-effectiveness of the treatments.
- To comment, in the light of the economic model, whether an RCT is needed, and whether one would be feasible and cost-effective.
- If such a trial is needed, to comment on its size and design.

Research methods

Overview of the economic decision model

Decision analysis enables pooled results to be assessed along with potential costs to determine cost-effectiveness. Models of this kind are established tools in medical evaluation and widely used because of their ability to capture published data and to incorporate known treatment pathways.[24] Models can be developed where clinical trial data are limited, or where published literature does not address the exact question required for policy making. The decision model used in this study uses both Markov modelling and Monte Carlo simulation techniques to analyse treatment practice and outcome. The model was written using the Data v4 software by TreeAge® and is detailed in Chapter 4.

Viewpoint of the study

The model was constructed from the point of view of society and the costs incurred for treatment are the full costs of treatment regardless of whether those costs are paid by the patient or the NHS. Costs specific to the NHS and patients have also been documented separately.

Data collection methods

An illustration of how the various aspects of data gathering combine to inform the model and lead to conclusions is given in *Figure 1*. The circles

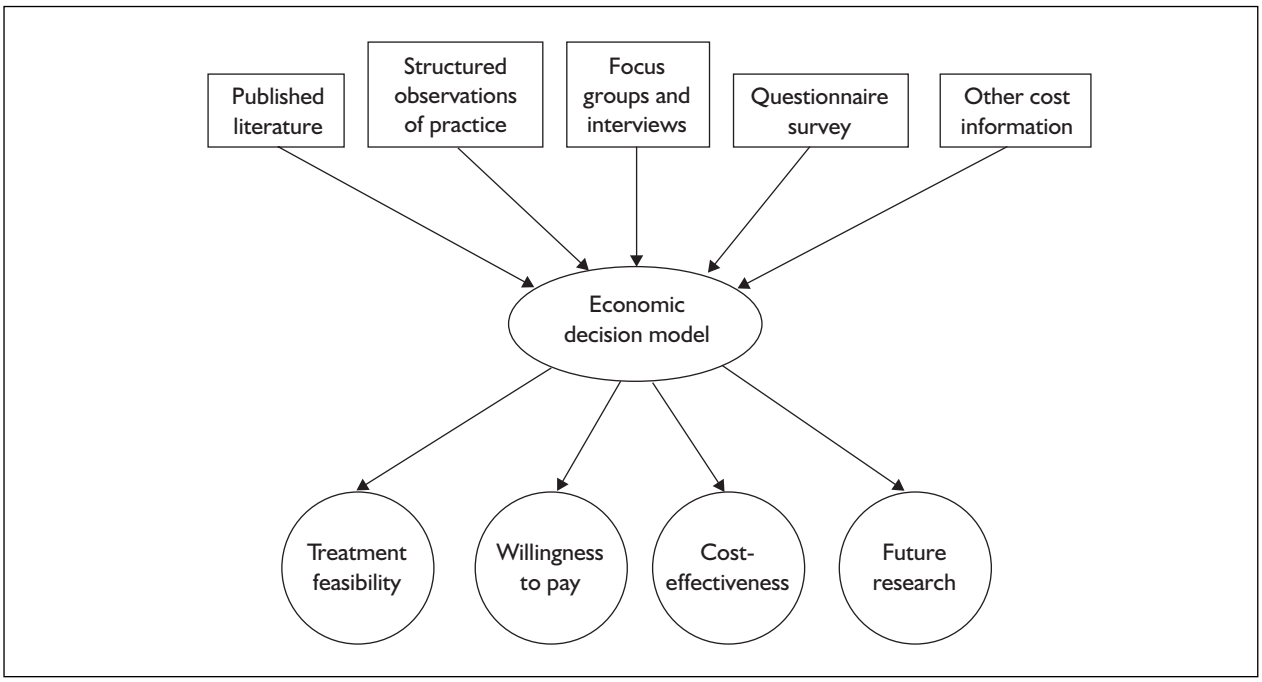

FIGURE 1 *Data collection methods used to inform the model*

indicate the outputs of the model and the rectangles indicate inputs to the decision model. There is some overlap between these entities; for example, cure probabilities are estimated from both published literature and the questionnaire survey, and treatment costs are estimated from both the questionnaire survey and published statistics.

Treatment outcomes

For the purposes of this research, a clinical cure is defined as being the complete disappearance of all elevated/warty skin. The model uses the person, rather than warts, as the unit of analysis. This categorisation of cure is in agreement with cure definitions in the majority of RCTs considered in the Cochrane review. Other secondary outcomes include side-effects (e.g. pain, blistering and scarring) and acceptability and convenience to patients. However, these cannot be incorporated into the main cost-effectiveness model.

Treatment options investigated

The management options for cutaneous warts shown in *Table 2* were included in the model.

Location of research

This was a collaborative venture between the University of Nottingham and the University of East Anglia (UEA, Norwich). The team in Nottingham was responsible for conducting the majority of primary research (postal survey, structured observation of clinical practice and focus groups), although the discrete choice experiment was shared between institutions. The team in Norwich were responsible for the secondary research aspects of the project (literature review, obtaining published data of relevance to the model and creating the decision model). Responsibility for producing the final report was shared among all members of the team.

Ethical arrangements

Full ethical approval was granted for this study (MREC/03/4/014) and all research and development (R&D) approvals and honorary contracts were obtained as required. This project was conducted in accordance with the Research Governance Framework.

Summary of structure of report

Further details of the information contained in each chapter are summarised in *Table 3*.

TABLE 2 *Treatment options included in the economic model*

Intervention	Treatment characteristics
OTC treatments	
Do nothing (DN)	Patient does not visit their GP or seek treatment for their warts
OTC salicylic acid (OTC SA)	Salicylic acid bought from the pharmacy and applied for 2–3 months
OTC cryotherapy (OTC CR)	Home cryotherapy purchased from pharmacy
Duct tape (Duct)	Duct/Gaffa tape applied to the wart for 2 months
Treatments offered in primary care	
Advice only (Advice)	Advice given by the GP that warts usually resolve themselves
GP-prescribed salicylic acid (GP SA)	SA recommended by the GP
Cryotherapy ×1 (CR1)`	One session of cryotherapy from the GP
Cryotherapy ×2 (CR2)	Two sessions of cryotherapy from the GP
Cryotherapy ×3	Three sessions of cryotherapy from the GP
Cryotherapy from the nurse ×3 (CRNurse)	Three sessions of cryotherapy delivered by a practice nurse
SA then cryotherapy (SACR)	OTC SA followed by cryotherapy ×3
Cryotherapy then SA (CRSA)	Cryotherapy ×3 followed by OTC SA
Combination (COMB)	Both cryotherapy and SA administered at the same time
Treatments offered in secondary care	
Cryotherapy (CR2C)	Cryotherapy offered in secondary care

TABLE 3 *Data collection methods*

Source of data	Type of data collected	Comments
Chapter 2		
Focus groups/structured interviews	Attitudes of patients and health professionals; factors governing decision to treat; views on whether a trial is needed	Three focus groups and seven semi-structured interviews were conducted. Two focus groups involved consumers and one involved health professionals (three GPs, one pharmacist, one practice nurse and one chiropodist). Structured interviews included four GPs, two pharmacists and one practice nurse
Observation of practice	Usual care pathways; treatment costs (time and resources involved)	Included observations at several GP surgeries, teaching hospitals and district general hospitals. In total, 35 patients were observed
Chapter 3		
Primary care survey	Treatment costs; usual care pathways; cure probabilities in primary care; side-effects and reasons for seeking treatment; opportunity cost of wart treatment; willingness to pay; impact of warts on health-related quality of life	Included patients presenting at their GP's surgery for the treatment of warts within the last 3–6 months. Quality of life assessed using validated instruments appropriate to the responder's age
Secondary care survey	Treatment costs; usual care pathways	Survey sent to all hospitals in the Trent region
Chapter 4		
Systematic review	Cure probabilities	Review updated in May 2003.[11] Cochrane Skin Group performed a search on behalf of the research team in February 2004: no new studies of relevance were located
Published statistics	Treatment costs	Sales data on OTC products and data on GP prescribing were obtained from the Prescription Pricing Authority. The pharmacy department at UEA provided details of costs of OTC wart treatments
Computer simulation	Cost-effectiveness; sensitivity analysis	All costs and outcome data combined in the economic decision model

Chapter 2

Qualitative research

Overview

Qualitative research methods have been used in this study to ensure that, as far as possible, the subsequent economic model reflects the wider picture of living with and treating warts in the UK. Various techniques were used, including focus groups (with both patients and health professionals), structured interviews and observation of practice. These methods provided a clearer picture of the importance of various factors in dictating the choice of treatments by patients and physicians. They were used to inform both the design of the subsequent postal survey and the development of appropriate assumptions when creating the economic decision model.

Aims

The focus groups and structured interviews were conducted with the specific aim of drawing together opinions of both health professionals and consumers with regard to the treatment of cutaneous warts, specifically with regard to:

- attitudes towards cutaneous warts and the treatment options
- perceptions of the relative efficacy of the available treatments
- factors governing the decision to prescribe or request cryotherapy
- the type of evidence that would encourage consumers or health professionals to change current practice
- cost information that would inform willingness to pay for wart paint or cryotherapy.

Structured observation of practice was used to gather data regarding treatment pathways offered in primary and secondary care, to ensure that the economic model reflected current practice.

Participants and methods

Focus groups and semi-structured interviews

Participants in the focus group for consumers were identified from a pilot study of patients with cutaneous warts who had indicated on a questionnaire that they would be willing to take part in further research (unpublished). They were approached initially by their GP and asked to contact the research team if they were interested in taking part in a focus group. The focus groups were held on the University of Nottingham campus. The participants were a mix of adults who had recently had warts and others who still had warts. Two consumer focus groups were conducted, with seven participants in each (nine females, five males). An inconvenience allowance of £25 was given to each participant and lunch was provided.

Health professionals were identified through the Trent Focus Collaborative Research Network. One focus group and seven semi-structured interviews were conducted. The participants were:

- focus group: three GPs, one pharmacist, one practice nurse, one chiropodist
- semi-structured interviews: four GPs, two pharmacists, one practice nurse.

All focus groups were conducted by a moderator (JD) who was independent of the research team. The semi-structured interviews were conducted by the research associate (JC). All focus groups and interviews were audiotaped and fully transcribed for analysis. Transcripts were then systematically analysed using the framework approach.[25] Themes were predetermined as areas of interest for the study and these determined the questions used as prompts. A coding index was developed and applied across each transcript. The questions used are detailed in *Table 4* (health professionals) and *Table 5* (consumers).

Observation of practice

Observation of practice was carried out by the research associate (JC) at three general practices, one district general hospital and one teaching hospital. The observations were made during cryotherapy clinics and notes were taken at the time of observation. A copy of the note-taking template can be found in Appendix 1. The hospitals were identified through personal contacts and the GP surgeries through the Trent Focus Collaborative Research Network. A previous

TABLE 4 *Questions used in health professional focus groups and interviews*

Question 1	Approximately, how long have you all been treating patients with cutaneous warts and verrucae?
Question 2	I would like you to think now about when a patient FIRST presents with warts. Could you discuss what you normally do in this situation?
Question 3	After you have seen the patient for the first time, what usually happens next?
Question 4	Could you discuss what factors influence your treatment decisions?
Question 5	Could you discuss how well you think the different treatment options work?
Question 6	What else do you think it would be useful for us and others, to know about the treatments that you use/prescribe?
Question 7	What do you think patients' opinion would be if they were offered cryotherapy at a cost to themselves?
Question 8	I would like you now to suppose that the results of the economic decision model in this study have suggested that the difference in cost-effectiveness of cryotherapy and salicylic acid is so large that doing a large clinical trial may not be cost-effective. Could you discuss whether you would be prepared to change your current practice based on this evidence?
Question 9	Finally, can you suggest any changes in treatments or services that it might be helpful for us to hear about?

TABLE 5 *Questions used in consumer focus groups*

Question 1	Approximately how long have you all had warts/verrucae?
Question 2	What did you think when you first discovered/noticed/spotted you had these 'things' growing?
Question 3	Once you knew what they were, what did you do next?
Question 4	Could you discuss how well the treatment you are thinking about worked?
Question 5	For those of you who have tried more than one treatment, how well have any of the others worked?
Question 6	What else do you think it would be useful for us and others to know about the treatments that you have used/were given?
Question 7	(a) It is clear from all of your discussion so far that there is a cost attached to having warts – what do you think about this expense? *or* (if nobody has mentioned costs) (b) Do you think there is expense attached to having warts?
Question 8	Finally, can you suggest any changes in treatments or services that it might be helpful for us to hear about?

study carried out by the Trent Focus compared Trent Focus practices with other practices in Trent in terms of practice and population demography, morbidity and mortality. This showed that there were no important differences in the demography of registered patients, or in morbidity, mortality, access to or use of secondary care.[26]

In total, 35 patients were observed. The cryotherapy clinics were all nurse led, with the involvement of a doctor for complicated or unusual cases.

Results

Patients' attitudes towards warts and reasons for seeking treatments

Patients were asked to talk about how they felt about their warts and what drove them to seek treatment (*Table 6*). A number of reasons emerged:

- The warts were painful.
- The warts were spreading to other parts of the body.
- The warts were an inconvenience or a nuisance.
- They were embarrassed by their warts.
- They had memories from childhood warts and associated fears.
- They were worried about them spreading to rest of the family, especially to children.
- The perception of warts being highly contagious was interfering with their everyday life, e.g. they were not sure whether they could go swimming with their warts.
- They were worried that the wart could be something more serious, e.g. skin cancer.
- They think that warts are a medical problem and should be treated by a doctor.
- They had tried self-treating but it did not work, so they went to a doctor.

TABLE 6 *Summary of patients' attitudes towards warts*

Many reasons for seeking treatment
Some patients very bothered by warts and desperate to remove them
Other patients see warts as a minor problem
Patients not always making a specific appointment to see GP about their warts

TABLE 7 *Summary of what influences the treatments offered by health professionals*

More willing to treat if painful or spreading
Warts are not important enough to justify resources used to treat them
Patients need to be more educated about spontaneous resolution of warts
Often treating the 'fear' of warts
Involve patients in treatment decisions
Children often pushed into treatment by parents

Most patients seemed to fall into one of two categories. One group saw their warts as a big medical problem and were desperate to get rid of them. Subsequently, they were often very aggressive towards their warts, suggesting a personal battle against them. This group was generally proactive in both self-treating and seeking treatment from their GP.

> "Just chop my finger off"
> "I'm going to beat you"

The other group was far less bothered by their warts and viewed them as a minor problem. Some considered that seeing their GP about warts was an unfair use of their GP's time within the limited NHS budget.

Some patients reported that they first mentioned their warts to the nurse or doctor when visiting the surgery on another matter, rather than making a specific appointment. This sometimes resulted in treatment being suggested by the health professional, rather than the patient actively seeking treatment. In this group of patients, few were seeking a diagnosis from the health professionals as most already knew they had a wart.

Factors that influence how the health professionals treat warts

Predictably, GPs were generally more willing to treat the warts if they were painful or if they were spreading to other parts of the body (*Table 7*). Some felt that cutaneous warts were not important enough to justify the resources used to treat them. GPs felt that patients had a lack of understanding about the self-limiting nature of the warts. In support of this, the patients seemed confused about the nature of warts and few believed that they would go away by themselves. There was a suggestion by GPs that it was probably quicker and easier to treat warts, despite the fact that the treatments may not work, rather than to try to convince patients that the warts would go away by themselves. As a result of this lack of understanding about warts, health professionals reported a feeling of treating the 'fear' of warts and their spread, rather than the actual warts. This is supported by the reasons why patients seek treatment, such as childhood memories or embarrassment. In an attempt to overcome patients' lack of understanding, most surgeries and hospitals have written their own patient information leaflet on warts and their treatments.

When treating adults, most health professionals reported that patients were involved in deciding which treatment option to undertake. This was supported by the observation of practice which showed that new patients were usually given the choice as to whether to have cryotherapy or not. However, the time available for each patient is 5 minutes on average, which allowed only a short time for discussion, and most patients opted to have the cryotherapy.

Health professionals stated that when treating warts in children, they are often responding to the wishes of the parent or carers, rather than the child. Most are reluctant to treat very young children, but are happy to treat older children, as long as the child is in agreement.

Experiences with treatment options and opinions towards them

An issue raised by a number of GPs was that they were unsure about how well either topical

TABLE 8 *Summary of attitudes towards topical treatments*

Patients	Health professionals
Most think they are ineffective	Most think they are ineffective or unsure of efficacy
Admit to non-compliance	Non-compliance/lack of education regarding treatment regimens a factor in lack of efficacy
Product information was poor quality	Product information was poor quality
Difficult not to get on surrounding skin when applying	Had seen damage to healthy skin owing to incorrect application

treatments or cryotherapy worked. Because warts are a minor medical problem, patients given topical treatments are not asked to come back for follow-up appointments, and if they are undergoing cryotherapy they are not followed up if they fail to return to the wart clinic when an appointment has been offered. It is therefore difficult for GPs to establish whether the treatment has been successful or not. Despite this, most health professionals had opinions regarding the efficacy and suitability of wart treatments.

Topical treatments

For both service users and health professionals, the overall attitude towards topical treatments was fairly negative (*Table 8*). Most patients believe from their experience that wart paints are ineffective, although a minority had experienced success with them. The health professional group had more mixed opinions. Some offered topical treatments as first-line therapy, but others had reservations and preferred to recommend another treatment option. One of these reservations was the damage that they had observed when patients had mistakenly applied the paint to the healthy skin surrounding the wart. Indeed, patients reported that they often found it difficult to apply the wart paint only to the wart and not to the surrounding skin.

There was a view among the group of health professionals that compliance with the topical treatments was low and that this was a major factor in treatment failure. This was supported by patients, many of whom freely admitted to not having used them properly. However, a small group of patients had treated aggressively with topical preparations and their warts had resolved. Health professionals suggested that patients need to be better educated in how to use topical treatments correctly and this might increase the success rate of these treatments. Patients and pharmacists both reported that the written information provided with the topical treatments was poor and difficult to understand.

Patients used a wide variety of topical treatments both before seeing their GP and as recommended by their GP or pharmacist. Often, patients had used more than one type of topical treatment. A wide variety of topical treatments had been used by patients, but one that was mentioned several times was Bazuka®.

Cryotherapy

The opinion towards cryotherapy was generally quite positive (*Table 9*). The response from both patients and health professionals was that it is quite effective, although the health professionals' response was more mixed than that of the patients. One of the main concerns from some patients was that they were forced to leave a long gap between cryotherapy treatments owing to either:

- clinics being booked up in advance so that there was no available appointment at the next clinic
- work or personal commitments meaning that they could not attend the surgery during scheduled cryotherapy clinics.

This meant that the warts were less likely to respond to treatment. Observation of practice supported this, with many patients experiencing long gaps between treatments. This differs from best practice, which is to treat every 2–3 weeks. Patients who could not get appointments owing to the clinics being booked up stated that they would like to be able to book a block of clinic appointments to help to alleviate this problem. In addition, all of the focus group participants had received their cryotherapy from a GP and questioned why nurses could not carry out the treatment. Observations showed that many cryotherapy clinics are nurse led and that patients who were treated by a nurse were happy with this arrangement. Some surgeries are happy for the cryotherapy sessions to be carried out by the nurse without a doctor seeing the patient at all.

TABLE 9 *Summary of attitudes towards cryotherapy*

Patients	Health professionals
Overall opinion that it is an effective treatment	Mixed opinion regarding efficacy
Often forced to leave long gaps between sessions allowing the wart to grow back	High demand for service from patients
Pain did not deter adults, but did deter children	Warts not important enough to justify the resources used to treat them with cryotherapy
OTC cryotherapy not well received	Selecting patients more carefully may improve success rate

TABLE 10 *Summary of attitudes towards changing current practice*

Need for more high-quality study data
Need data regarding specific treatments for different wart types
Some GPs would change practice based on an economic model

Although treating warts with cryotherapy was deemed by the health professional group to be an acceptable form of treatment, it was felt that the demand for this service from patients was high. It was suggested that cutaneous warts are not important enough to justify the resources that cryotherapy treatment uses, both in the time taken to run the clinics and in the cost of equipment.

There was also a suggestion from the health professionals that if patients were selected more carefully (and they were therefore treating fewer patients), then perhaps cryotherapy would be a more effective treatment. Observations showed that, when appropriate, the discussions with patients before starting a course of cryotherapy treatment included warnings to patients that their warts were so located or of a size such that it was unlikely that the cryotherapy would be effective. This did not deter patients generally as they wished to have the wart removed and were prepared to try it anyway.

As would be expected, most patients reported that they experienced pain during the cryotherapy treatment, but this did not appear to deter adult patients. However, observations showed that this was the major factor in children refusing treatment.

A few patients in the study had tried the recently launched Wartner (OTC freezing with DMEP). There was no positive feedback about this product; most thought that it was expensive and none of the health professionals had recommended it to patients.

Changing current practice

When health professionals (GPs, pharmacists and practice nurses) were asked to discuss what would encourage them to change current practice, there was generally a desire for good-quality study data regarding the various treatment options (*Table 10*). They also felt that more information was needed regarding the best types of treatment for different types of wart (e.g. feet versus hands or more persistent warts). There was a mixture of attitudes towards changing practice based on the results of an economic decision model and some GPs felt that their own experiences were more likely to dictate practice, rather than the results of further studies.

Willingness to pay for treatments and cost data

Information regarding willingness to pay was difficult to obtain in a focus group setting since it depends very much on individual financial circumstances. However, there appeared to be a willingness by patients to pay for treatments if they were likely to work (*Table 11*). There was generally resentment for paying for treatments that failed to work, such as topical treatments.

In terms of costs to patients, most felt that travelling to the cryotherapy clinics was not an issue as they are held at their local surgery (rather than needing to travel to a hospital). However, the need to take time off work was mentioned as an issue by some patients. Observations showed that surprisingly few patients had to take time off work and reasons for this included patients being shift-workers, retired, self-employed and on annual

TABLE 11 *Summary of willingness to pay for treatments and cost data*

Patients	Health professionals
Willingness to pay for treatment is affected by the lack of efficacy	Charging patients for cryotherapy would reduce the number of patients requesting it
Travel to clinics is not a cost issue	Prescriptions for topical treatments offered if patients do not pay for them
Few take time off work for cryotherapy clinics	New GP contract may make it less viable for surgeries to offer cryotherapy
	Would like to involve nurses more in cryotherapy clinics

leave. This suggests that there may be a group of patients who do not view their warts as a severe enough problem to warrant requesting time off work and who prefer to self-treat.

Health professionals felt that cryotherapy would be less popular if patients had to pay, but recognised that there are some patients who are determined to get rid of their warts and would be prepared to pay for their treatment (*Table 11*). When recommending topical treatments, most GPs stated that they would offer a prescription if the patient was exempt from paying. If they are not exempt, they would advise the patient to purchase the treatment OTC as this is usually cheaper, or let the patients choose whether they would like a prescription.

In terms of costs to the NHS, under the new GP contract, cryotherapy will no longer attract a minor surgery payment. Some GPs suggested that this will make it less viable to perform cryotherapy for minor problems such as cutaneous warts. There was a suggestion that the provision of this service may be reduced or changed in some way, perhaps by becoming more primary care trust based.

Several of the GPs in the study stated that they would like to involve practice nurses in cryotherapy clinics more. The two main reasons why they had not done this previously were a shortage of nursing staff in the practice and the need for a GP to carry out the cryotherapy in order to attract the minor surgery payment.

Discussion

Main results

The main aim of this aspect of the study was to assist in the design of the questionnaire and to ensure that the terminology was appropriate. Several issues that arose from the focus groups and the observations of practice were used in finalising the design of the questionnaire (*Table 12*).

First, it was clear that there was no dominant treatment pathway. Patients differed greatly in what they were prepared to do in terms of self-treatment, and between surgeries there were differences in terms of the treatments offered and the availability of those treatments. Patients had varying reasons for stopping treatment and it was important to capture this in the survey. Therefore, the questionnaire was designed in such a way as to allow patients to tell their own 'treatment story'.

Patients often used several different types of wart paint before visiting their GP about their warts and for cost purposes it was essential to establish exactly how many were used. Compliance was deemed to be an issue with using topical treatments, so the frequency of application and length of use were incorporated into the questionnaire. GPs reported that they usually only offered prescriptions for topical treatments to patients who were exempt from paying. Since this issue impacts on the cost to the NHS of treating warts, a question about prescriptions was asked.

An important potential social cost of cutaneous warts is the time taken off work or school by patients. Self-treating at home potentially impacts less than attending a surgery for cryotherapy treatment. Few of the patients observed or who took part in the focus groups took time off work to attend the cryotherapy clinics. This suggests that many patients do not see their warts as a serious enough problem to warrant requesting time off work and therefore only those who do not have to take time off attend the clinics. It was important to find out in the questionnaire whether this was the case in a larger sample size.

Observation of practice highlighted considerable variation in how each of the surgeries carried out

TABLE 12 *Summary of points that were incorporated into the questionnaire*

No dominant treatment pathway
Patients often used several different wart paints before visiting GP
Patient reasons for stopping topical or cryotherapy treatment
Compliance with topical treatments
Exemption from paying for prescriptions for topical treatments
Time off work or school to attend cryotherapy clinics
Frequency and number of the cryotherapy treatment sessions
Did patient make a specific appointment or not when first attending surgery about warts?

the cryotherapy and this was supported by the focus groups, where patients' experiences differed greatly. Surgeries varied in the equipment that they used to apply the liquid nitrogen (e.g. gun or cotton bud), the advice given alongside the cryotherapy, the method of application, and the frequency and number of treatments recommended. The questionnaire reflected this by asking patients about the frequency and number of cryotherapy sessions that they received. These differences could potentially explain why there is such mixed opinion with regard to the effectiveness of cryotherapy. They also highlight the difficulty in designing a pragmatic clinical trial that mimics real-life treatments, since standard best practice is rarely adhered to.

Policy implications

Patients stated that they often mentioned the wart for the first time when at the surgery for another matter and that the treatment was often suggested by the surgery rather than the patient seeking treatment. This is an opportunity to educate patients about the spontaneous resolution of warts, rather than encouraging treatment. In addition, it was often the practice nurse, rather than the GP, who was told about the wart by patients, and it was they who suggested a treatment. It is possible that clearer training for practice nurses as to when the treatment of warts is indicated could reduce demand generated in this way.

The views of health professionals as to the factors most likely to change treatment practice were strongly in favour of high-quality RCT evidence. The need for evidence relating to specific types of wart was also highlighted.

Caveats

One potential difficulty in conducting qualitative research is ensuring that the participants are appropriate to the purpose of the discussion. In this case, for the service user's focus group, participants were recruited from patients who had visited their GP about their warts. Since this research was used to inform the subsequent postal survey in a similar population, this would seem to be appropriate. The health professionals who took part in the focus group and interviews were all in current practice in the Trent region and all are involved in managing patients with warts.

Although the participants of the service user's focus groups were appropriate for this study, their opinion may not be representative of the general population, for two reasons:

- These were patients who were keen enough to return a questionnaire in the pilot study.
- Of the patients who returned the questionnaire, they were the subset who were sufficiently concerned about their warts to volunteer for the focus group.

It is likely that the average person may consider warts to be far less of an issue than the people in these groups and would not present to the NHS at all.

It would be interesting to compare the opinions of patients who have only self-treated or have left their warts to resolve spontaneously with the opinions of those who have sought treatment from their GP. Their experiences and opinions may be very different. There may also be more of a willingness to accept that warts are self-limiting in the general population than in the patients selected for this study.

The only feasible way in a study of this duration to observe patients in a clinical setting was to attend cryotherapy clinics, as patients presenting with warts for the first time to their GP would be too

infrequent. This meant that all patients observed were those who were at least offered cryotherapy, and those who were given topical treatments only were not observed. However, data were collected on this latter group of patients from the health professional's point of view in the focus groups and interviews, and from the patient's perspective through the questionnaire survey.

Chapter 3

Postal surveys

Overview

The data collected from the focus groups, structured interviews and observation of practice provided a fuller understanding of the typical wart treatments used by patients and the issues surrounding those treatments. This knowledge was then applied to the design of the postal questionnaire survey, which gathered cost and outcome data from a larger sample of patients treated in a primary care setting throughout the Trent region.

All previous RCTs looking at the efficacy of wart treatments have been conducted in a secondary care setting. At the time that these studies were conducted, this was the most appropriate source of participants, as warts were largely treated in outpatient clinics. However, in 1989, Keefe and Dick[27] instigated a radical change in the provision of wart treatments and recommended that provision should take place within primary care. Since most patients are now treated in this setting, it has been necessary to gather outcome data for the economic model that reflect current practice. In the absence of data from an RCT, this postal survey provides the best estimate of the likely outcomes seen in general practice.

Aims

The postal survey was conducted with the following specific aims:

- to gather data to populate the economic decision model
- to assess patients' willingness to pay for treatment
- to establish the impact of cutaneous warts on health-related quality of life.

Specifically, this included items relating to:

- personal costs: prescription charges, time off work or school and OTC wart paints
- NHS costs: number and frequency of treatments and prescriptions provided and who performed the treatments (doctor or nurse)
- clinical effectiveness: treatments received, compliance and outcomes, side-effects, patient preferences and acceptability
- willingness to pay
- health-related quality of life: Dermatology Life Quality Index (DLQI)[28] or Children's Dermatology Life Quality Index (CDLQI).[29]

Methods

Setting and participants

The postal survey was carried out in general practice between January and March 2004. Practices were recruited through Trent Focus, which coordinates a network of 55 practices with an interest in primary care research throughout the Trent Region. This region covers a mixture of urban and rural practices across a wide geographical area. A total of 13 general practices in the Trent region volunteered to search their databases for suitable patients (giving a total list size of 110,628). Eligibility was based on a diagnosis of cutaneous (non-genital) warts 3–9 months previously (i.e. an historical cohort). The total number of patients identified was 894. To achieve a spread of practices all practices were asked to limit their mailing and the maximum from any one surgery was 88 patients.

Each patient received a covering letter from their GP, a patient information leaflet, a questionnaire, a quality of life questionnaire and a reply-paid envelope. If the patient was under 14, the letter was addressed to the parents of the child. If the patient was over 14, the letter was addressed to the patient directly.

Reminders were sent to patients after 3–4 weeks, with the exception of three surgeries which had sent out their initial questionnaires too near to the closing date.

Patients were asked to answer the questions with relation to this recent episode of warts. The questionnaire was piloted on eight people at a GP's surgery who had experience of having warts (see Appendix 2 for a copy of the questionnaire). The quality of life instruments are available on-line at www.ukdermatology.co.uk.

TABLE 13 *Sample size*

	Cure rate									
	30%	**35%**	**40%**	**45%**	**50%**	**55%**	**60%**	**65%**	**70%**	**75%**
Sample size per treatment	81	88	93	96	97	96	93	88	81	73
Sample size allowing for 50% response	162	176	186	192	194	192	186	176	162	146

TABLE 14 *Details of site of wart*

Site of wart	Frequency	% of respondents
Hands only	58	21.5
Feet only	113	41.9
Elsewhere on body only	46	17.0
Hands and feet	30	11.1
Hands and elsewhere on body	15	5.6
Feet and elsewhere on body	4	1.5
Hands, feet and elsewhere on body	2	0.7
Missing data	2	0.7
Total	270	100

Sample size

Estimated cure rates for the three treatments (no intervention, SA or cryotherapy) vary from 30% to 75% depending on the target population, type of wart and treatment used (*Table 13*).[7] Assuming a confidence interval of 95%, an accuracy of ± 10% and a response rate of 50%, a sample size of 200 questionnaires per treatment provides sufficient power to estimate proportions with reasonable precision across all likely cure rates. Therefore, the aim was to send out at least 600 questionnaires.

Data analysis

All data were entered onto a Microsoft Access97 database and analysed using SPSS version 10 or S-plus 2000. The data were checked for errors by a second data-entry person and any corrections were made before the analysis.

Results

Demographics

In total, 723 questionnaires were sent out from 13 surgeries (median = 54), as early indications were that the response rate was going to be slightly lower than initially predicted. Of the questionnaires sent out, 437 were sent to adults (60%) and 286 to children or parents of children with warts (40%). The overall response rate was 37% (270/723 completed and usable questionnaires). Of the returned questionnaires, 163 (60%) were from adults and 107 (40%) were from children or parents of children with warts.

The mean age of responders was 29 and there was an approximately even ratio of male to female (128:140) (two had missing data).

Site of warts

The most common site of the warts was the feet – a total of 149 (55%) warts on feet, and a total of 105 (39%) of warts on the hands (*Table 14*).

The majority of patients had more than one wart when they first went to the surgery (163; 60%) but only 27 (10%) had ten or more warts. In the survey, nine patients (3%) reported having more than 20 warts.

The majority of patients (163; 60%) had had their warts for a relatively short time (6 months or less) before seeing their practice nurse or GP about them. However, the remaining 40% had had their warts for more than 6 months, with a significant number of patients (33; 12%) having persistent warts (i.e. warts present for at least 2 years before visiting their surgery).

When they first visited the surgery, most patients were seeking treatment for all of their warts, with only 40 patients (15%) seeking treatment for only some of their warts.

Treatments tried before going to the surgery

Details of which wart treatments patients tried before visiting the surgery are detailed in *Table 15*. Patients were asked to tick as many as applied to

TABLE 15 *Treatments tried by patients before visiting their surgery (multiple responses possible)*

Treatment	No. reporting treatment tried	% of responders
No self-treatment	116	43
At least one type of wart paint	116	43
Filing down wart	89	33
Wart plasters	29	11
Homeopathy	5	2
OTC cryotherapy	33	12
Gaffa/duct tape	2	1
Other	13	5

them. The most common treatment used was wart paint, with 116 patients (43%) reporting having tried one or more types of wart paint before visiting their surgery about their warts.

For those who used just one type of wart paint, the average number of packets purchased before visiting the surgery was 1.42. For those who had tried more than one type, the average number of packets purchased was 3.18. For those who used wart plasters, the average number of packs used was 2.12.

Four patients reported that they visited a chiropodist about their warts before visiting their surgery. Two patients tried to cut off their warts and other self-treatment options that were tried each by only one person were tea tree oil, banana skin, cotton thread, Vaseline® and clear nail varnish. Two patients had discussed their wart with the chemist, but not purchased treatment from them.

Reasons for visiting the surgery

Most patients (208; 77%) made a special appointment at their surgery about their warts, but 59 patients (22%) reported that they just mentioned their warts when they were there about another matter (three patients had missing data). The most common reasons given for deciding to go to their surgery for advice or treatment for their warts was that they were painful or causing discomfort (58; 21%), or that they were growing or spreading (62; 23%). Other common reasons for going to the surgery were the appearance of warts (13%), self-treatment had failed (11%) and the warts were not resolving (12%). Less common reasons given by patients included bleeding, worried about passing them on and pressure from partner or family. Some reasons were only given by one or two patients; these included affecting the nail, upon advice of the chemist and worried that it might affect other skin conditions.

Waiting times

The majority of patients reported that they did not have to wait for treatment once they had consulted their GP or practice nurse about their warts (170; 63%). However, 36 patients (13%) did have to wait for treatment and 27 (10%) waited for up to 2 months. Only nine patients had to wait longer than 2 months (one patient reported a wait of 12 months after first visiting the surgery). However, it is not known whether these waiting times were due to a waiting list for treatment or the patients waiting until it was convenient to undergo a course of treatment.

Treatments received from the surgery

Most patients received treatment from their surgery; only 43 patients (16%) reported that they were simply given advice regarding the self-limiting nature of warts and seven of these patients were known to return to their GP for further treatment. Further details are listed in *Table 16*.

Adults were more likely than children to have received cryotherapy; 28% of children who completed the questionnaire received cryotherapy compared with 58% of adults. Within the group of children, the vast majority were at least 10 years old and no one under the age of 6 received cryotherapy.

Cryotherapy was used to treat warts on hands, feet and elsewhere on the body, and there was no site that was more commonly treated with cryotherapy than another. Details of cure rates associated with different sites are summarised in Appendices 3 and 4.

The majority of patients reported that the doctor performed the cryotherapy (93; 74%) with only 15 patients (12%) reporting that they were treated by a nurse. Six patients (5%) reported that both the doctor and the nurse performed the cryotherapy, and one patient reported that the doctor carried

TABLE 16 *Treatments given by GP*

Treatment	Overall total	Overall total percentage	Total no. of children	% of children	Total no. of adults	% of adults
Advice	43	15.9	19	17.8	24	14.7
Wart paint at GP	125	46.3	63	58.9	62	38.0
Cryotherapy	125	46.3	30	28.0	95	58.3
Wart paint and cryotherapy	33	12.2	12	11.2	21	12.9

Treatments given here are not necessarily exclusive. Wart paint at GP includes those who also had cryotherapy. Cryotherapy includes those who also received SA treatment from their GP, and wart paint and cryotherapy includes those who also had advice.

out the treatment on the hand warts and their chiropodist carried it out on the warts on the feet. Ten patients (8%) did not complete this question.

Effectiveness of the treatments

Patients were asked which of the following statements best suited their situation: (i) warts/verrucae have now gone; (ii) some warts/verrucae have gone, but others remain; (iii) warts/verrucae cleared but the **same** ones have now come back; (iv) warts/verrucae cleared, but **new** ones have now appeared; or (v) warts/verrucae did not respond to treatment at all. This helped to inform the model regarding effectiveness in practice rather than the short-term outcomes reported in clinical trials following optimum treatment regimens. For the purposes of the model, participants were assumed to be clear of warts if they ticked either (i) or (iv) above. All other responses were treated as treatment failures.

A single estimate of the overall cure for cryotherapy treatment cannot be given since the order in which treatments were received is unclear for some patients. Cure estimates are therefore presented as a range of probable cures based on two types of information:

- a known cure rate from patients whose treatment order and outcome were known and so could be classified as a clear treatment cure or failure
- an uncertain cure rate from patients whose treatment had not finished, or where treatment ordering was unknown but the patient was known to be cured by their most recent treatment.

Together, these two pieces of information provide a cure interval to compare with the results from the systematic review.

Effectiveness of SA and cryotherapy

The overall cure rate for SA was between 38 and 50%, and for cryotherapy was between 44 and 56% (best and worst case scenarios). A breakdown of how these intervals were calculated appears in Appendix 5. Ignoring those treatments whose outcome or ordering is unknown, the 95% confidence interval for the known cure rate is 34 to 53% for SA and 41 to 59% for cryotherapy.

Application of treatments

Wart paints

Of the 125 participants who were advised to use wart paint by their GP, only 40 (32%) reported having used the wart paint correctly (at least five times a week for more than 2 months). There appeared to be little correlation between frequency and duration of application, and success of the treatment (known cure rates range from 18 to 50%, and the 95% confidence intervals are wide) (*Table 17*).

Cryotherapy

Eighty-seven participants reported on the frequency of their cryotherapy sessions. Of these, 40 (46%) had received just one treatment session, and 70% of these reported that their warts were clear following treatment. It therefore seems likely that treatment was stopped because the warts had resolved, rather than through a lack of desire to continue by either the patient or the doctor. The majority of responders (69%) had their cryotherapy sessions either once, or up to 2 weeks apart. These data were used to inform the frequency of cryotherapy sessions in the economic decision model.

Reasons for choosing a treatment

Patients were asked to state their main reason for choosing a treatment. The most common reason

TABLE 17 *Adherence to recommended wart paint regimens*

Regimen	Total no. of patients (%)	No. (%) known to be cured of those who complied in this way	95% CI	No. (%) who complied in this way but outcome is unknown
Used for more than 2 months and at least 5 times a week	40 (32.0)	13 (32.5)	(20.1 to 48.0)	3 (7.5)
Used for more than 2 months and less than 5 times a week	11 (8.8)	2 (18.18)	(5.1 to 47.7)	1 (9.1)
Used for less than 2 months and at least 5 times a week	33 (26.4)	16 (48.5)	(32.5 to 64.8)	1 (3.0)
Used for less than 2 months and less than 5 times a week	20 (16.0)	10 (50)	(29.9 to 70.1)	4 (20)
Missing data	21 (16.8)	7		5
Total	125	48		14

TABLE 18 *Reasons for choosing particular treatments*

Reason	Frequency	%
Wanted warts/verrucae removed quickly	95	35
Prefer a professional person treated the warts/verrucae	57	21
Able to treat myself at home	46	17
Tried wart paints already and it did not work	23	9
Other	16	6
No need to take time off work or school	5	2
Do not like messy treatments	1	0
Missing data or gave more than one reason	27	10

TABLE 19 *Incidence of adverse events*

Adverse event	No. (%) of incidences reported due to wart paint (n = 125)	No. (%) of incidences reported due to cryotherapy (n = 125)	95% CI for difference between percentages
Burning sensation	87 (70)	71 (57)	(0.8 to 24.3)
Pain	34 (27)	54 (43)	(–27.2 to –4.2)
Blistering	18 (14)	46 (37)	(–32.5 to –11.7)
Bleeding	14 (11)	13 (10)	(–7.1 to 8.7)
Scarring	3 (2)	4 (3)	(–5.8 to 4.0)
Other	9 (7)	10 (8)	(–7.8 to 6.1)
Total	165	198	

Percentages do not add up to 100% as responders were able to identify more than one adverse event.

given was to get the warts removed quickly (95; 35%). Other reasons are outlined in *Table 18*.

Adverse events

There were 165 adverse events reported for wart paints and 198 for cryotherapy (*Table 19*). These results were surprisingly similar, considering that wart paints are perceived to be the treatment with fewer side-effects compared to cryotherapy. Indeed, a burning sensation was significantly more likely to be reported by patients using SA (95% CI 0.8 to 24.3). More predictably, patients receiving cryotherapy were more likely to experience blistering and pain.

Referral to secondary care

Very few patients reported that they were referred to hospital for their warts (6; 2%), with three patients not answering this question. All the hospitals in the Trent region stated in the secondary care survey that they have a policy of encouraging GPs to treat viral warts in primary

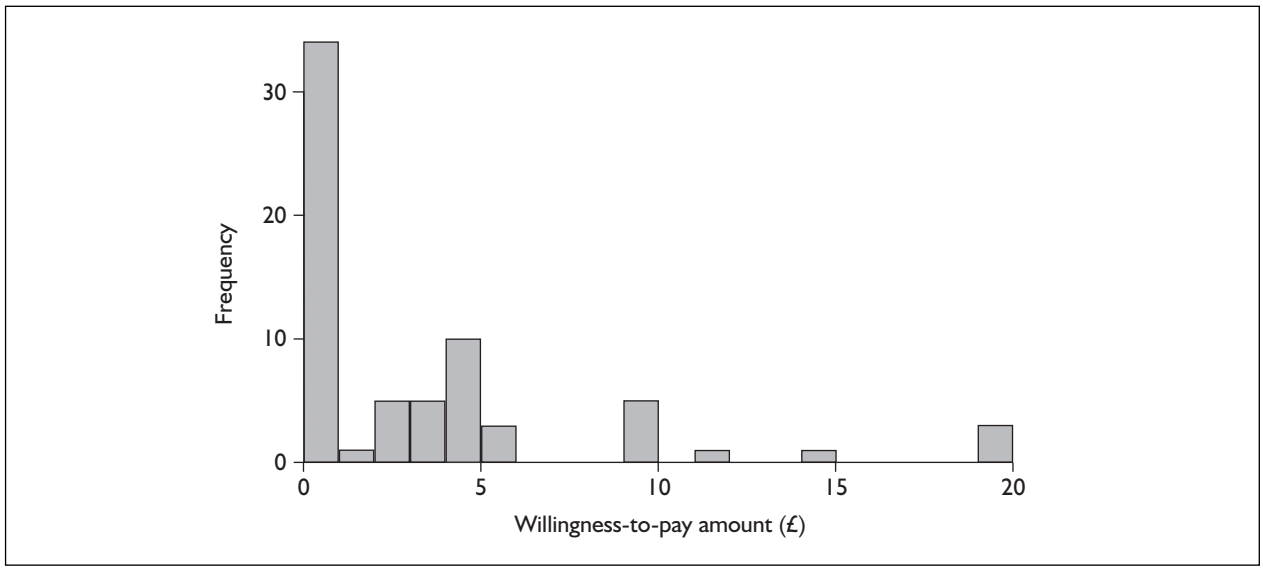

FIGURE 2 *Histogram of overall SA willingness-to-pay values*

care. Similarly, only three patients (1%) reported seeing a chiropodist for the treatment of their warts.

Costs

Cost to both the individual and the NHS was assessed through the questionnaire.

Of the 109 patients who answered a question about wart paint prescriptions, a surprisingly high percentage of patients were given a prescription (74; 68%). However, 62 (84%) of these patients did not have to pay for their prescription. Most patients were given just one prescription (59; 54%), although some patients received two or three. Thirty-three (30%) bought their wart paint OTC as a result of it being recommended by their surgery. Presumably, these were patients for whom the GP did not issue a script as it would have been more expensive to buy a prescription than to buy the medication.

The opportunity costs of taking time off work or school to attend the surgery for cryotherapy sessions were also explored. Of adult patients attending their surgery for cryotherapy, only 20 (16%) took time off work for treatment. Similarly, only 14 children (11%) took time off school.

Willingness to pay

Seventy-two patients (26.7%) declared a preference for SA treatment, of whom 68 (23 adults) declared an amount that they would pay for treatment. The mean willingness to pay for these patients overall was £3.54 (median £1.00, SD 5.03) and for adults the mean was £4.28 (median 0, SD 6.11). An indication of the spread of these values is plotted in the *Figures 2* and *3*. The maximum stated willingness-to-pay amount was £20.

The cost of the most popular SA product (Bazuka) was estimated to be £4.75, but 45 patients (66%) who declared a preference for SA and declared an amount to pay indicated that they were not willing to pay the price of this product [14 (61%) of these were adults]. Of the 45 patients who expressed an amount to pay, four (9%) had never received SA treatment in any form, so might have been unaware of the cost, but 41 of these patients had experience of SA treatment. Of those with experience of SA treatment 31 were children, but only 22 of those children had received SA treatment from their GP. There were therefore 19 patients who stated a preference for SA treatment, had purchased it in the past, but were unwilling to pay the cost of the treatment.

Nine patients had received SA treatment OTC which failed, but still stated a preference for SA treatment.

Twenty-three patients (34%) and nine adults (40%) were willing to pay £5 or more for their SA treatment. Of these, two had never received SA and six had received SA OTC, but were not cured. All other patients received SA treatment from their GP.

In total, 72 patients declared a preference for SA treatment rather than cryotherapy. Of these patients, 12 overall (six adults) had tried

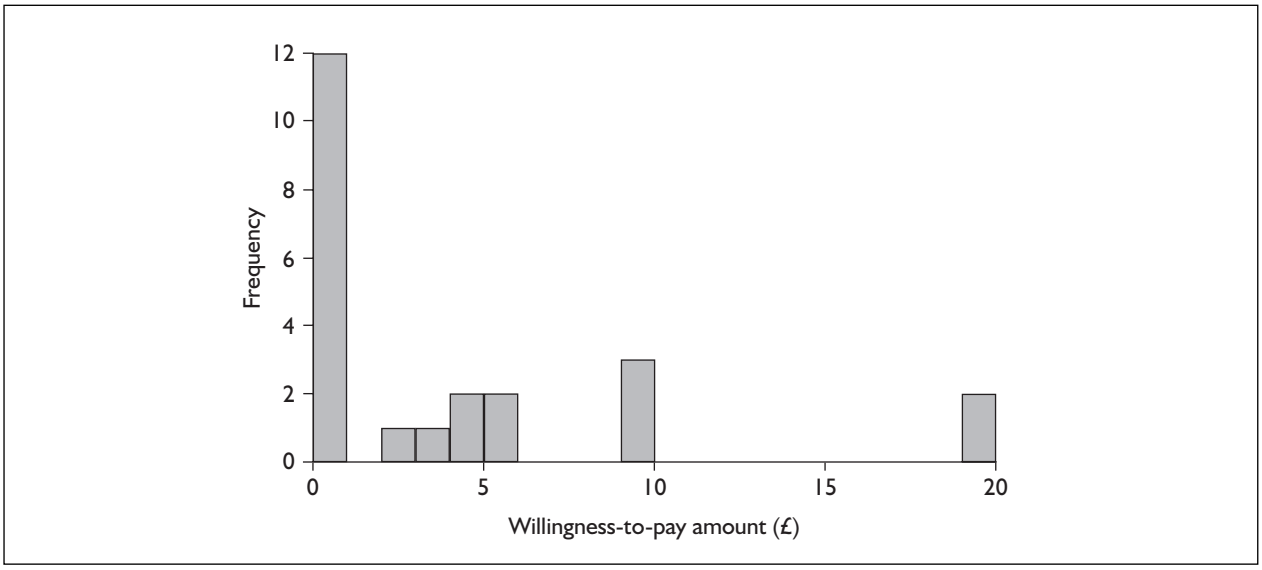

FIGURE 3 *Histogram of willingness-to-pay for SA by adults*

cryotherapy on this set of warts, three (two adults) had tried cryotherapy on this and other sets of warts, and 15 patients overall (four adults) had previous experience of cryotherapy.

Of the 72 patients who preferred SA, just 27 overall and seven adults were cured by SA and two (one adult) had an unknown result (not finished). The mean willingness to pay of patients cured by SA was £2.70 (median 0, SD 4.04) overall, and £3.33 (median 0, SD 4.35) for adults, which is less than the average willingness-to-pay amount for those preferring SA treatment. This suggests that even the success of a treatment does not increase the patients' willingness to pay.

Upon removing the patients who despite being cured by SA treatment that they had purchased declared that they were willing to pay nothing for treatment, the mean willingness to pay rises to £4.63 (median 3.75, SD 5.29) overall, and £8.21 (median 6, SD 6.29) for adults, which indicates that patients are willing to purchase one pack of SA treatment, but the overall suggestion is that warts and verrucae are not considered sufficiently serious by many patients to warrant an expensive treatment.

One-hundred and twenty-eight patients stated a preference for cryotherapy over SA treatment, and 103 of these (76 adults) declared a willingness to pay for cryotherapy treatment, the mean of which was £7.86 (median 0, SD 16.17) overall, and £9.10 (median 5, SD 17.6) for adults. This value is highly influenced by outliers, as shown in *Figures 4* and *5*.

Eight patients (8%) (six adults) were willing to pay more than £20 for cryotherapy, two patients (1%) (one adult) were willing to pay £50 and two patients (2%) (both adults) were willing to pay £100. Replacing these outliers with the maximum willingness to pay for SA (£20) gives a mean willingness to pay for cryotherapy of £5.38 (median 0, SD 6.96) overall, and £6.27 (median 5, SD 7.21) for adults. Of the 103 patients who declared a willingness to pay for cryotherapy, 69 overall (67%) and 48 adults (63%) have experience of SA in some form, 70 overall (68%) and 59 adults (78%) have experience of cryotherapy and 46 overall (45%) and 36 adults (47%) have experience of both.

Performing univariate analysis on the willingness-to-pay amounts did not reveal any strong correspondence between the amount that patients are willing to pay and any of the following:

- previous experience of the treatment
- number of warts (either total number or the number for which treatment was sought)
- side-effects of treatment
- demographic information such as age or gender.

The willingness-to-pay amount for cryotherapy is larger than that for SA, but clearly does not come close to the cost of cryotherapy described in Chapter 4. The preference data indicate that although an equal number (125 patients) received cryotherapy or SA at their GP's surgery, a greater number of patients expressed a preference for cryotherapy treatment. However, it is not

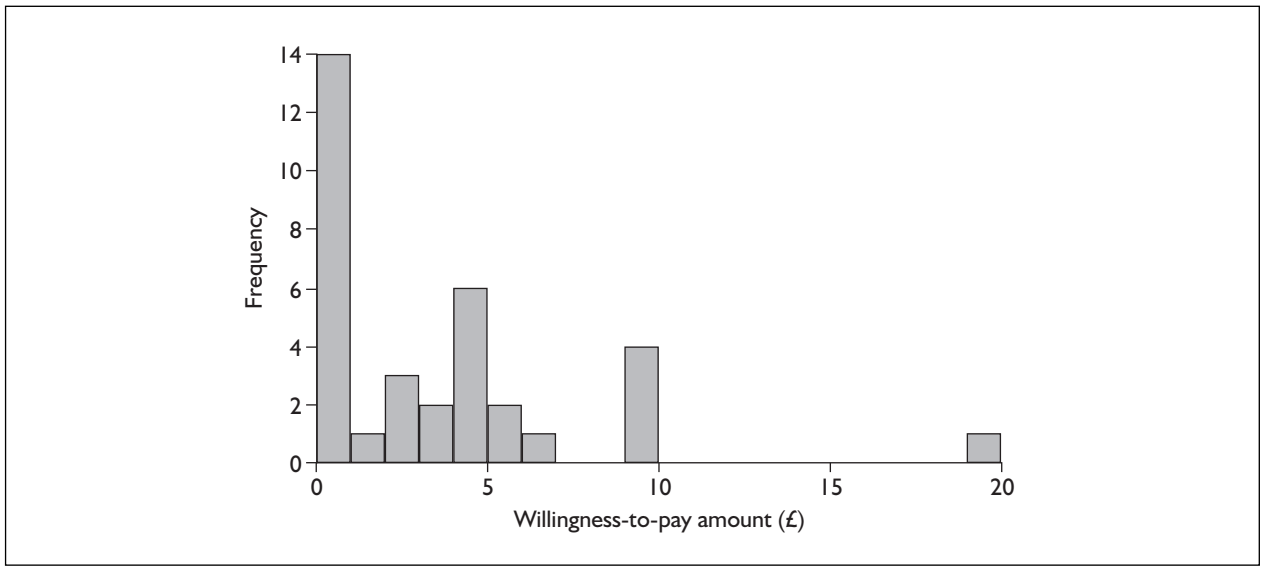

FIGURE 4 *Overall willingness-to-pay values for cryotherapy*

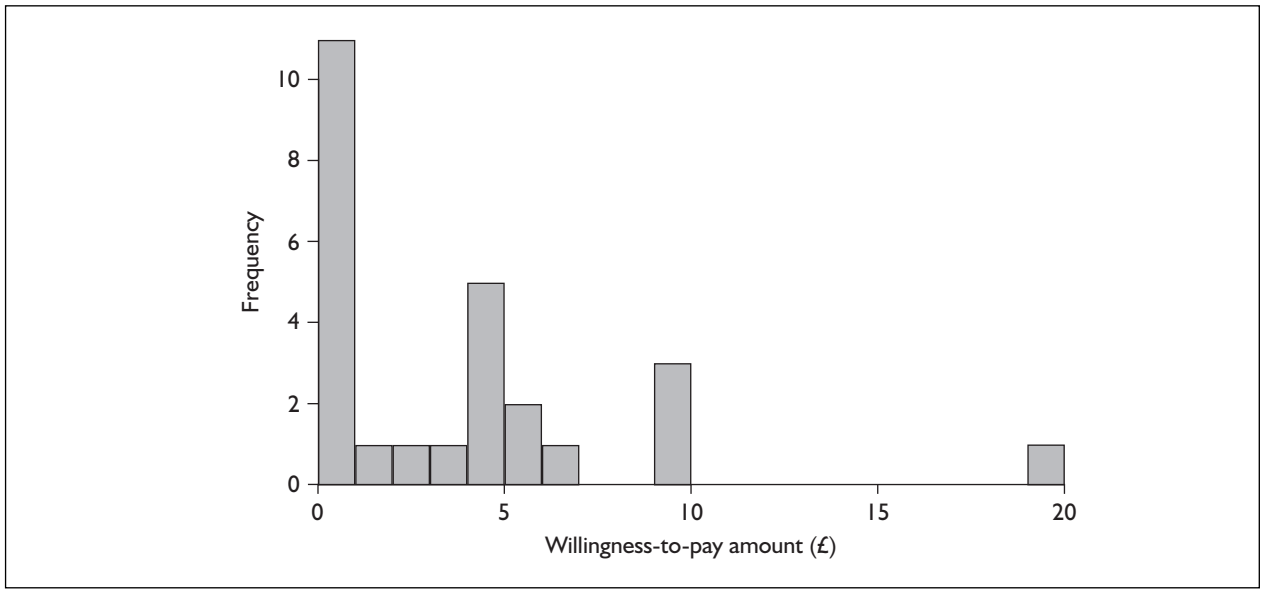

FIGURE 5 *Histogram of willingness-to-pay for cryotherapy by adults*

surprising to see that the patients in the postal survey are biased towards cryotherapy in both their willingness to pay and stated preferences, since the patients sampled consist of those seeking doctor's treatment, and also contain a significant number of people (at least 68; 25%) who had tried OTC SA without success: the corresponding sample who had self-treated successfully did not feature in a GP postal survey.

Overall, there is no evidence to suggest that patients are willing to pay the large difference in treatment cost between SA and cryotherapy treatment. The minor difference between willingness-to-pay values would only be significant in cases where the cost-effectiveness between treatments is similar. The indications of the declared willingness-to-pay values is that many patients with experience of warts and wart treatment would not be willing to pay the cost of wart treatment in future, since their declared willingness-to-pay costs are lower than the amounts that they have paid in the past for treatment. This viewpoint is summed up in the comment by one respondent:

> "I just keep getting them back elsewhere, when I get rid of them, so I keep the ones I have."

TABLE 20 *Comparison of quality of life scores for adults and children (higher scores represent greater impairment)*

	N	Range	Mean	SD	Median	IQR
Adults	74	0–21	4.14	4.94	2.5	(1 to 5.25)
Children	34	0–16	5.41	4.54	4	(2 to 8)

TABLE 21 *Breakdown of the quality of life score: adults (n = 74) (higher scores represent greater impairment)*

	Maximum possible score	Range	Mean	SD	Median	IQR
Symptoms and feelings	6	0–6	1.59	1.60	1	(0 to 3)
Leisure	6	0–6	0.73	1.40	0	(0 to 1)
Personal relationships	6	0–4	0.69	1.10	0	(0 to 1)
Treatment	3	0–3	0.43	0.83	0	(0 to 1)
Work and school	3	0–3	0.28	0.65	0	(0 to 0)
Daily activities	6	0–5	0.41	0.91	0	(0 to 0.25)

Quality of life questionnaire

The impact of warts on quality of life is poorly documented in the literature. A historical survey of this kind could not identify the possible change in quality of life experienced by patients following treatment of their warts.

As part of the postal survey, validated questionnaires were used to assess health-related quality of life in those participants who still had warts at the time of returning the questionnaire. For adults, this was assessed using the DLQI[28] and for children the CDLQI.[29] Both instruments have been widely used in previous dermatological research (see www.ukdermatology.co.uk for a full list of publications). The scales consist of ten questions covering six general areas (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment). For both questionnaires, the maximum possible score is 30 and the minimum possible score 0. Higher scores indicate greater impairment of quality of life.

Participants

Quality of life data were available for 108 participants (74 adults, 34 children). This represents 86% of those who reported that their warts had not yet resolved at the time of returning the questionnaire. The total number of warts per participant ranged from one to 27 [median 3, interquartile range (IQR 2 to 5)]. Of these, 29 (27%) reported[28] having warts on the hands, 44 (41.5%) had warts on the feet and ten (9%) had warts on other parts of the body. Twenty-three participants (22%) had warts at a combination of these sites. Twenty-six participants (24%) had had the warts for more than 12 months before contacting their GP.

Data management and analysis

Descriptive data are reported for total quality of life scores, and for each domain of the questionnaire. In addition, a multiple regression model was developed to explore the impact of various factors in determining quality of life in these patients. Factors investigated in the model were type of patient (adult/child), gender, location of the warts, total number of warts and duration of warts before visiting the GP.

Results

Quality of life scores ranged from 0 to 21 (median 3, IQR 1 to 7, mean 4.54, SD 4.83). The range of scores was greater for adults than for children, although children had a higher median score and wider IQR (*Table 20*).

For each of the six domains, the only one to show any consistent impairment was the symptoms and feelings domain, with a median score of 1 for both adults and children. All other sections had a median score of 0, except for the treatments domain, which had a median score of 1 for children, but not for adults (*Tables 21* and *22*).

The multiple regression analysis showed that type of patient, gender and number of warts had a significant effect on the reported quality of life. The total proportion of variability explained by the model was 11.8%.

The regression coefficients for the model are shown in *Table 23*. These data indicate that,

TABLE 22 *Breakdown of the quality of life score: children (n = 34)*

	Maximum possible score	Range	Mean	SD	Median	IQR
Symptoms and feelings	6	0–6	2.00	1.76	1	(1 to 3.25)
Leisure	9	0–5	1.18	1.59	0	(0 to 2)
Personal relationships	6	0–6	0.82	1.40	0	(0 to 1)
Treatment	3	0–3	0.97	0.90	1	(0 to 2)
School or holidays	3	0–1	0.24	0.43	0	(0 to 0.25)
Sleep	3	0–2	0.26	0.51	0	(0 to 0.25)

TABLE 23 *Results of multiple regression model: quality of life*

Variable	Regression coefficient	95% CI	*p*-Value
Constant	–3.172	(–7.688 to 1.345)	0.167
Type of patient (adult/child)	2.015	(0.027 to 4.004)	0.047
Total number of warts	0.268	(0.102 to 0.433)	0.002
Gender (male/female)	2.475	(0.619 to 4.332)	0.009

having adjusted for the other variables in the model, quality of life scores were worse for children than for adults, and were worse for females than for males. In addition, those with multiple warts were more likely to report greater impairments in quality of life.

Discussion

The results of this survey are from 270 patients who attended their GP's surgery about their cutaneous warts and who completed the postal questionnaire.

Cure rates

The cure rates for cryotherapy (44–56%) and wart paints (38–50%) reported in the survey were comparable to each other and to those reported in the Cochrane systematic review.

A high percentage of patients reported that they had their warts frozen only once. It is possible that patients who received just one session of cryotherapy were those who had small, easily treated warts, whereas those who had had more than one session had warts that were more difficult to treat. However, it is also worth noting the policy differences between surgeries in the manner in which cryotherapy is offered to patients. Some routinely offer just one session of cryotherapy and then recommend that patients wait for the wart to resolve, whereas other surgeries offer patients as many sessions as required.

In terms of wart paints, few patients were applying the preparations in the recommended way. The impact of this on cure rates is possibly something that warrants further study, as the numbers involved were small and the resulting confidence intervals wide.

Side-effects of wart paint and cryotherapy

Patients were asked to report all side-effects of the treatments that they experienced. As would be expected, there was a high incidence of burning, pain and blistering reported with the application of cryotherapy. What was more surprising was the high incidence of side-effects associated with the use of wart paints. This treatment has commonly been offered as a safer alternative to cryotherapy and justification for the more laborious aspect of using it. However, the results presented here would suggest that this distinction is inappropriate. Indeed, the focus groups highlighted concerns about the side-effects commonly seen with wart paint usage, and these concerns could lead to recommendation of cryotherapy rather than wart paint as first-line therapy by the GP.

Implications of the new GP contract and potential changes in practice

The new GP contract came into force in April 2004 and it is possible that this may influence the availability of cryotherapy for the removal of warts, since it will no longer attract a minor operations payment. As a result, possible ways of reducing the

demand for cryotherapy may become an issue for debate in the future. The results of this survey, taken alongside the qualitative data, suggest that there are several areas where patient-led demand for cryotherapy could be reduced.

Make the most of willingness to self-treat

There is a willingness to attempt self-treatment (just over half of patients reported that they had tried some form of self-treatment before going to the surgery). This willingness to try self-treatment could be encouraged if better information were available to patients before they approached their GP or practice nurse.

Encourage a wait-and-see policy

Most patients had had their warts for a relatively short time before seeking advice from their GP. By increasing community awareness that warts spontaneously resolve over time, the demand for GP consultations and treatment could be reduced.

Introduce a short wait for cryotherapy clinics

Only a small number of patients (13%) reported having to wait for treatment once they had visited their surgery. Although this situation is pleasing from the patients' perspective, it is possible that a short waiting time of 1–2 months would allow for further spontaneous resolution of the warts.

If warts are a secondary problem, treat them as such

Almost a quarter of respondents reported that they did not make a special appointment to see the GP or nurse about their warts, but mentioned it when they were there about another matter. If patients are not driving the treatment request, this is a potential chance to educate patients about the likelihood of spontaneous resolution or self-treatment, rather than encouraging patients to attend a cryotherapy clinic or to see their GP and obtain a prescription for wart paint.

Do not offer treatment routinely

Once patients had visited their surgery, most were offered a treatment, either wart paint or cryotherapy, and in only a minority of cases was the patient given advice only. It was suggested by health professionals in the focus groups that it was easier and quicker to offer patients a treatment rather than to try and educate patients about the self-resolving nature of warts. One surgery that simply offered advice rather than cryotherapy reported that over time patients gradually came to accept that cryotherapy was not a treatment option. This model shows that education rather than treatment may be the key to reducing demand over the long term.

Personal and social costs of treatments

For a large number of patients there is little individual cost when undertaking either wart paint or cryotherapy from the surgery. A surprisingly high percentage of patients who were recommended wart paint by their surgery to treat their warts were given a prescription for it (68%), and the majority of these received free prescriptions. Only a small percentage of patients reported taking time off work or school to attend cryotherapy clinics, so the opportunity cost of receiving treatment was generally low.

By comparison, the costs to the NHS of both cryotherapy and prescriptions for wart paints are significant and these are examined in more detail in the economic model (Chapter 4).

Impact of warts on quality of life

Results of the quality of life survey suggest that warts have a relatively low impact on patients' health-related quality of life (median 3, mean 4.45), although patients with multiple warts report a greater impact. By way of comparison, it is helpful to compare these scores with published data for other skin conditions such as atopic eczema (mean scores 4.14–16.2), psoriasis (mean scores 4.5–13.9), urticaria (mean scores 7.5–15) and epidermolysis bullosa (mean score 10.7). These values have been taken from a review paper,[30] in which the lower scores reflect mild disease and the higher scores reflect patients with more severe disease. It would appear that warts have a similar impact on patients' quality of life to that found for mild eczema or psoriasis. Limited data have been reported in a primary care setting,[31] but this survey covered a variety of dermatological conditions and only included five patients with warts (mean DLQI 3.8, SD 2.8).

Caveats

This survey sought to capture the likely cure rates for cryotherapy and SA as they are currently used in the community. It was not intended to provide cure rates for more detailed questions such as the impact of applying the treatments in different ways (e.g. one session of cryotherapy versus multiple applications) or differences in cure rates for different types or location of warts. Clearly, a much larger survey would be required to answer questions of this nature with any degree of certainty.

As with any survey of this kind, these data are limited to capturing the health impact of warts in

patients who chose to return the questionnaire. The response rate for this survey was low (37%), and it is quite possible that individuals who returned the questionnaire are more likely to have strong opinions about their warts, especially since they originally chose to contact their GP about their condition. One can only presume that those patients who choose to self-treat are less bothered by the presence of their warts than those identified in the current survey.

Secondary care survey

Although the majority of patients with warts are now treated in primary care, a survey of dermatology departments in the Trent region was also conducted to establish what treatments are currently used in secondary care and the number of patients typically seen in this setting.

Methods

Questionnaires were sent out in January 2004 to all of the secondary care centres in the Trent region that have a dermatology department (n = 10). These included four teaching hospitals and six district general hospitals. Each questionnaire was addressed to a specific member of staff, who received a covering letter, an information leaflet, a questionnaire and a reply-paid envelope. A copy of the questionnaire can be found in Appendix 6.

Results

A 100% response rate was achieved. The median number of consultants and specialist registrars in dermatology departments was 3.2 and 1.3, respectively. This was equivalent to 1.08 consultants per 100,000 of population served.

As expected, the number of patients referred each month to secondary care for cutaneous warts was low. Most centres reported between 0 and 20 patients per month in total, which equated to an average of 4.9 patients per 100,000 of population served. All centres reported that their policy was to encourage GPs to treat cutaneous warts in the community.

The most common treatments for cutaneous warts offered by secondary care were cryotherapy and SA. *Table 24* shows all treatments offered by the hospitals surveyed (respondents were asked to indicate up to two treatments).

All centres reported that they used liquid nitrogen when carrying out cryotherapy, rather than DMEP (Histofreezer). Half of the hospitals held a cryotherapy clinic at which warts could be treated on a regular basis, and these were all held weekly.

Discussion

The results of the survey confirm that warts are now rarely treated in secondary care. When they are, patients generally receive the same options as those given in primary care (i.e. cryotherapy or SA). This suggests that the primary reason that patients are referred is not to be offered a different type of treatment (unless they are

TABLE 24 *Treatments currently offered in secondary care*

Treatment	No. of centres
None	3
SA	7
Cryotherapy	9
Excision/cautery	1
5-Fluorouracil	0
Imiquimod	1
Other	0

TABLE 25 *Results of postal survey used to inform the economic decision model*

Cure probabilities	Wart paint (38–50%), cryotherapy (44–56%) Used to inform sensitivity analysis
Frequency of application	Most received either one cryotherapy session or sessions up to 2 weeks apart Adherence with SA treatment was poor Used to inform assumptions for model and sensitivity analysis
Likely treatment pathways	Helped to decide which treatment options should be included in the model
Costs	Number of prescriptions per person (1–2) Number of OTC purchases per person (average = 1.42) Likely duration of cryotherapy sessions (5 minutes) Travel costs (per GP visit) and opportunity cost of treatments (generally low)
Secondary care	Warts rarely treated in secondary care

referred from a surgery that does not offer cryotherapy).

Summary of main conclusions from postal surveys

While usual practice for the treatment of warts and verrucae varies widely across the region, the cure rates observed in this postal survey are remarkably similar to those observed in published RCTs. A summary of those findings used to inform the design of the economic model is presented in *Table 25*. It is possible that clearer guidelines on the most cost-effective ways of delivering treatments for warts would be helpful in reducing the overall cost to the NHS. This issue is addressed more fully in Chapter 5.

Chapter 4

Cost-effectiveness model

Overview

Where it is not feasible to obtain original data from an RCT, a decision-analytic approach is a useful means of determining the likely cost-effectiveness of alternative treatments.[32] This study used a decision tree modelling approach that allows synthesis of existing clinical evidence (published and unpublished) with other sources of available information (e.g. costs) for a range of different assumptions. Decision analysis can be used to perform cost-effectiveness analysis.

Uncertainty may be readily expressed in a model using probabilistic assumptions to take account of known variability in areas such as clinical effectiveness, treatment compliance and cost. In this way, sensitivity analyses can also be performed to take account of uncertainty and a predicted range of cost-effectiveness ratios obtained within which the true cost-effectiveness ratio is most likely to be found.

A diagram of a typical treatment arm in the model is given in Appendix 7.

Aims

The aims were:

- to estimate the costs of commonly used treatments for cutaneous warts
- to estimate the health risks and benefits associated with these treatments
- to create an economic decision model using the above data that will evaluate the cost-effectiveness of the treatments.

Methods

Structure of the decision tree

A decision tree is made up of branches that are joined together by 'nodes' (decision points). Branches usually illustrate the outcomes of an event or decision, to which probabilities may be attached. There are different types of node to represent different operations.

Choice nodes

Choice nodes are usually denoted by squares and are used to represent an uncertain event with multiple possible outcomes. In this case, a choice node is used to represent the range of wart treatments from which a patient might choose (e.g. SA, cryotherapy). An illustration of this part of the decision tree is in *Figure 6*. Since warts are largely self-diagnosed, this represents the patient's ability to choose freely which action to take with regard to their wart treatment.

Chance nodes

Chance nodes are denoted by circles and are used to represent an event with multiple possible outcomes where each possible outcome has an attached probability. It is important that these possible outcomes are mutually exclusive, and that one of the outcomes is certain to take place. In this case, a typical use of chance nodes is to determine the outcome of a treatment: cure or not cure. These events exclude each other and the probability of one of them occurring is 1. An example of this is shown in *Figure 7*.

Terminal nodes

Terminal nodes are illustrated by triangles and indicate a payoff. Payoffs can be measured in terms of effects, costs and/or utility to the patient being in that health state. Terminal nodes can also be used to make transitions between Markov states (described below). An example of the use of terminal nodes is shown in *Figure 7*. The value beneath each branch indicates the probability of

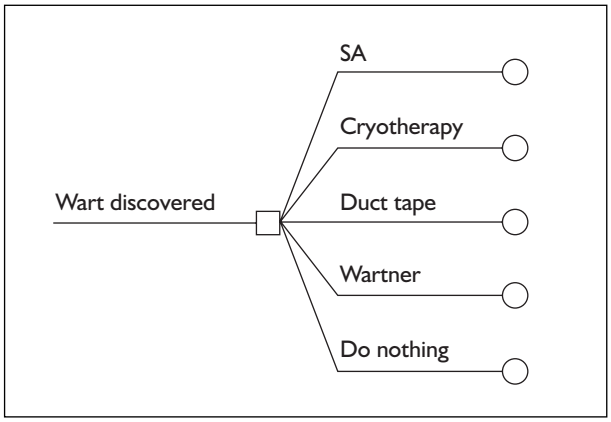

FIGURE 6 *Illustration of choice node (square)*

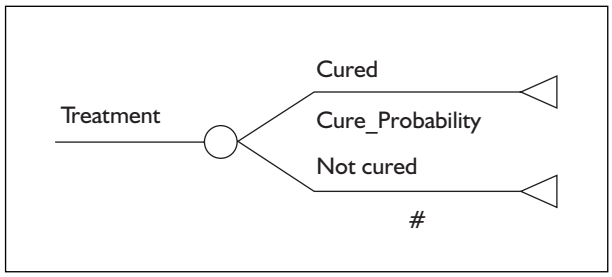

FIGURE 7 *A chance node with probabilities*

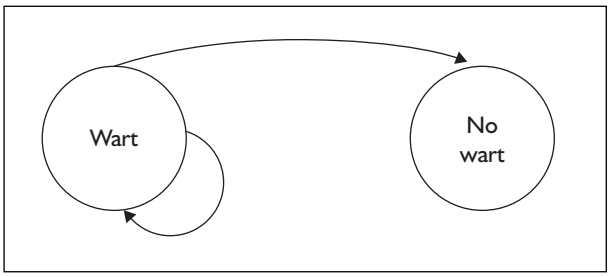

FIGURE 8 *Diagram of state transitions*

that branch being selected. The '#' symbol represents one minus the sum of the probabilities of all other chance node outcomes; that is, if none of the other events occurs, then the event with probability # will occur. This method ensures that one of the possible outcomes is certain to occur.

There is no known health utility measurement for warts. Instead, the effectiveness of treatment in the model is measured either in terms of the average number of weeks for which a patient is likely to have a wart (once treatment begins) or in terms of the effectiveness of treatment at certain time intervals since treatment began (e.g. 10% cured after 3 weeks). This method takes into account both the duration of treatment and the likelihood of cure.

The Markov property

The Markov property is used to represent recurring events over time (e.g. one application of a treatment requiring several applications). As the patient is the unit of analysis and in order to model the patient's condition with a Markov model, it is necessary to define the two entities: states and cycles.

There are only two patient conditions that are directly relevant to this study: (1) the patient still has a wart (or warty skin); and (2) the patient has no wart (or no warty skin): the wart has been cured or has resolved. These two conditions are represented by the two Markov states called, respectively, 'Wart' and 'No wart'. This simplifying assumption was necessary for the model, although in practice there are other eventualities, for example, cure of some of a patient's multiple warts.

Cycles represent the time-points at which one considers a possible transition between the two Markov states [i.e. the transition from having a wart(s) to the wart(s) being cured]. Since wart treatment or resolution times vary, from a few weeks to several months or even years, cycles of length 1 week were chosen. The data from which cure rates are estimated are not sufficiently detailed to allow cure rates to be estimated at shorter time-scales than 1 week. In fact, adapting cure rates to 1-week intervals requires simplifying assumptions. A diagram of the transitions possible from the Markov states is given in *Figure 8*.

Modelling cures

Cure rates for treatment provided by published literature are most frequently declared in terms of the number of patients cured after a certain number of weeks. From this value, certain assumptions have been made (listed in Appendix 8) and the number of patients cured/resolving per week was calculated. For example, suppose a treatment has a cure rate of approximately 50% over 5 weeks. Given 100 patients, it was assumed that approximately ten will resolve each week for 5 weeks. An even cure rate over time was assumed in the model.

The only published studies that have been used to estimate treatment effectiveness are those that use patients as the unit of analysis. The results in terms of patients cured are often quite different from the results where wart cures are considered. This is because one patient may have more than one wart, but the study is interested in 'wart-free' patients from both the economic and medical welfare points of view.

Modelling costs

Treatment costs are independent of treatment cures. This is because some treatments are indivisible. In practice, a patient whose wart(s) is cured before he or she has completed the recommended course of treatment can cease treating their wart (this situation would correspond to a transition from state 'wart' to state 'no wart'). However, the cost of treatment cannot necessarily be determined by the number of weeks (or cycles) for which the wart was treated. Instead, the cost of treatment can only be divided into treatment sessions or treatment materials: it is not

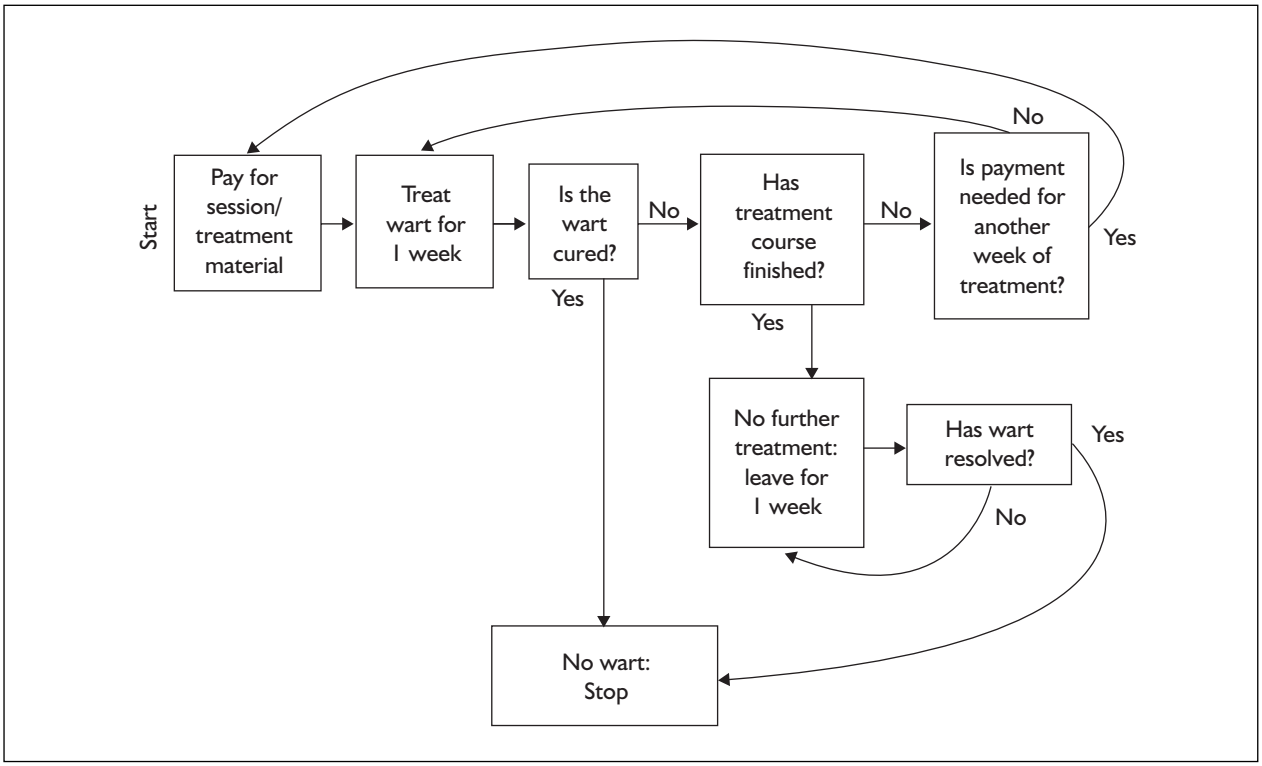

FIGURE 9 *Treatment modelling diagram*

possible to receive half a session of cryotherapy or purchase a quarter of a bottle of SA. In the case of cryotherapy, the cost of treatment can be divided into individual cryotherapy sessions, so the charge for cryotherapy treatment is made at the time of the cryotherapy session and then nothing more is charged until the next session. A payment is unlikely to be made for cryotherapy after the wart is cured. In the case of SA, duct tape and OTC cryotherapy, this indivisibility is a particular problem since a complete pack, roll or container of treatment must be purchased regardless of whether the treatment is completed to its full course or not. For this reason, the full charge for a pack or bottle of SA, OTC cryotherapy or duct tape is made in the first week of the treatment course. The model reflects this indivisibility of costs. (The method used to introduce these costs in TreeAge is explained in Appendix 9.) A simplified diagram is shown in *Figure 9* to illustrate the pattern of behaviour included in the model to reflect treatment practice and the introduction of cost. The model is deterministic, fixing the patient's pathway according to the state of his or her wart.

The boxes in *Figure 9* require some explanation. After a patient has finished a course of treatment, their warts may not be cured. Although it is known that warts will gradually resolve over time, 'time' in this instance can vary from weeks to years. To accommodate this pattern of behaviour in the model, warts remaining uncured after a full course of treatment pass into the spontaneous resolution arm of the model. The spontaneous resolution arm permits warts to resolve gradually (i.e. pass from state 'wart' to state 'no wart') over weekly periods (cycles). In this sense, spontaneous resolution works in exactly the same way as other treatments (*Figure 8*), except that the probability of cure (or resolution) is much smaller for spontaneous resolution than it is for treatment.

Incremental cost-effectiveness ratios

For each treatment, incremental cost-effectiveness ratios (ICERs) are calculated using the following formula:

$$\frac{\text{Cost of treatment being investigated} - \text{Cost of baseline comparator}}{\text{Effect of treatment being investigated} - \text{Effect of baseline comparator}}$$

For the main cost-effectiveness analysis, interventions are compared with spontaneous resolution (do nothing). However, data are also presented using advice from the GP as the baseline comparator to reflect the perspective of the NHS more clearly.

Treatment costs

Treatment costs have been estimated from various sources and these are indicated for each treatment in *Table 26*.

Throughout these results the following abbreviations are used to refer to the treatments included:

- DN represents do nothing (spontaneous resolution).
- OTC SA represents salicylic acid bought over the counter.
- OTC CR represents cryotherapy bought over the counter.
- Duct represents duct tape (Gaffa tape).
- Advice represents advice given by the GP.
- GP SA represents GP-prescribed salicylic acid.
- CR1, CR2 and CR3 represent one, two and three sessions of cryotherapy, respectively.
- CRNurse represents a course of cryotherapy (three sessions) delivered by a practice nurse.
- COMB represents SA and cryotherapy used at the same time.
- CRSA and SACR represent multiple treatments: cryotherapy followed by salicylic acid OTC and salicylic acid OTC followed by cryotherapy, respectively.
- CR2C represents cryotherapy delivered in secondary care.

Multiple and combination treatments

In certain cases, patients can receive multiple or combination treatments. Multiple treatments are used to illustrate the situation where the first-line treatment fails to cure the wart(s) so further treatment is sought. For example, a patient may try SA at home for several weeks, but seek cryotherapy if this treatment is unsuccessful. An illustration of a multiple treatment tree is given in *Figure 10*.

Multiple treatments are modelled in a similar way to individual treatment. However, instead of the uncured patients passing from the first-line treatment into spontaneous resolution, they pass from first-line treatment to second-line treatment. Patients whose warts remain uncured after the second-line treatment pass into spontaneous resolution. Costs of multiple treatments (cryotherapy and SA) are simply the sum of the costs of the treatments applied.

Combination treatments can be used to increase the power of a single treatment. The most common example of this (and the only combination treatment used in the model) is the combination of applying cryotherapy and SA at the same time. In this case, cryotherapy is administered every 2 weeks, but SA is also applied daily to the wart between cryotherapy sessions as soon as pain or blistering has settled down.

Combination treatments are implemented in the model in the same way as a single treatment (although the probability of cure is adjusted according to the estimated effectiveness of the combination).

Secondary care cryotherapy

Only 2% of patients who returned the postal survey were referred to secondary care for the treatment of their warts. However, for the sake of completeness, this scenario was included in the model. It was assumed that patients will receive cryotherapy from their GP surgery in the first instance and that patients will only be referred to secondary care if that treatment fails. In reality, this may not be the case as some GPs may refer patients to secondary care because they do not provide cryotherapy at their surgery. An illustration of the procedure of cryotherapy in secondary care is in given in *Figure 11*.

Cure probabilities

Where possible, cure probabilities have been estimated from the Cochrane review using a weighted average of the RCT cure rates. Not all cryotherapy trials in the Cochrane review have been included in this weighted average calculation since some trials used warts rather than patients as

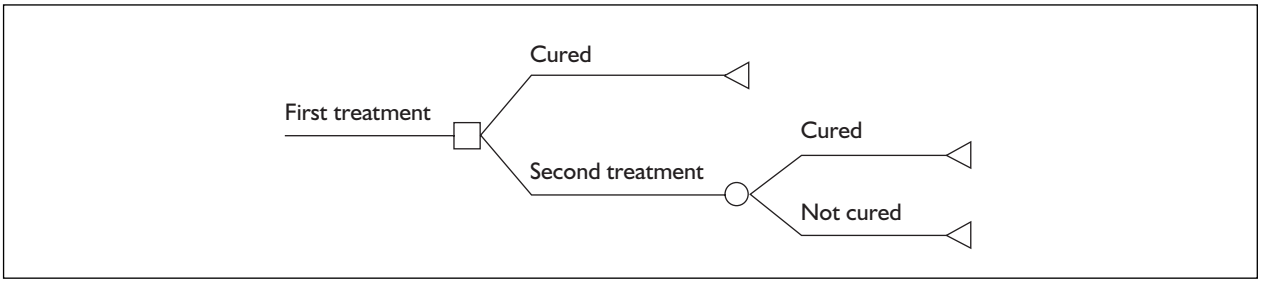

FIGURE 10 *Example of a multiple treatment*

TABLE 26 *Cost of interventions and sources of cost estimates*

Intervention	Costs included	Source of cost estimate	Cost used in model
Home treatments			
OTC SA	SA purchase (market leader: Bazuka): £4.75 per pack Two packs required (second pack introduced after week 6) Travel cost to pharmacy (£6.90)	UEA pharmacy department Netten and Dennett[33]	£23.30
Duct	£2.50 per 10-m roll Travel to shop (same as travel to pharmacist) (£6.90)	Average from several hardware stores Netten and Dennett[33]	£9.40
OTC CR	35-ml can (£11) Sufficient for up to ten applications Travel costs (£6.90)	UEA pharmacy department Netten and Dennett[33]	£17.90
Treatments in primary care			
Advice	GP consultation (£20) Travel to GP (£6.90)	Netten and Dennett[33]	£26.90
GP SA	GP consultation (£20) Travel to GP (£6.90) Assumes two prescribed items (as per OTC SA, but cost all introduced at week 0) (£5.50) Dispensing charge (£1.00) Costs not independent of size and number of warts. However, model not designed to reflect extremes	Netten and Dennett[33] Prescription Pricing Authority (April 2001 to March 2003) <5% wart plasters, therefore not included in price estimate	£40.30
GPCR	Initial GP consultation (£20) Travel to surgery (£6.90 per visit) Cryotherapy administered by GP (£11 for 5-minute clinic) Costs of sessions introduced at 0, 2 and 4 weeks Reasonably independent of size and number of warts (relatively quick procedure and equipment set up in advance)	Netten and Dennett[33] Includes overheads and equipment	£80.60 for three sessions (although only those with warts remaining will receive a full course of treatment)
CRNurse	Initial GP consultation (£20) Travel to surgery (£6.90 per visit) Cryotherapy administered by nurse (£2.50 per 5-minute clinic)	GP CR	£55.10 for three sessions
Treatments in secondary care			
CR2C	Cost of 3-week treatment at GP surgery (£80.60 delivered via GP) Assumes referral time of 12 weeks For patients still uncured, a second cycle of three treatments is initiated, but delivered by consultant (£22 per session) Probability of cure replaced with cure following aggressive treatment Travel to hospital (£6.90 per visit)	GP CR	£167.30

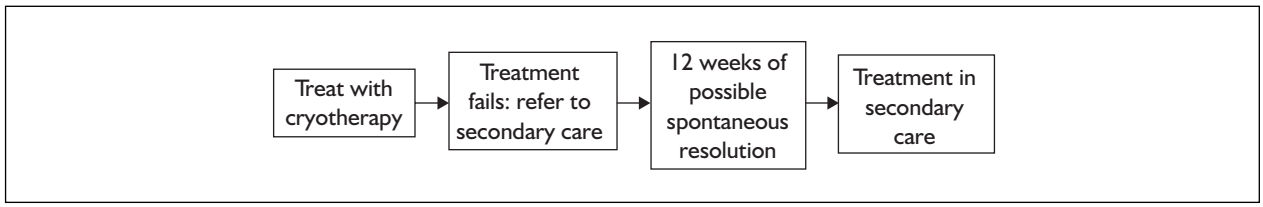

FIGURE 11 *Illustration of secondary care cryotherapy*

the unit of cure analysis and others quoted only the percentages of patients cured rather than numbers of patients and therefore could not be weighted. Details of the papers used to calculate cure probabilities are given in Appendix 10. Cure rates were also estimated from the results of the patient survey and these results compared with those from the Cochrane review in sensitivity analysis.

The interquartile range was used to calculate the range of cure probabilities used in the model, since confidence intervals for the weighted means produced very narrow intervals. The interquartile range was therefore used to allow for greater uncertainty. In the case of duct tape, the uncertainty in probability estimates was expressed in terms of confidence intervals since duct tape cure is estimated from a single trial.

In the model, the cure rates are divided equally between the number of weeks for which the treatment is applied. This ensures that an equal number of patients is likely to be cured/resolved for each week of treatment. A summary of the treatment cure probabilities is presented in *Table 27*.

Assumptions

In the above description it has been necessary to refer to some of the underlying assumptions of the model. The main modelling assumptions are detailed in Appendix 8.

Results

Preliminary analysis: time to cure

To analyse the results of the model, it is necessary to decide upon a cure period at which to study effectiveness. To provide a clearer picture of the effectiveness of treatments at various time intervals of relevance to patients and physicians, consider the plot given in *Figure 12*.

The lines cross at various time-points, indicating a relative change in effectiveness between treatments. However, by week 18 the order of effectiveness remains unchanged (with the exception of cryotherapy in secondary care). This is because SA treatment is assumed to take 12 weeks and the SACR (OTC salicylic acid followed by cryotherapy) and CRSA (cryotherapy followed by OTC salicylic acid) treatments take 18 weeks. Therefore, considering a period of less than 18 weeks would be unadvisable as it would involve an analysis of treatments that may not have fulfilled their course. In addition to this, the estimates of cure rates before the end of treatment, although justifiable and reasonable from the point of view of the model, may not be sufficiently accurate estimates on which to base a conclusion.

However, although the above reasoning suggests that a period of approximately 18 weeks is a minimum time limit for effectiveness, from the patient's perspective a cure is required as rapidly as possible. In addition to this, examination of the effectiveness values at long periods suggests that effectiveness values of treatments become similar in time because of spontaneous resolution, so it is important to choose a sufficiently short period to illustrate the speed of cure produced by the treatments. To satisfy these two opposing influences, a period of 18 weeks was chosen as being a sufficiently long period to permit conclusions to be drawn from stable effectiveness values, but sufficiently short to be of interest to patients and to avoid an overly long period of spontaneous resolution.

Selecting 18 weeks as the time-point at which to compare effectiveness excludes cryotherapy in secondary care (which is still ongoing at this time-point). However, this treatment is not a standard wart treatment.

Cost-effectiveness at 18 weeks

The total costs and cure rates at 18 weeks are included in *Table 28*. The lower the ICER, the more cost-effective the treatment is predicted to be. Not treating the wart (DN) leads on average to 46% resolution by week 18 at no cost. This represents the baseline of the cost-effectiveness analysis. Several treatments (e.g. cryotherapy × 3,

TABLE 27 *Cure probabilities used in the model sources of cost estimates*

Treatment	Source of cure probabilities	Cure probabilities used
Home treatments		
DN	Cochrane review	30% (after 10 weeks)
OTC SA	11 trials in Cochrane review (591 patients, 336 cured)	57% (IQR 35 to 68%)
OTC CR	Based on trials for Histofreezer (freezes using same medium, but administered by a GP) Two trials in Cochrane review	54% (IQR 53 to 59%)
Duct tape (Gaffa tape)	One trial in Cochrane review (26 patients, 22 cured)	85% (95% CI 66.5 to 94%)[a]
Treatments in primary care		
Advice only	As above for DN	As above for DN
GP SA	Above for OTC SA	As above for OTC SA
CR	Nine trials in Cochrane review (479 patients, 260 cured) Estimates for one, two and three sessions based on an even cure rate over the treatment period	54% (IQR 53 to 59%)
SA CR	Four trials in Cochrane review (487 patients, 261 cured)	54% (IQR 42 to 76%)
Multiple treatments	Treatments applied second line are ascribed same cure probability as first-line treatments	As for treatments prescribed first line
Treatments in secondary care		
Aggressive cryotherapy	Two trials in Cochrane review (cure definitions not clear) (64 patients, 42 cured)	58.5% (range 45 to 71%) Note: IQR not applicable for two trials

[a] This confidence interval was calculated using the Wilson (score) interval, which is cited by Simon[34] to be more accurate for small sample confidence intervals.

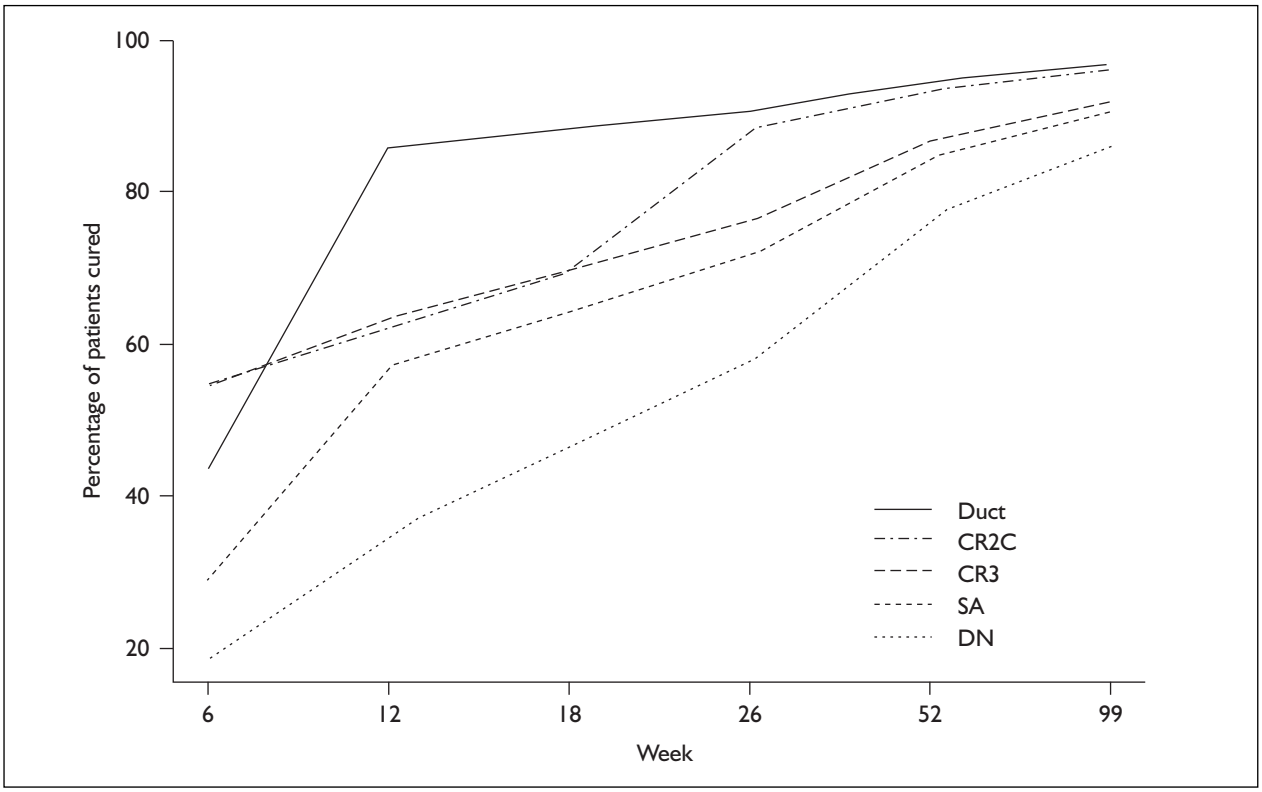

FIGURE 12 *Effectiveness of treatments at specific time intervals*

TABLE 28 *Effect and total cost values at 18 weeks*

Treatment	Effect (% cured)	Cost (£)	Incremental effect (% cured)	Incremental cost (£)	ICER (£/% cured)
Home treatments					
DN	45.92	0.00	0.00	0.00	
OTC SA	64.22	20.47	18.30	20.47	1.12
OTC CR	69.51	17.90	23.59	17.90	0.76
Duct	88.27	9.40	42.35	9.40	0.22
Treatments in primary care					
Advice	45.92	26.90	0.00	26.90	NA
GP SA	64.22	40.30	18.30	40.30	2.20
CR1	52.27	44.80	6.35	44.80	7.06
CR2	64.85	59.41	18.93	59.41	3.14
CR3	69.51	70.67	23.59	70.67	3.00
CRNurse	69.51	49.27	23.59	49.27	2.09
SACR	80.00	66.33	34.08	66.33	1.95
CRSA	80.13	80.01	34.21	80.01	2.34
COMB	69.51	82.32	23.59	82.32	3.49
Treatments in secondary care					
CR2C[a]	69.53	72.58	23.61	72.58	3.07

Costs and outcomes do not reflect the totals outlined in *Tables 26* and *27* since those patients who are cured at each weekly cycle no longer incur costs.
[a] Treatments delivered in secondary care have not yet incurred the full treatment costs and benefits as this treatment pathway takes 24 weeks to complete.
NA, not applicable.

OTC cryotherapy and cryotherapy by a nurse) have the same cure rate, although their costs are quite different.

The ICERs are illustrated graphically in *Figure 13*. Interventions closest to the line are those that are most likely to be cost-effective.

Of the treatments delivered in primary care, SA prescribed by a GP (GP SA), three cryotherapy sessions administered by a nurse (CRNurse) and OTC SA followed by cryotherapy (SACR) all fall on a similar line of incremental cost-effectiveness, and are equally cost-effective. However, OTC SA followed by cryotherapy is only apparently cost-effective because it relies on patients self-treating for a period of 12 weeks before visiting the GP.

The ICER for SA treatment prescribed by a GP is actually higher than the ICER for nurse-administered cryotherapy, which suggests that nurse-administered cryotherapy can, in some circumstances, be more cost-effective than SA. However, this favouring of nurse-administered cryotherapy is dependent on a nurse administering every cryotherapy session (just 12% in the postal survey) at 2-weekly intervals and not providing more than three sessions to any patient. Failure to meet any of these criteria would increase the ICER of nurse-administered cryotherapy beyond that of GP-prescribed salicylic acid. Nevertheless, it represents a potentially cost-effective way of meeting the demand for cryotherapy.

A single application of cryotherapy offers a 6% average improvement over spontaneous resolution at a much higher proportional cost than the other treatments (£44.80). Part of the reason for this high cost is due to the usual practice of a GP consultation before referral to the wart clinic.

An explanation for the low incremental cost-effectiveness of following one treatment with another is as follows. By applying a treatment such as SA after cryotherapy, SA will only be applied to those patients who were not cured by cryotherapy (approximately 45% of the original cohort since cryotherapy is assumed to cure 55%). Therefore, since the measure of effectiveness is the percentage of patients cured, the effectiveness of the second treatment, say SA, will be multiplied by a factor of 0.45 and will therefore need to cost 0.45 times as much as cryotherapy just to retain cryotherapy's ICER.

The ICER value plotted for OTC cryotherapy is by no means robust. It simply provides an indication

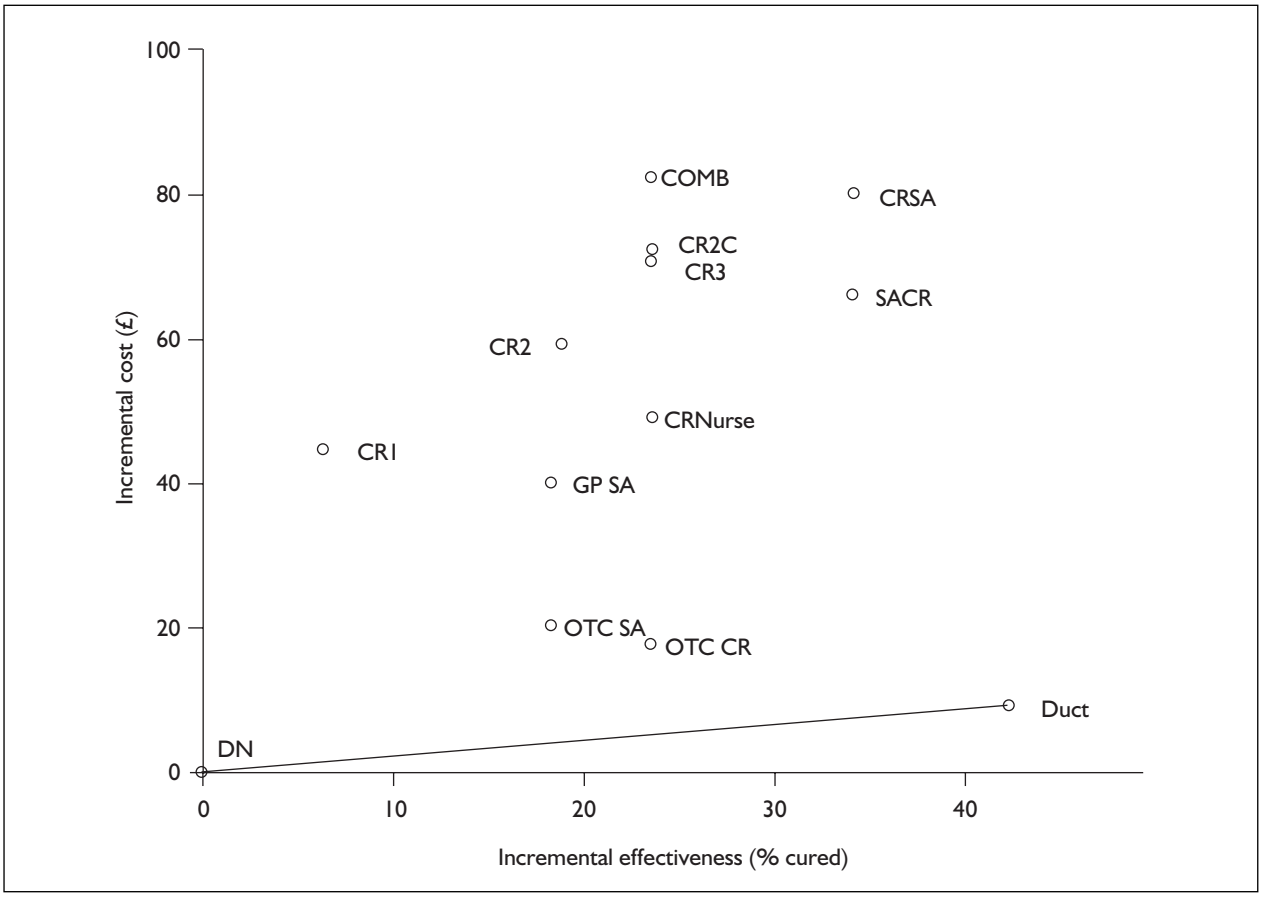

FIGURE 13 *Incremental cost-effectiveness at 18 weeks. The line illustrates the dominating treatment.*

that, if OTC cryotherapy could be shown to be as effective as cryotherapy delivered by a health professional, then it would provide a cost-effective alternative to SA.

As already mentioned, duct tape dominates all other treatments, owing to its negligible costs and high cure rate. However, the effectiveness of duct tape requires further verification since the cure rate data are from a single RCT.

Cost-effectiveness of treatments provided in primary care

The above comparison enables all treatments to be compared using the same baseline (do nothing). However, it is also informative to compare the GP-administered treatments with a GP-administered baseline. For this reason, a treatment 'advice only' (Advice) is also considered. This treatment represents the situation where the patient visits their GP and is advised to allow the wart(s) to resolve spontaneously. Advice only is an identical treatment to the do nothing (DN) option, but carries the additional cost of the GP consultation fee (£20) and the patient's travel to the consultation (£6.90).

Introducing this treatment as the baseline, we obtain the data shown in *Table 29*. These values are illustrated in *Figure 14*.

SA prescribed by the GP is now the dominant treatment. Nurse administered cryotherapy has a slightly higher ICER (indicating reduced cost-effectiveness), but remains the most cost-effective way of delivering cryotherapy in primary care.

Sensitivity analysis

One-way sensitivity analysis was conducted for a variety of cure probabilities. Details of these analyses are presented in Appendices 11 and 12. The results do not significantly alter the ordering cost-effectiveness of treatments and the key conclusions remain unchanged.

Perspective of analysis

Up to this point, costs have been estimated as the total costs to all parties concerned. In one sense, this is the only fair method of comparison since, for

TABLE 29 *Treatments provided in primary care using advice only as the baseline scenario (18-week effect and total cost values)*

Treatments in primary care	Effect (% cured)	Cost (£)	Incremental effect (% cured)	Incremental cost (£)	ICER (£/% cured)
Advice	45.92	26.90	0	0	
GP SA	64.22	40.30	18.30	13.40	0.73
CR1	52.27	44.80	6.35	17.90	2.82
CR2	64.85	59.41	18.93	32.51	1.72
CR3	69.51	70.67	23.59	43.77	1.86
CRNurse	69.51	49.27	23.59	22.37	0.95
SACR	80.00	66.33	34.08	39.43	1.16
CR3 SA	80.13	80.01	34.21	53.11	1.56
COMB	69.51	82.32	23.59	55.42	2.35

Costs and outcomes do not reflect the totals outlined in *Tables 26* and *27* since those patients who are cured at each weekly cycle no longer incur costs.

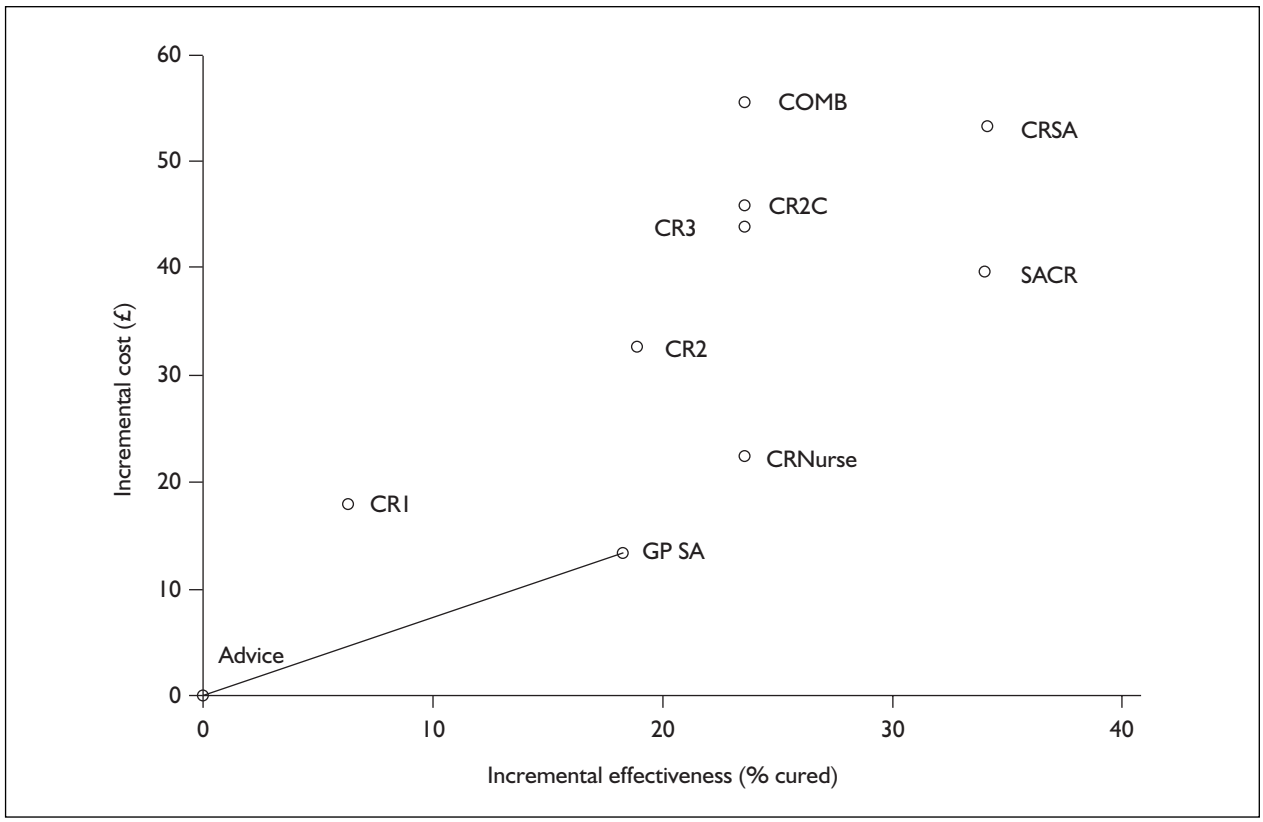

FIGURE 14 *Primary treatments only ICER with primary care baseline*

some treatments, the burden of cost falls completely on the patient, whereas for other treatments the cost falls mainly on the NHS. However, to provide a complete picture, the analysis also considers separately the costs to patients and the cost to the NHS of each treatment.

NHS perspective

Although only the cost of treatment is determined by the perspective from which it is viewed, the effectiveness values as well as the costs for each treatment are included (*Table 30*). Advice from the GP has been used as the baseline value for this analysis.

Since OTC treatments have no cost to the NHS, these treatments dominate the primary and secondary care treatments. Since duct tape is the most effective of these 'free' treatments, it again dominates a cost effectiveness analysis using the do-nothing baseline. Therefore, an analysis of the primary care treatments is included, compared with the advice-only baseline. This analysis is shown in *Figure 15*.

TABLE 30 *Costs and effects from the NHS perspective*

Treatment	Effect (% cured)	Cost to NHS (£)	Incremental effectiveness (% cured)	Incremental cost (advice only baseline) (£)	ICER (£/% cured)
Home treatments					
DN	45.92	0	0	NA	
SA	63.38	0	18.09	NA	
OTC CR	68.92	0	23.63	NA	
Duct	87.28	0	41.99	NA	
Treatments in primary care					
Advice	45.92	20	0	0	
GP SA	63.38	26.50	18.09	6.50	0.36
CR1	51.18	31.00	5.89	11.00	1.87
CR2	64.24	39.91	18.95	19.91	0.95
CR3	68.92	46.77	23.63	26.77	1.13
CRNurse × 3	68.92	25.37	23.63	5.37	0.23
SACR	79.67	31.43	34.38	11.43	0.33
CRSA	80.02	46.81	34.73	26.81	0.77
COMB	68.92	46.82	23.63	26.82	1.13
Treatments in secondary care					
CR2C[a]	69.21	46.58	23.92	26.58	1.11

Minor discrepancies between effects shown in this table compared with those reported in the previous tables are due to a different choice of random seed in the NHS simulation.

[a] Treatments delivered in secondary care have not yet incurred the full treatment costs and benefits as this treatment pathway takes 24 weeks to complete.

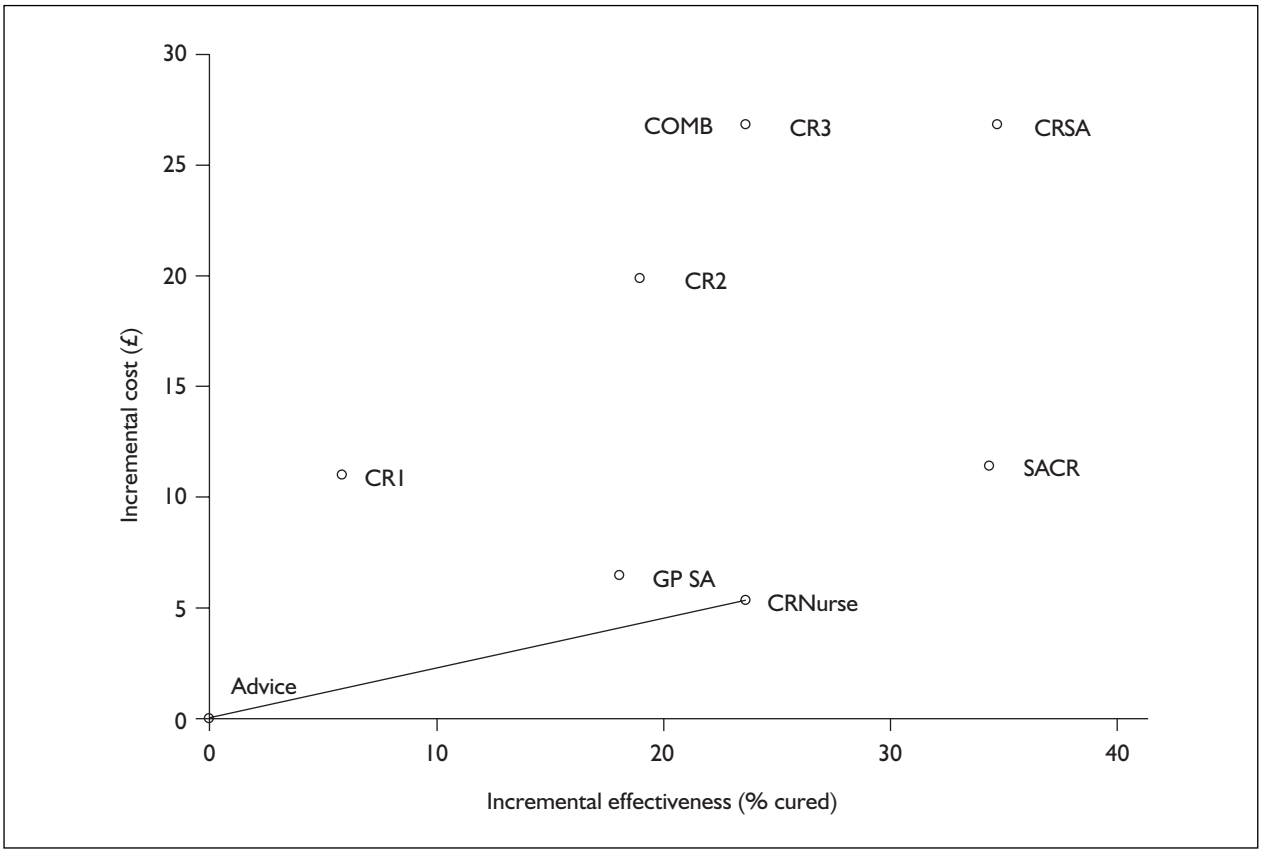

FIGURE 15 *ICER plot using NHS costs*

TABLE 31 *Costs and effects from the patient's perspective*

Treatment	Effect (% cured)	Cost to patient (£)	Incremental effectiveness (% cured)	ICER (£/% cured)
Home treatments				
DN	44.68	0	0	
SA	64.23	20.6	19.55	1.05
OTC CR	69.52	17.9	24.84	0.72
Duct	87.62	9.4	42.94	0.22
Treatments in primary care				
Advice	44.68	6.90	0	NA
GP SA	64.23	13.8	19.55	0.71
CR1	52.22	13.8	7.54	1.83
CR2	64.99	19.5	20.31	0.96
CR3	69.52	23.9	24.84	0.96
CRNurse	69.52	23.9	24.84	0.96
CRSA	80.34	33.2	35.66	0.93
SACR	79.84	34.9	35.16	0.99
COMB	69.52	35.5	24.84	1.43
Treatments in secondary care				
CR2C[a]	69.71	26.0	25.03	1.04

Minor discrepancies between effects shown in this table compared with those reported in the previous tables are due to a different choice of random seed in the patients' cost simulation.
[a] Treatments delivered in secondary care have not yet incurred the full treatment costs and benefits as this treatment pathway takes 24 weeks to complete.

From the perspective of the NHS, GP SA and OTC SA followed by cryotherapy remain cost-effective treatment options. Nurse-led cryotherapy is the dominant treatment overall (ICER = 0.23 £/% cured), although this is dependent on the assumption that up to three cryotherapy sessions would be provided at 2-weekly intervals.

The explanation for this is that GP prescribed the nurse's time is less expensive to the NHS than SA, and the total cost of cryotherapy administered by a nurse is strongly influenced by the initial GP consultation.

Patients' perspective

When viewed from the perspective of the patient, a very different view of the treatment is gained. For this analysis, do nothing (spontaneous resolution) has been used as the baseline value (*Table 31*).

A plot of the incremental cost-effectiveness of these treatments is included below in *Figure 16*. The baseline used for this analysis is the do-nothing option, which is the most relevant baseline from this perspective.

Duct tape is again the most cost-effective treatment and dominates all others. However, the other treatments are now more closely bunched in terms of their cost-effectiveness, illustrating that the majority of the costs are incurred by the NHS. SA prescribed by a GP from the perspective of the patient is a more attractive treatment: the absence of prescription costs and the NHS's payment of the GP fee means that this treatment costs the patient little more than a journey to the GP and a journey to the chemist. OTC cryotherapy is also relatively attractive from the patient's perspective because it only involves a single trip to the chemist.

From the patient's perspective there is no benefit in receiving nurse-administered cryotherapy rather than GP-administered cryotherapy, but the frequent travelling to the GP for both consultation and wart clinics means that two sessions of cryotherapy are marginally more cost-effective for the patient than SA, and three sessions of cryotherapy have similar cost-effectiveness to SA. This is because the cost of travel to the GP was estimated to be the same as travel to the pharmacist. In addition, since SA costs almost as much as a single journey to a GP or pharmacist, so a single pack of SA costs almost as much to the patient as two cryotherapy sessions.

These results may provide an explanation for some patients' preference of particular treatments. From the patient's perspective, there is little evidence to suggest that one standard treatment is preferable over another. This may explain why patients object to treatments such as SA because of

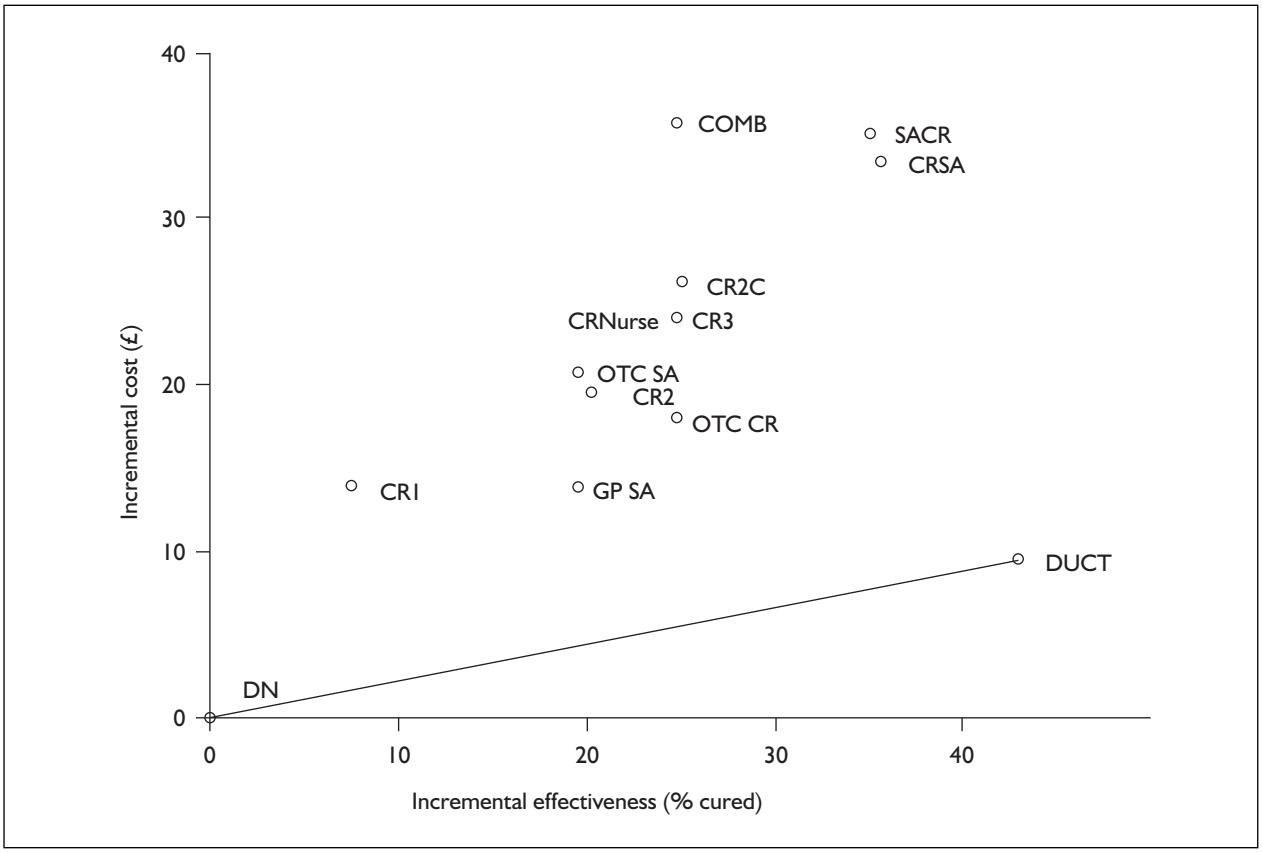

***FIGURE 16**: ICER from the patient's perspective*

the mess and need for daily reapplication, or object to cryotherapy because of the pain, discomfort and inconvenience of travelling to the GP. In the absence of any financial benefit or increased efficacy of a treatment, patients may become more selective on the basis of secondary aspects of treatment.

Expected value of perfect information

Expected value of perfect information (EVPI) calculations are used to assess the uncertainty surrounding each possible intervention, and thus to decide whether it would be more cost-effective to collect more data (thus reducing the uncertainty) or to risk making a wrong decision based on the current information.

Having considered this issue, it was felt inappropriate to conduct an EVPI analysis as this would have required a much greater level of sophisticated utility quality-adjusted life-year (QALY) data than currently available in regard to the different wart treatments available. The group decided not to attempt to measure the health utilities of warts since such data collection went well beyond the remit of the project. It was also feared that such a minor condition may yield results close to 1 in many cases (given current utility measures), or even potentially wide estimates in subgroups of others (a small group of whom find warts socially debilitating and a barrier to employment).

For the purposes of this project, a cohort simulation was produced, followed by sensitivity analysis. Given the scale of the project, this course of action was deemed the most practical way forward. In the event, the results of the model raised sufficient new results to inform substantially the design of future clinical trials.

Discussion

Cost-effectiveness of SA and cryotherapy

SA is a treatment that has been widely used and its effectiveness is more certain than some of the other treatments discussed in this report. It is relatively inexpensive to purchase and both the postal survey data and the Cochrane review suggest that its probability of cure is approximately equivalent to that of cryotherapy. There is evidence to suggest that treatment

duration is longer than for cryotherapy and therefore its efficacy at 18 weeks is lower than for cryotherapy. This estimate of the cure speed depends on a GP being able to administer cryotherapy at 2-weekly intervals. In cases where a monthly wart clinic is the only opportunity to receive cryotherapy, the estimate of three cryotherapy sessions per treatment equates to a cure duration closer to that of SA.

SA prescribed by a GP is more expensive than self-treatment using OTC remedies since it includes an initial consultation with the GP. Nevertheless, a course of SA prescribed by the GP is still more cost-effective than a course of cryotherapy from the GP (ICER 2.20 versus 3.00 £/% cured, respectively), although the difference is not marked if the course of cryotherapy is limited to three sessions. If cryotherapy is administered exclusively by a practice nurse at 2-weekly intervals and for not more than three sessions, this method of delivering cryotherapy may be cost-effective (ICER = 2.09 £/% cured) and is comparable to GP-prescribed SA.

Cryotherapy is an attractive treatment to patients because many of the charges involved are met by the NHS. It is faster acting and of similar effectiveness to SA. However, the costs incurred by the NHS mean that it is not necessarily a cost-effective standard treatment for all warts. The possibility of reducing cryotherapy costs by implementing nurse-led wart clinics is appealing, and this may prove a cost-effective option for surgeries wishing to provide a cryotherapy service.

Similarly, the scenario whereby OTC SA is tried as a first-line therapy before initiating cryotherapy proved relatively cost-effective (ICER = 1.95 £/% cured). It is possible that a policy of insisting that all patients try an OTC preparation before initiating cryotherapy from the GP would be a useful way to reduce the demand for cryotherapy. In reality, an education campaign would be required to achieve this result, but in time it is possible that those presenting to their GP for treatment would be more appropriately selected.

Cost-effectiveness of OTC preparations

Home treatments for cutaneous warts are generally very cost-effective as they do not involve the additional cost of a GP consultation. Overall, duct tape was the most cost-effective wart treatment, although it is rarely used in the UK at this time. Duct tape owes its favourable cost-effectiveness ratio to its high estimated cure rate and extremely low cost.

OTC cryotherapy may prove to be a cost-effective alternative to cryotherapy administered by the GP. However, the effectiveness of OTC cryotherapy has not yet been demonstrated in any published RCTs. It is possible that the estimates of cure probabilities used in the model are overly optimistic. Using cryotherapy at home requires the patient or carer to apply the probe to the skin for a sufficient length of time to ensure an appropriate freeze temperature. Since this procedure can be painful, it is likely that the freeze will not be completed successfully and the resulting cure probabilities could be substantially lower.

Cost-effectiveness of treatment in secondary care

Cryotherapy in secondary care is a very expensive treatment option. Although referral to secondary care may be appropriate in some circumstances, it is not recommended for most wart patients. As reported in Chapter 3, results of the postal survey of dermatology departments in the Trent Region suggested that the types of treatment offered in secondary care were no different to those provided in primary care. Although it is possible that treatments such as cryotherapy will be delivered more aggressively in a secondary care setting, this is unlikely to change the conclusion that treatment in this way is an expensive option.

Handling of uncertainty

Cure probabilities for each treatment were estimated primarily from the systematic review, allowing for some uncertainty in these estimates. The methods used to estimate these probabilities and the limits on their uncertainty varied and the estimation methods were adapted to make the best use of the data available. In the case of duct tape, the single trial available was used and the resulting confidence interval for the proportion cured was large. In the absence of any further data with regard to this treatment, this estimation method is the logical choice.

In the case of well-reported data, such as cryotherapy and SA, a weighted mean was used as the main estimate of effectiveness together with an interquartile range to reflect the uncertainty of this effectiveness estimate. It was anticipated that the cost-effectiveness estimates would be relatively insensitive to change, so it was important to ensure that the effectiveness intervals were sufficiently wide. The estimates of SA and cryotherapy cure rates were compared with those reported in the postal survey of patients treated in primary care. The weighted mean estimates and

interquartile range limits of the cure probabilities were similar to the postal survey data rates and, despite the small differences between these two sources, estimates from either source would lead to similar conclusions with regard to the order of cost-effectiveness.

The cost data were also estimated from various sources. Pharmacist estimates and Personal Social Services Research Unit (PSSRU) data were used, together with estimates taken from prices advertised by chemists and hardware stores. In most cases, the most influential costs were those estimated by the PSSRU, since so much of the treatment cost was attributable to patient travel, GP consultation and medical procedures. As a result, although the costs estimated from chemists and other stores were subject to wide variability, this variability is unlikely to alter the choice of cost-effective treatment. However, the precise ICERs attached to treatments may be altered slightly by variations in supplier cost.

Caveats

As with any model of this kind, the validity of the conclusions drawn from it depends on the nature of the underlying assumptions used. While every effort has been made to reflect actual practice, it is possible that some assumptions may have had a significant impact on the conclusions drawn. For example, the frequency of cryotherapy sessions is something that varies greatly from surgery to surgery. If cryotherapy sessions were held at intervals of greater than 2 weeks, then the ICER would be correspondingly increased and cryotherapy would appear less favourable as a treatment option. Similarly, cure rates for OTC cryotherapy have been based on published cure rates for Histofreezer when used by a GP or nurse. It is quite likely that cure probabilities will be lower when the product is used as a home treatment, but there are currently no data available to inform this scenario.

The cost-effectiveness of multiple treatments may have been overestimated, as it was assumed that warts that resist one treatment do not resist another. This may not be the case, although there is little more than anecdote to inform this belief.

Nevertheless, sensitivity analysis would suggest that conclusions drawn from the model are relatively robust and large differences in the cure probabilities would be required to change the ordering of the various treatment options.

Summary of main conclusions from the economic model

A summary of the main conclusions arising from the model is presented in *Table 32*.

TABLE 32 *Summary of main conclusions from the economic model*

OTC treatments	Represent a very cost-effective means of treating warts/verrucae Largely because a consultation with the GP is avoided Cure probabilities for all except for SA are based on very limited data Costs are met entirely by the patient
Treatment provided in primary care	SA represents a cost-effective treatment option in this setting With less certainty, it is possible that nurse-led cryotherapy clinics may provide a cost-effective alternative The recommendation to try OTC SA before attending the GP for cryotherapy may also prove cost-effective
Treatments provided in secondary care	Treatment in secondary care is rarely warranted and not a cost-effective treatment option

Chapter 5

Summary and conclusion

Summary of findings

This research brought together a wide variety of data types and sources to inform an economic decision model. The results of the model suggest that the routine use of cryotherapy for the treatment of warts in primary care may not be justified on the grounds of cost-effectiveness. Despite widespread belief in the efficacy of cryotherapy, among both patients and physicians, the evidence base to support this stance is relatively poor. What evidence that does exist would suggest that cryotherapy and SA are of broadly comparable efficacy, although it is possible that cryotherapy may be able to deliver these outcomes more quickly. Nevertheless, the faster response to treatment and marginally higher cure probabilities are not sufficient to make cryotherapy a cost-effective treatment option. Despite this, patients express a preference for cryotherapy and this probably reflects the improved speed of response and the fact that the majority of the costs are borne by the NHS.

The most cost-effective treatments considered in the model are those that are bought by patients (the OTC products) and applied in the patients' homes (OTS SA, OTC cryotherapy and duct tape). This is not surprising, since the treatments do not require a costly initial consultation with the GP and are assumed (even with patients' time factored in) to be of comparable efficacy to similar prescribed treatments.

Of the treatments prescribed by GPs, the two most cost-effective options proved to be SA and cryotherapy delivered by a nurse. Although these two options had surprisingly similar ICERs (2.20 and 2.09 £/% cured, respectively), this is based on very clear assumptions for the delivery of cryotherapy; namely, no more than three sessions, held at 2-weekly intervals. Any change to this optimum pattern of delivery would reduce the cost-effectiveness of this option compared with SA. Nevertheless, results from the postal survey suggested that the majority of patients treated in primary care currently receive cryotherapy from their GP. The possibility of extending the availability of nurse-led cryotherapy clinics is something that warrants further attention.

Given the minor nature of most cutaneous warts, coupled with the fact that the majority spontaneously resolve in time, it is tempting to conclude that a shift towards self-treatment is warranted. To achieve a shift in service delivery and to reduce patient demand for costly cryotherapy services, a public awareness campaign is required to educate patients about the self-limiting nature of warts, and the possible OTC treatment options available. Costs of OTC treatments, although small, may still be a barrier to self-treatment, especially among low-income groups, and this needs further consideration.

Limitations of the research

These results are based on the best available evidence at this time. As concluded in the Cochrane systematic review, the evidence base for the treatment of warts is currently limited, and this is particularly so for treatments such as OTC cryotherapy (no RCT data available) and duct tape (one small RCT). Nevertheless, sensitivity analysis suggested that the conclusions were relatively robust and large differences in the cure probabilities would be required to change these conclusions substantially.

As with any study of this kind, various assumptions have been made to populate the model. It is possible that the assumptions used have tended to favour cryotherapy rather than other treatments. However, if these assumptions were shown to be overly optimistic, this would simply serve to strengthen the belief that cryotherapy represents the least cost-effective treatment option available.

It was not considered practical to undertake an EVPI calculation as this would have required a much greater level of sophisticated utility/QALY data than currently available in regard to the different wart treatments available. Given the scale of the project, this course of action was deemed the most practical way forward. In the event, the results of the model raised sufficient new results to inform the design of future clinical trials substantially.

Finally, the new GP contract was introduced towards the end of the data collection period for this study. Since GPs will no longer receive additional payments for minor surgery involving cryotherapy of warts, it is possible that this may influence the way in which practices choose to deliver cryotherapy in the future.

Recommendations for future research

This research was commissioned by the NHS HTA Programme to explore the need for further research into the most cost-effective treatments for cutaneous warts. As a result of this model, several recommendations can be made.

RCT of cryotherapy versus SA

The initial question posed by the research brief was to assess whether or not a trial of cryotherapy versus SA was justified. It is possible that a head-to-head trial of SA versus cryotherapy is still warranted, but it is unlikely to show cryotherapy, as presently delivered, to be more cost-effective than other treatment options. The evidence base used to estimate cure probabilities for these two treatments is currently limited, of poor quality and based on out-of-date treatment practice. However, for a therapy as ingrained as cryotherapy, it is possible that nothing other than a full-scale RCT will be sufficient to change current practice. This belief was supported by findings from the focus group discussions and structured interviews, which highlighted the need for further evidence before initiating any change in practice.

However, cryotherapy may be a cost-effective treatment option if delivered through dedicated wart clinics run by practice nurses. This provides an ideal opportunity to investigate further the likely cost-effectiveness of SA and cryotherapy when delivered in this way.

Preliminary data for home treatments

There are currently no trials of DMEP in its OTC form, and only one RCT of duct tape. Before these products can realistically be included in a large-scale RCT, it is advisable that some preliminary data be collected to inform the design of the trial. A case series of patients using the products would be useful in determining the acceptability to patients, and the likely difficulties experienced when using the treatment at different sites and in different age groups. Through this process, patient-friendly guidelines could be developed that describe how best to apply these preparations in the community.

RCT of home treatments (OTC SA, duct tape and OTC cryotherapy)

The clear implication from the economic model was that a shift towards increased use of OTC preparations and away from treatment in primary care was the most cost-effective option. Since there is evidence to suggest that OTC treatments may be as effective as those available from the GP, this provides an opportunity to reduce the burden on the NHS without compromising treatment success.

SA could reasonably be included as a 'standard care' arm in a trial of home-based wart treatments involving the less well-researched, but potentially cost-effective treatment options of duct tape and OTC cryotherapy. These treatment options have been poorly researched to date. Nevertheless, if the assumptions used in the economic model are correct, these treatments may reflect cost-effective alternatives to traditional cryotherapy. For example, the model suggests that duct tape is possibly the most cost-effective treatment of those considered. However, the estimates used for the cure probabilities of duct tape are based on a single trial involving 48 participants. These findings now need to be confirmed in a large RCT.

A three-arm trial comparing OTC SA, duct tape and OTC cryotherapy would provide a greater understanding of the efficacy of these home treatments. This would give doctors a wider choice of treatment options, and may help to reduce the overall demand for cryotherapy. However, given the limited knowledge of how best to apply these OTC treatments, further work is required to assess best practice for their use, before inclusion in a clinical trial. For treatment using OTC cryotherapy, which relies on the patient paring the wart and freezing the skin to a point that could be painful, it is unlikely that optimal usage will be achieved with ease. This has important implications for future use and cost-effectiveness.

Recommended trial design

Future trials of SA and cryotherapy should ideally be pragmatic in nature as these are well-established technologies that are currently in wide-scale use. Trials should be run in the community, as this is where the majority of patients with warts are now treated, and should be of sufficient duration to capture treatment response (12–18 weeks), with planned follow-up at 1 and 2 years (to capture long-term recurrence rates). Inclusion criteria should be kept reasonably broad

to inform subgroup analyses and sample size estimates should be sufficiently large to allow for this. Important response predictors could include factors such as the location of the wart (hands versus feet) or the type of wart (mosaic versus common warts). It is preferable to use patient as the unit of analysis rather than wart since it makes the analysis and clinical interpretation much simpler. If patients have multiple warts then these warts are not independent and a more complicated analysis such as hierarchical modelling would be necessary to adjust for this. If the patient is taken as the unit of analysis, then patients with multiple warts could have a single wart randomly chosen for inclusion in the study. Useful outcomes might include measures of treatment success (wart gone), side-effects, patient compliance, acceptability to patients and cost-effectiveness. Given the importance of speed of response in determining cost-effectiveness and patient preference, it may be advisable to include time to cure as a key outcome.

In relation to treatment delivery, previous trials have been reasonably uniform in this respect. Most used approximately 20-second freezes, delivered until a halo had formed around the wart. The present study identified 2-week intervals as the optimum fast cryotherapy treatment time. Paring may improve the treatment, so should also be performed, and liquid nitrogen with a cotton bud is cheapest and should be administered by a nurse to be cost-effective. Trials also show that SA is most effective over 12 weeks of daily treatment including filing of the wart, and that effectiveness is greatest towards the end of the 12 weeks. These methods are reasonably well established as the optimum delivery methods. Paring and filing of warts may have little additional benefit, but they do not adversely affect cure rates.

One recommendation to arise from this research is the possibility of delaying cryotherapy treatment, or of insisting that patients try cheaper alternatives, such as SA for a period before cryotherapy treatment. This could be usefully incorporated into a trial design either by including a delayed treatment arm or by rerandomising treatment failures at the end of the initial treatment phase.

A useful adjunct to a trial could be the inclusion of a comprehensive willingness-to-pay study to determine whether there is sufficient perceived utility in self-administered treatments to make the likelihood of their take-up realistic.

Sample size calculations for both of the suggested RCTs are summarised in *Table 33*. It has not been possible to perform sample size calculations based on an important difference in ICERs as the necessary QALY data required to inform this calculation are unavailable. Sample size calculations are therefore based on estimated cure rates and the ability to detect a minimum difference in cure rates of between 5 and 20%. In each case, a power of 80% and a significance level (α) = 0.05 have been assumed.

For an RCT of nurse-led cryotherapy versus SA in primary care (two-arm trial), a total sample size of 872 (allowing for a dropout rate of 10%) would be required to detect a 10% difference in cure rates in either direction. This calculation assumes that the cure rate of nurse-led cryotherapy is the same as GP-led cryotherapy; that is, 54%.

TABLE 33 *Sample size calculation for future RCTs: sample size based on detecting a difference in cure rates ranging from 5 to 20%, assuming that cryotherapy has a higher cure rate of 54%*

	Effect size			
	5% difference	**10% difference**	**15% difference**	**20% difference**
Cure rate for cryotherapy	54%	54%	54%	54%
Cure rate for alternative treatment group(s)	49%	44%	39%	34%
Sample size per group	1568	392	173	96
Total sample size (two arms)	3136	784	346	192
Total sample size allowing for 10% dropout rate (two arms)	**3486**	**872**	**386**	**214**
Total sample size (three arms)	4704	1176	519	288
Total sample size allowing for 10% dropout rate (three arms)	**5229**	**1308**	**579**	**320**

For an RCT of home treatments (three-arm trial: OTC SA, duct tape and OTC cryotherapy), a total sample size of 1308 (allowing for a dropout rate of 10%) would be required to detect a 10% difference in cure rates in either direction. This calculation assumes that the cure rate of OTC cryotherapy is the same as GP-led cryotherapy; that is, 54%. Since the cure rates used in the economic model suggest that the SA and cryotherapy cure rates are similar, but that the cure rate for duct tape is considerably higher (at least 67%), this calculation is based on the detection of a minimum difference between treatment cure rates of 10%. Such a study would have sufficient power to detect larger differences in cure rates where relevant.

The authors suggest the number of subgroup analyses to be performed should be one or at most two, since the adjustment for several subgroup analyses is likely to result in a considerably larger study. Although there are no well-recognised ways of adjusting sample size calculations for subgroup analyses, a recent HTA monograph[35] states that the extent to which a sample size should be inflated to allow for subgroup analyses depends on the magnitude of the interaction (between treatment group and subgroups) in relation to the magnitude of the overall effect. Inflation factors range from 2 when the magnitude of the interaction is 1.5 times that of the overall effect to 4 when the magnitude of the interaction is equal to that of the overall effect.

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Contribution of authors

KS Thomas (Chief Investigator for the project) contributed to the intellectual development of the study, attended regular study meetings, helped to draft the final report and coordinated responses to referees' comments. MR Keogh-Brown (Research Associate) designed and built the decision model, analysed model results, performed data analysis, organised and attended study meetings, and helped to draft the final report. JR Chalmers (Research Associate) organised and attended study meetings, undertook primary data collection and analysis, and helped to draft the final report. RJ Fordham (Senior Lecturer in Health Economics) contributed to the grant application, designed the economic model, commented on the draft report until completion, and led on economic results and analysis. RC Holland (Senior Lecturer in Public Health Medicine) contributed to the grant application, attended regular study meetings, and provided interpretation and comments on the final report. SJ Armstrong (Study Statistician) contributed to the grant application, attended regular study meetings and provided advice on statistical aspects of the study and commented on the final report. MO Bachmann (Professor of Health Care Interfaces) contributed to the design of the decision analysis model, attended study meetings and commented on the final report. AH Howe (Professor of Primary Care) gave advice regarding primary care aspects of the study, including data collection and governance. S Rodgers (Research Fellow) contributed to the study design and grant application, and provided advice on primary care aspects of the study. AJ Avery (Professor of Primary Care) contributed to the grant application, attended steering group meetings providing advice on primary care aspects of the study and commented on the final report. I Harvey (Professor of Epidemiology and Public Health), grant co-applicant, contributed to design and methods, was a member of the project management group and commented on the final report. HC Williams (Professor of Dermato-Epidemiology) contributed to the grant application, attended study meetings, and contributed to the study design, execution, interpretation and final report.

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Appendix 1

Observation of practice

Patient initials:

Gender: M/F

DOB/Age:

New/FU:

Time arrived in reception:

Time of consultation – Start:

Finish:

Time spent in discussion with patient:

Time spent treating:

Observations of treatment:

Questions:

Have you had to have time off work to come here?:

Notes:

Appendix 2

Patient questionnaire

Survey – Warts and Verrucas in the Community

- **We are doing a study of commonly used wart and verruca treatments.**
- **We would be very grateful if you could complete this questionnaire so we can find out what treatments you have tried and if they worked for you. It shouldn't take you more than 7 or 8 minutes to fill it in.**
- **We are asking you to fill in this questionnaire because you have been to your GP surgery about warts/verrucas in the last 9 months.**
- **Please think about these warts/verrucas when you are answering the questions, rather than any previous warts/verrucas you may have had.**
- **It doesn't matter if your warts/verrucas have all gone, we would still like you to fill in the questionnaire**
- **Please return this questionnaire in the pre-paid envelope provided.**

ID number: _____ ***(for office use only)***

If you have any comments or questions about this survey, please contact:

Joanne Chalmers
Centre of Evidence-based Dermatology
Ward C51, South Block
Queen's Medical Centre
Nottingham
NG7 2UH

Tel: 0115 924 9924 ext 43250
Email: jo.chalmers@nottingham.ac.uk

A couple of questions about yourself

1. Age: _____

2. Sex: _____ (M/F)

When you are answering the following questions, please think about the warts/verrucas you have visited your GP surgery about in the last 9 months.

3. Before you went to the surgery about your warts/verrucas, what did you do?
(tick as many of these that apply to you):

Nothing, I waited for a while to see if they would just go away by themselves	☐	
I tried one type of wart paint	☐	How many packets ? _____
I tried more than one type of wart paint	☐	How many packets in total? _____
I tried filing down the wart/verruca	☐	
I tried wart plasters	☐	How many packs? _____
I tried a homeopathic remedy	☐	Which one? _____
I tried Wartner (DIY freezing)	☐	
I tried Gaffa/duct tape	☐	
I went straight away to see the Doctor/Nurse about it before trying any treatments	☐	
Other	☐	please describe _____ _____

4. How long did you have these warts/verrucas before you went to your surgery?
_____ months

5. What made you decide to go to your surgery about your warts/verrucas?
_____
_____

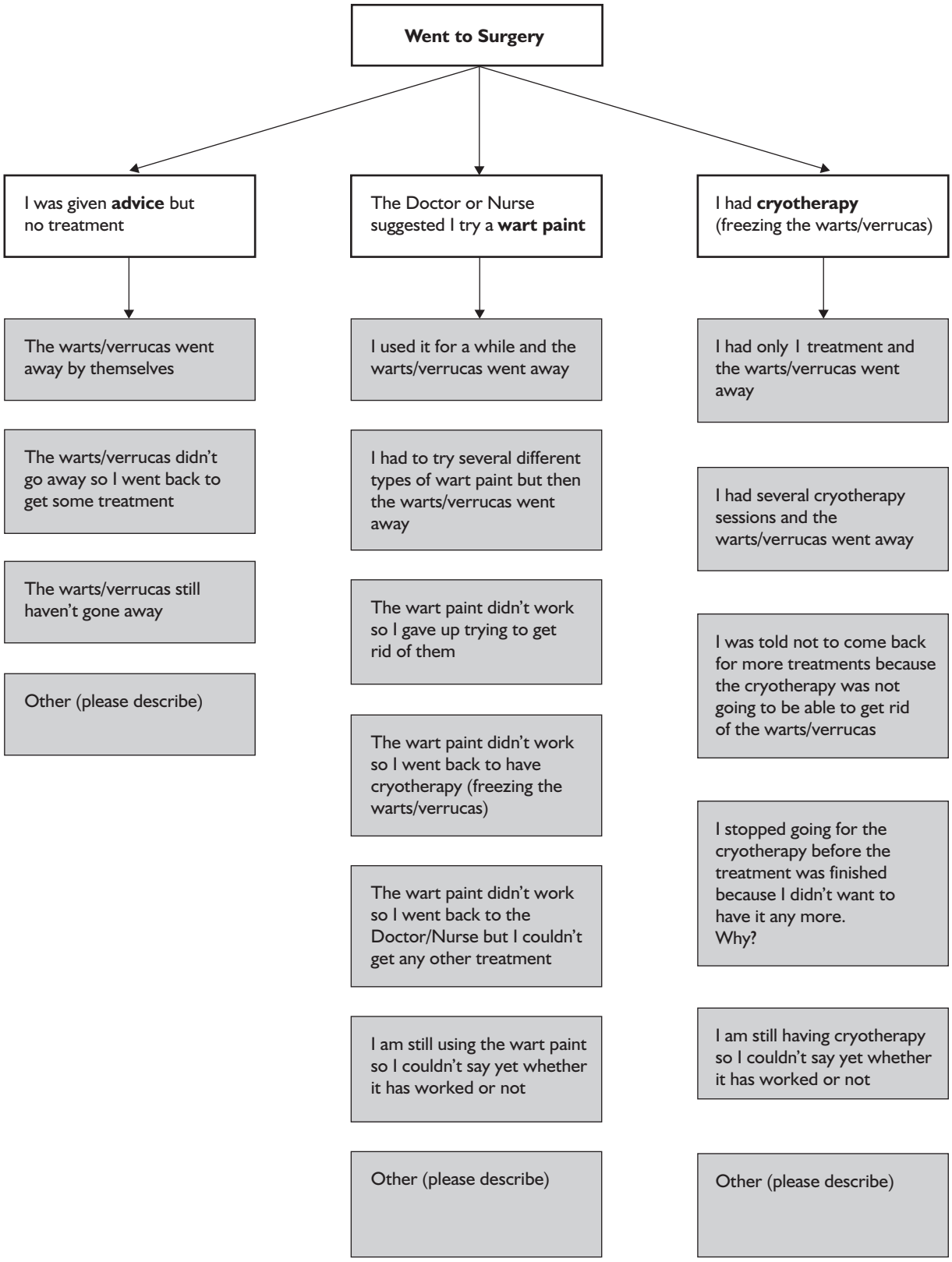
6. When you decided to go to the surgery about your warts/verrucas, did you :
☐ make a special appointment
or
☐ mention it in passing when you were there about another matter?

7. a) How many warts/verrucas did you have when you first went to the surgery:
   - On your hands _____
   - On your feet _____
   - On other parts of your body _____

   b) How many warts/verrucas were you seeking treatment for?
   _____

8. How long did you have your warts/verrucas for before you got treatment for them from your GP surgery (please tick one box)?
_____ months
OR
☐ Not applicable, I didn't get any treatment for them

9. We would like to know what treatments you had from your surgery and if they worked.
   Please put a circle round the grey box which best describes what happened to you. If more than one description applies to you, please circle as many grey boxes as you need to in any of the columns.



10. Have you used **wart paints** on this recent episode of warts/verrucas?

YES ☐ please answer the questions below (questions 11–13).

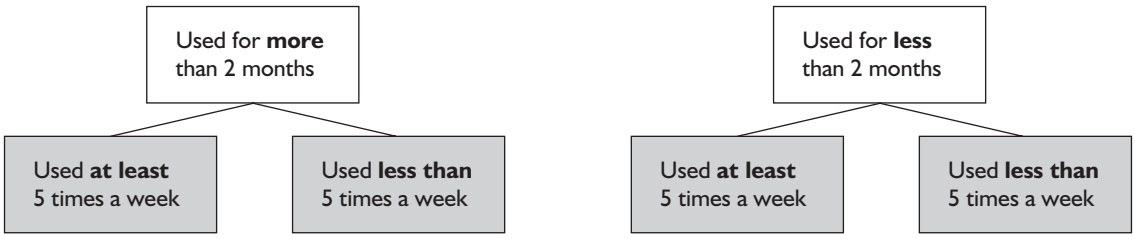
NO ☐ please leave the questions 11–13 below blank and go to question 14.

11. When you used the wart paints, did you experience any of the following problems?

☐ burning sensation ☐ blistering ☐ pain ☐ scarring ☐ bleeding

☐ other. What was it? _____

12. Please circle the grey box which best describes how you used the wart paint:



13. Did you get wart paint because it was recommended by the nurse or doctor when you went to the surgery?

☐ NO
☐ YES, if yes, did you get it:
☐ on prescription? or ☐ from the chemist?

If yes

How many prescriptions were you given? _____

Did you pay for these prescriptions? YES/NO

If yes

How many packets did you buy?

_____

14. Have you had **cryotherapy** (freezing) on this recent episode of warts/verrucas?

YES ☐ please answer the questions below (questions 15–19).

NO ☐ please leave the questions 15–19 below blank and go to question 20.

15. Did you experience any of the following problems?

☐ burning sensation ☐ blistering ☐ pain ☐ scarring ☐ bleeding

☐ other. What was it? _____

16. Who performed the treatment? (please circle)

Doctor/Nurse/Chiropodist/Other

17. a) Did you take time off work to go to the surgery? YES/NO/Not Applicable (please circle one)

    b) Did you take time off school to go to the surgery? YES/NO/Not Applicable (please circle one)

If you have ***finished*** your cryotherapy treatment:

18. How many times did you have the cryotherapy treatment? _____

19. How long did the treatment last for? _____ (weeks)

Thinking about the warts that you had when you went to the surgery about them, which of these statements describes you best?

- ☐ The warts/verrucae have now gone
- ☐ Some warts/verrucae have gone, but others remain
- ☐ The warts/verrucae cleared but the same ones have now come back
- ☐ The warts/verrucae cleared, but new ones have now appeared
- ☐ The warts/verrucae did not respond to treatment at all

20. What would be your **MAIN** reason for choosing a treatment?
    *(Please tick **one** choice only)*

- ☐ Able to treat myself at home.
- ☐ Warts/verrucas removed quickly.
- ☐ No need to take time off work/school.
- ☐ Don't like messy treatments.
- ☐ Would rather a professional person treated the warts/verrucas.
- ☐ Tried wart paint already and it didn't work.
- ☐ Other (please explain) _____

_____

21. Did you get referred to hospital for your warts/verrucas?

YES/NO (please circle)

22. All the questions so far have been about your recent warts and verrucas, but now please tell us below if you have had warts/verrucas before this:

YES/NO (please circle)

If YES:

a) How many times _____ ?

b) Did you use any of the following treatments?

- ☐ wart paints
- ☐ cryotherapy
- ☐ other

23. These last questions are about the **cost** of wart/verruca treatments.

Please read the descriptions below of 2 common treatments for warts/verrucas:

Wart paint	**Cryotherapy (freezing)**
You can get this either on prescription or from the chemist	You need to go to your GP surgery to have this treatment
Every day you file away the dead skin, apply the paint and cover it with a plaster. You do this at home	You have the wart/verruca frozen for a few seconds with liquid nitrogen
You need to use the treatment every day for two to three months	Sometimes gets rid of the wart/verrucae after one application but you might need up to 5 applications, once every few weeks
Can be messy and it can cause skin irritation	You would need to go back to the GP surgery for each treatment
No serious side-effects	Can cause some pain and/or blistering around wart/verruca for a while after you have had the treatment

Tests have shown that there is not much difference between the ability of wart paint and cryotherapy to successfully treat warts on the hand.
However, they have shown that cryotherapy may be slightly better than wart paint for treating warts/verrucas on the feet.

Now you have read these descriptions, please answer questions A, B, C and D.

Question A
If you were offered wart paint **OR** cryotherapy for the treatment of your warts/verrucas, would you prefer:

- ☐ Wart paint over cryotherapy (then go to **question B**)
- ☐ Cryotherapy over wart paint (then go to **question C**)
- ☐ No preference

Question B
If cryotherapy was the ONLY wart/verruca treatment available **FREE** on the NHS, how much would you be willing to pay for a course of wart paint?

£ _____ (write 0 if you would be **unwilling to pay** and go to **question D**)

Question C
If wart paint was the ONLY wart/verruca treatment available **FREE** on the NHS, how much would you be willing to pay for a course of cryotherapy?

£ _____ (write 0 if you would be **unwilling to pay** and go to **question D**)

Question D *(Only complete if you have entered £0 for question B or C)*

Please state why you would be unwilling to pay for your preferred treatment:

- ☐ I cannot afford to pay for wart/verruca treatment
- ☐ Wart/verruca treatment should be freely available on the NHS
- ☐ Because wart/verruca treatments don't work very well
- ☐ Other, please specify _____

In the future, we may wish to run a study that compares wart paint with cryotherapy (freezing of the wart). It would be helpful to have a rough idea of how many people might be prepared to help with such a study.

Would you consider helping with a study like this?

☐ Yes ☐ No ☐ Yes, but I no longer have warts

Thank you very much for taking the time to complete this questionnaire.

Your answers will help us decide if it is worthwhile doing a large clinical trial comparing different wart treatments.

Appendix 3

Cure rates for cryotherapy

TABLE 34 *Cryotherapy: cure rates for different sites*

Site	Number	Known cryotherapy cure	Known cryotherapy fail	Unknown cure	CI for known cures (%)
Hands only	31	11	16	4	24.5 to 59.3
Feet only	31	10	12	9	26.9 to 65.3
Other only	26	19	7	0	53.9 to 86.3
Hands and feet	19	8	10	1	24.6 to 66.3
Hands and other	11	2	8	1	5.7 to 51.0
Feet and other	4	3	1	0	30.1 to 95.4
Hands and feet and other	1	0	1	0	0 to 79.3
Missing	2	2	0	0	34.2 to 1
Total	125	55	55	15	40.8 to 59.1

'Unknown cure' for cryotherapy are those who had not finished treatment at the time of the postal survey or who were cured by more than one treatment (including cryotherapy), but the order in which they received treatment is unknown. It is therefore possible that any number of these patients have been, or will be, cured by cryotherapy.

Appendix 4

Cure rates for salicylic acid

TABLE 35 *SA: cure rates for different sites*

Site	Number	Known SA cure	Known SA fail	Unknown cure	CI for known outcomes (%)
Hands only	33	9	21	3	16.7 to 48.9
Feet only	57	31	18	8	49.3 to 75.3
Other only	10	3	5	2	13.7 to 69.4
Hands and feet	15	3	12	0	3 to 56.4
Hands and other	7	1	5	1	
Feet and other	0	0	0	0	
Hands and feet and other	2	0	2	0	
Missing	1	1	0	0	20.7 to 1
Total	125	48	63	14	34.4 to 52.5

'Unknown cure' for SA are those patients whose treatment was not finished at the time of the postal survey. It is therefore possible that any number of these will be cured.

Appendix 5

Effectiveness of cryotherapy

TABLE 36 *Cryotherapy: effectiveness*

Description of cryotherapy treatment received	Interpretation of this treatment	No. of patients	No. of cures
Cryotherapy failed, patient asked not to return	Cryotherapy fail	7	0
Patients whose warts were not cured, but gave up on treatment	Cryotherapy fail	16	0
Still receiving treatment	Unknown result, could be cure or fail	10	Between 0 and 10
Received cryotherapy and no other intervention	Result of treatment can be attributed to cryotherapy	67	44
Advice, then SA then cryotherapy	Result of treatment can be attributed to cryotherapy	2	2
Advice, SA and cryotherapy (order unknown)	Unknown result, could be cure or fail	4	Between 0 and 2
SA then cryotherapy	Result of treatment can be attributed to cryotherapy	10	8
SA and cryotherapy (order unknown)	Unknown result, could be cure or fail	7	Between 0 and 3
Advice then cryotherapy	Result of treatment can be attributed to cryotherapy	1	1
Advice and cryotherapy (order unknown)	Unknown result, could be cure or fail	1	0
Total		125	Between 55 (44%) and 70 (56%)

The table excludes those who self-treated with SA at home before visiting their GP, since all respondents were recruited from GP surgeries; therefore, only self-treating patients whose treatment failed would be considered. Therefore, including those who had self-treated with SA at home but received a different treatment from the GP, would bias the SA cure rate.

Appendix 6

Secondary care questionnaire

Centre of Dermatology Evidence Based

ID number: D

Treatment of Cutaneous Warts in Secondary Care

We have been commissioned by the NHS Health Technology Assessment Programme to create an economic model looking at the most cost-effective way of treating patients with cutaneous warts. As part of this study we are hoping to assess how many patients are treated in a secondary care setting and the treatment options most commonly used.

If you could spare **2 minutes** to answer the following questions, we would be very grateful.

All data collected will be anonymous. Please do not enter your name anywhere on this questionnaire.

1. **How big is your department?**
   Number of Consultants: _____
   Number of Specialist Registrars: _____

2. **Approximately, what is the catchment size for your hospital?** _____

3. **Approximately, how many patients are referred to your department for the treatment of cutaneous (non-genital) warts?**

   _____ per month

4. **Is it your department's policy to actively encourage your local GPs to treat cutaneous warts in the community?**

   Yes ☐
   No ☐
   Don't know ☐

5. **What treatments do you offer?** (Tick 2 max) **Preferred options**

   None (refer back to primary care) ☐
   Salicylic acid (or other topical keratolytic) ☐
   Cryotherapy ☐
   Excision/cautery ☐
   5-Fluorouracil ☐
   Dinitrochlorobenzene (DNCB) ☐
   Photodynamic therapy (PDT) ☐
   Imiquimod ☐
   Other ☐ Please state _____

6. **Who normally performs the treatment?**
   - Consultant ☐
   - Specialist Registrar ☐
   - SHO ☐
   - Dermatology Nurse ☐
   - Other ☐ who _____

7. **If you use cryotherapy, what do you use to freeze the warts (e.g. liquid nitrogen, dimethyl ether propane)**
   - Liquid nitrogen ☐
   - Dimethyl Ether Propane (Histofreezer) ☐
   - Other ☐ please state _____

8. **Do you have a regular clinic for treating warts patients?**
   - Yes ☐
   - No ☐

9. **If yes, how frequently do you run the sessions?** _____

10. **Do you keep a waiting list of patients for these wart clinics?**
    - Yes ☐
    - No ☐

Thank you very much for completing this questionnaire.

Please return the completed questionnaire in the pre-paid envelope enclosed to:

Dr Joanne Chalmers
Centre of Evidence Based Dermatology
Ward C51, South Block
Queen's Medical Centre
Nottingham
NG7 2BR

Tel: 0115 9249924 ext 43250

Appendix 7

Treatment arm diagram

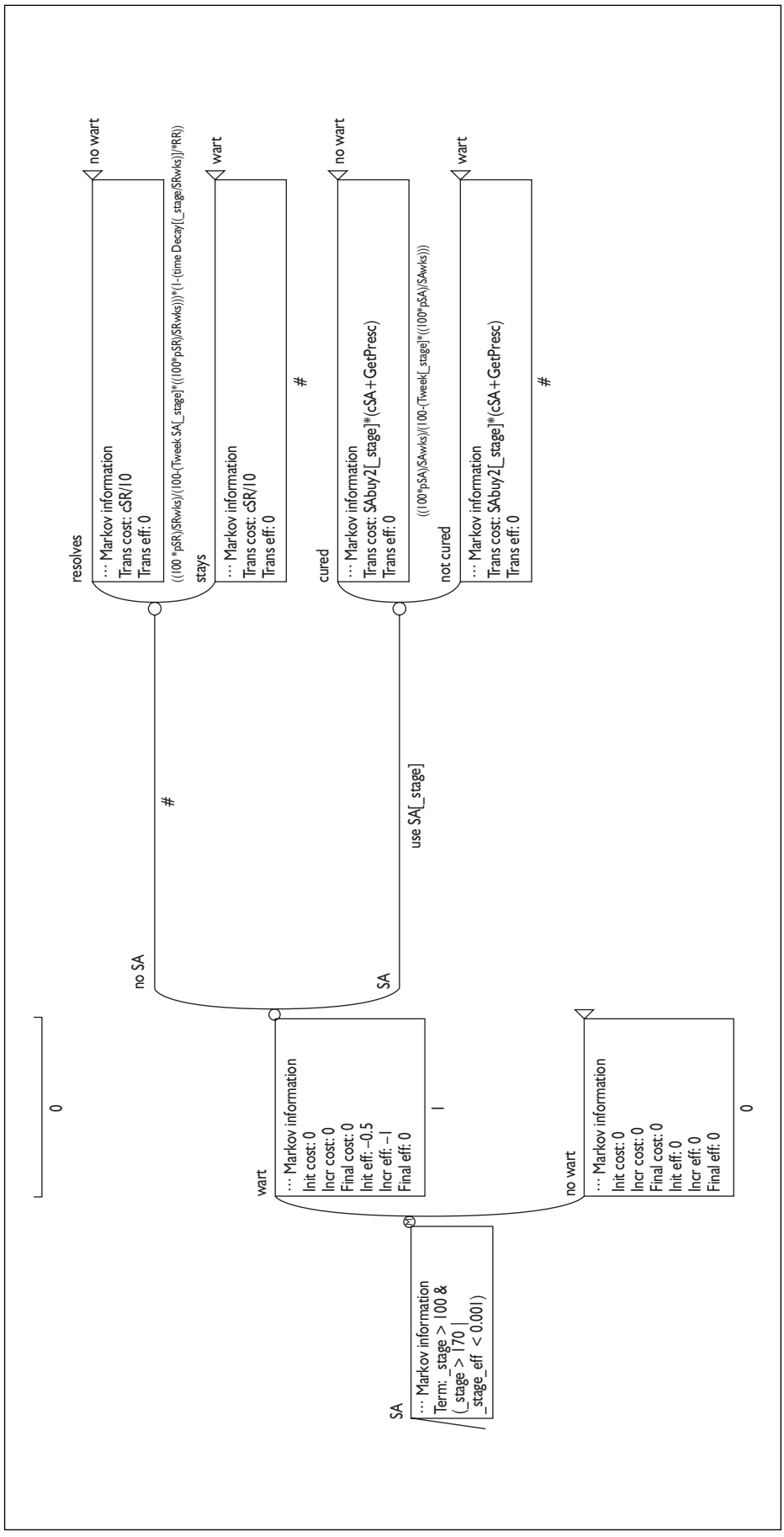


FIGURE 17 *Single treatment arm from decision tree*

Appendix 8
Assumptions

To implement treatments of warts as a decision-analytic model it is necessary to make certain assumptions about wart treatment to enable the transition from practice to model. Some of the main simplifying assumptions are listed below, with justification.

Assumption 1: Cycles are defined as 1-week periods
Cure rates in the Cochrane review are usually given at 4, 6, 8, 10 or 12 weeks, therefore a common multiple of these periods was required. Since cure rates over a 12-week period may not be easily generalisable to daily cure rates, it seemed reasonable to select either 1- or 2-week periods as the cycles, and the authors selected 1-week intervals.

Assumption 2: The model is terminated after a 2-year simulation
From Bridger and Banatvala,[8] it was known that most warts/verrucae resolve naturally within 2 years, so it was assumed that 30% of patients resolve every 10 weeks which, in the model, results in most warts being cured within 2 years, thus reflecting practice; those warts that remain after 2 years may be considered resistant and have been known to remain for 10 years. Since the authors are not aware of any research on the resolution of warts beyond 2 years, it seemed reasonable to cease the model rather than guess the behaviour.

Assumption 3: Spontaneous resolution occurs at a rate of 30% every 10 weeks
This figure for spontaneous resolution corresponds to the placebo treatment cure rates considered in the Cochrane review. The trials from which these placebo cure rates were taken in general did not exclude patients according to the duration of their warts. It is therefore reasonable to assume that the warts used in these trials were of various duration and therefore it was concluded that, regardless of the length of time for which a wart has existed (although less than 2 years), the probability of spontaneous resolution in any 10-week period is approximately 30%.

Assumption 4: After treatment, uncured warts are left to resolve spontaneously
Since many of the patients included in the RCTs involving placebo treatment in the Cochrane review may have received previous treatment for warts, a resolution rate of 30% may be assumed for warts that have received previous treatment. It would be reasonable to argue that warts that fail to respond to treatment are likely to be more resistant in the future; however, in the absence of any research to suggest a resolution rate post-treatment, the spontaneous resolution rate is reported in PCTs and is the most natural one to assume.

Assumption 5: For all treatments, cures occur at an equal number each week over the treatment period
Since 1-week cycles were assumed for the model, some assumptions are needed with regard to the spread of cures during the treatment period. However, there are few data available with regard to the spread of cure rates for other treatments. Trials such as Bunney[18] considered the cure rates of cryotherapy which, for 2-weekly treatment, suggested a fairly even cure rate, although cures were slightly higher for the first few weeks of treatment. In the absence of any concrete data to the contrary, it was assumed that an equal number of patients will resolve for each week of the treatment period.

Assumption 6: Treatment duration for SA is 12 weeks
This assumption is in agreement with the majority of the SA trials in the Cochrane review. Trial data are available for shorter periods, but there is some evidence to suggest that SA cures are slower in the early weeks; therefore, the most popular treatment period of 12 weeks is the most suitable choice for the estimated cure rate.

Assumption 7: Treatment duration for cryotherapy is 2 weeks per session (average three sessions per treatment)
Cure durations for cryotherapy vary according to the time elapsed between cryotherapy sessions. However, papers comparing treatment durations for cryotherapy, such as Bunney,[18] suggest that 2-weekly cryotherapy provides the most even cure rate, which is in agreement with assumption 5. Therefore, standard cryotherapy treatment in the model is assumed to be 6 weeks: treatment at weeks 0, 2 and 4 with resolution by 6 weeks.

Assumption 8: Treatment duration for duct tape is 8 weeks
This assumption comes directly from the only RCT trial data known with regard to duct tape treatment, by Focht.[20]

Assumption 9: Treatment duration for Wartner is 6 weeks
From the three trials referenced with regard to DMEP treatment, there is some evidence to suggest that DMEP treatment effectiveness is similar to that of cryotherapy. For this reason an equal treatment period was also assumed.

Assumption 10: Costs of treatment are applied at the beginning of each treatment course or session
This assumption is explained in Chapter 4 in the section 'Modelling costs'. It is reasonable to assume that a patient will purchase either the package or roll of treatment shortly before making the first application; it is also reasonable to introduce the cost of each cryotherapy session at the time when the session is provided.

Assumption 11: Costs of treatment are charged in indivisible fixed cost units (containers of treatment, rolls of tape or sessions of cryotherapy)
This assumption is also explained in Chapter 4. Since a patient cannot pay for part of a package of treatment or part of a cryotherapy session, costs are assumed to be indivisible units.

Assumption 12: Cured/resolved patients are removed from treatment/resolution arms at the end of the week (cycle) in which the wart has disappeared (i.e. do not necessarily complete the treatment course)
Since assumptions 5 and 6 allow patients to be cured/resolved before the treatment course has been fully completed, it is reasonable to assume that cured patients stop applying treatment or attending cryotherapy sessions after they are cured. This allows time taken for treatment cure to be calculated and reflects practice.

Assumption 13: In the case of multiple treatments, the cure probability of a particular treatment is unchanged when it appears as a second-line treatment
This assumption is made in the absence of any data from which to estimate cure rates of second-line treatments. The postal survey suggests that the cure rates are similar to those estimated from the Cochrane review, and many of these patients self-treated at home before visiting their GP. It is therefore reasonable to assume that second-line treatments are similarly effective to first-line ones, and there is an absence of data from which to estimate second-line treatment cure differences.

Appendix 9

TreeAge

Introduction of treatment costs

The model uses different methods to introduce the costs of treatment according to treatment type and whether treatment is first or second line. In the case of duct tape and Wartner, a complete container/roll of treatment must be purchased to commence treatment. Therefore, a cost must be in the model as soon as the treatment branch for duct tape or Wartner is reached. This is implemented by assigning the treatment cost to the 'init cost' attribute of the treatment node. Therefore, at cycle 0 of treatment, the charge is made, following which flow passes into the first week of treatment. By this method, a charge is made once at the beginning of treatment, which corresponds to practice.

Although SA requires a similar introduction of cost at the beginning of treatment, allowance is made for the purchase of an additional pack of SA half way through the treatment. Therefore, the introduction of costs for SA is implemented in a different way from that of Wartner and duct tape.

A truncation table called SAbuy2 is used to implement a charge for SA at weeks 0 and 6. An expression of the form *SAbuy*2[*_stage*]∗*cSA* uses the variable '_stage', which represents the number of weeks of treatment elapsed to extract an indicator variable from the table SAbuy2. This indicator is then multiplied by the cost of salicylic acid (cSA) which can include the costs of patient travel to the pharmacist, depending on whether the model is viewed from the perspective of total cost, NHS cost or patient cost. The table SAbuy2 is included below (*Table 37*).

TABLE 37 *Table SAbuy2, used to implement SA charges*

Index	Value
0	1
1	0
2	0
3	0
4	0
5	1
6	0

SA is also considered as a second line treatment in the model. In this case, the cost can be introduced simply by altering the index supplied to the table SAbuy2. Since the first-line treatment (cryotherapy) takes 6 weeks to complete, the expression *SAbuy*2[*_stage* – 6]∗*cSA* can be used to delay the charges for SA by 6 weeks.

Except for the charges introduced via 'init cost', a certain stage needs to be reached before a charge is made. Therefore, if the patient should be cured before they reach a chargeable stage, they will pass to the termination node 'no wart', and the stage incrementation will stop. In this way, patients who are cured will not be charged for further treatment.

The cost of a cryotherapy clinic is to be introduced whenever the patient receives this treatment and no other charge is to be made for weeks where no treatment is received. This is implemented using two tables of the form of *Tables 38* and *39*.

TABLE 38 *cryCharge*

Index	Value
0	1
1	0
2	1
3	0
4	1
Etc.	**Etc.**

TABLE 39 *useCR*

Index	Value
–1	0
0	1
1	1
2	1
3	1
4	1
5	1
6	0

The expression used to calculate the cost is of the form:

cryCharge[*_stage*]∗*CrySingle*∗*useCR*[*_stage* + 1]

The expression *cryCharge*[*_stage*] is used to decide whether the patient needs to pay for treatment during this cycle or not. Since cryotherapy is received up to three times on alternate weeks, this expression will take a value of 1 for even weeks (and week 0) and a value of 0 for odd weeks, indicating that cryotherapy can only be charged for every other week. The expression *useCR*[*_stage*+1] also takes values of 0 and 1 and is used to indicate whether treatment will be received in the next cycle. This takes a value of 1 for all treatment weeks except for the last week, and prevents a charge being made at the end of the last treatment week (i.e. with treatment being provided for 6 weeks, charge should be made on weeks 0, 2 and 4, but not on week 6). Multiplying these two expressions corresponds to an indicator value of 1 for weeks when treatment is received and a value of 0 at other times. This indicator value is then multiplied by the cost of a single cryotherapy session, which is represented by the value *CrySingle*. The table useCR (*Table 39*), is adjusted for the single cryotherapy and double cryotherapy treatment arms: for single cryotherapy all indices 2 and above take a value of 0, and for double cryotherapy all indices 4 and above take value zero. These costs are all introduced to the model using the TreeAge method 'Trans cost' and so are added to previous costs incurred.

Combination treatment costs (SA and cryotherapy together) are introduced simply by simultaneously introducing the costs for each individual treatment; that is, a charge for salicylic acid is introduced at week 0 and cryotherapy charges are introduced at weeks 0, 2 and 4. However, since combination treatment lasts for just 6 weeks in the model, only one pack of SA is purchased in combination treatment.

Costs for cryotherapy in secondary care are the same as those for cryotherapy so far as the first 18 weeks of treatment are concerned. After 18 weeks (6 weeks of cryotherapy, 12 weeks of spontaneous resolution while awaiting referral to secondary care), the costs of aggressive cryotherapy are implemented in the same manner in which cryotherapy costs are introduced.

Appendix 10

Papers used to calculate cure probabilities

Tables 40 and *41* show the number of patients with warts cured used in the weighted averages.

TABLE 40 *Cryotherapy*

Study	No. treated	No. cured	Comments
Bunney *et al.*, 1976[18] 2 weeks	34	18	
Bunney *et al.*, 1976[18] 3 weeks	31	18	
Bunney *et al.*, 1976[18] 4 weeks	35	10	
Bunney *et al.*, 1976[18]	99	68	Vs SA and both
Connolly *et al.*, 1999[36] 10s	71	42	No. of warts recorded, clearance = no warts
Connolly *et al.*, 1999[36] Gentle	75	25	No. of warts recorded, clearance = no warts
Erkens *et al.*, 1992[21]	43	25	All warts cured
Steele and Irwin, 1988[19]	66	39	Fewer than five warts vs SA and both
Focht *et al.*, 2002[20]	25	15	

TABLE 41 *Salicylic acid*

Study	No. treated	No. cured	Comments
Auken *et al.*, 1975[37]	84	43	Includes both hands and feet
Bart *et al.*, 1989[38]	28	19	Maximum three treated
Bunney *et al.*, 1971[39]	76	64	Includes multiple simple warts
Bunney *et al.*, 1976[18]	71	55	
Bunney *et al.*, 1976[18]	43	19	
Bunney *et al.*, 1976[18] 40%	50	15	
Bunney *et al.*, 1976,[18] lactic	43	17	
Flindt-Hansen *et al.*, 1984[40]	31	8	Includes both hands and feet
Spanos *et al.*, 1990[41]	10	0	Fewer than three warts on average
Bunney *et al.*, 1976[18]	95	64	Vs cryotherapy and both
Steele and Irwin, 1988[19]	60	32	Fewer than five warts vs cryotherapy and both

Appendix 11

Results of sensitivity analysis

The values of effectiveness in the main analysis are fixed by the deterministic cohort simulation. While they represent the best point estimates available from the Cochrane review, some sensitivity analysis of the cure probabilities is beneficial in providing an illustration of the amount of variability in the estimates that would be required to alter the conclusions (i.e. the robustness of these results). This is therefore a one-way sensitivity analysis.

Because of the construction of the even cure rates in the model, TreeAge Data's built-in sensitivity analysis cannot be used (since, to allow an even number of cures per week, the cure probabilities depend on time). However, the assumption of even cure rates permits an algebraic sensitivity analysis for a given time-point such as 18 weeks. (A sample of one of the Maple worksheets used to perform this sensitivity analysis is included in Appendix 12).

Using this method of sensitivity analysis, it is possible to calculate equations representing the effectiveness of treatment at week 18. It is therefore also possible to use these results to calculate:

- the cure probabilities required for the effectiveness of two treatments to be equal
- the cure probabilities required for the ICER of two treatments to be equal given their costs.

To test the robustness of the economic evaluation, the sensitivity analysis focuses on those areas of uncertainty that are most likely to impact on the ordering of ICERs for each of the treatment options.

SA and cryotherapy

Because cryotherapy works more quickly than SA, its efficacy at a fixed time-point, such as 18 weeks, is higher than SA: this is because at week 18 a patient could have received either 12 weeks of SA treatment followed by 6 weeks of spontaneous resolution or 6 weeks of cryotherapy followed by 12 weeks of spontaneous resolution (i.e. by week 18, cryotherapy patients have had 6 more weeks of spontaneous resolution than SA patients).

Figure 18 is a plot of the probability values required for equal effectiveness of SA and cryotherapy at week 18.

The model assumes the cryotherapy cure rate to be 0.54, which means that by week 18, 70.4% of cryotherapy patients would be wart free. For SA to have equal effectiveness at week 18, the SA cure rate must be 0.63 (see dashed line). From the interquartile range of the SA cures, the true cryotherapy cure rate is estimated to lie between 34.75 and 67.65%. Therefore, although there is evidence to suggest that the effectiveness of cryotherapy is greater at week 18 than SA, it is possible that they could be of equal effectiveness, although this is at the limit of SA's effectiveness range. For completeness, the cryotherapy cure probabilities that correspond to the interquartile range limits for SA are stated. If SA's lower probability limit (0.35) were correct, cryotherapy would have equal effectiveness at week 18 if the probability of cryotherapy cure was as low as 0.19. Alternatively, taking the upper limit for SA cure probability (0.68), the cryotherapy cure probability required for equal effectiveness at week 18 would be 0.60. This seems to be pushing the bounds of the cryotherapy effectiveness and would make them equally effective. Therefore, overall, given the variation in current evidence, it would seem likely that cryotherapy is a more effective treatment at 18 weeks.

Using the same sensitivity analysis, it is possible to estimate the point at which cryotherapy and SA would have equal ICERs (i.e. the same additional cost per patient cured/wart free). This is more useful as it shows the resources (patient and NHS) required to effect a cure.

The diagonal line in *Figure 19* represents equal ICER between SA and cryotherapy, and the axes represent PSA and PCR.

Nurse-administered cryotherapy

Using the same method of sensitivity analysis, SA is compared with nurse-administered cryotherapy. *Figure 20* shows that the incremental cost-effectiveness of cryotherapy administered by a nurse is more favourable than GP-administered cryotherapy. However, the improvement in

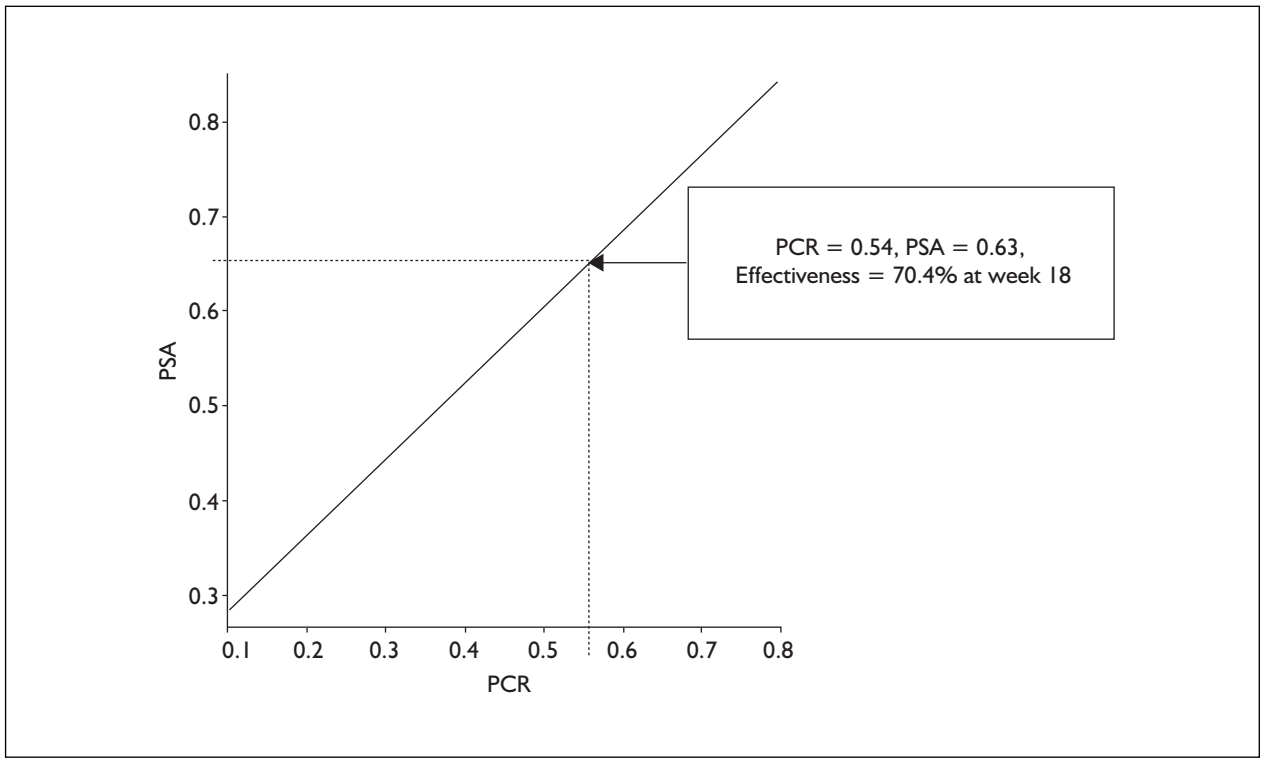


FIGURE 18 *Probability of SA (PSA) versus probability of cryotherapy (PCR) for equal effectiveness at week 18. The dashed line indicates the cryotherapy cure estimate in the model.*

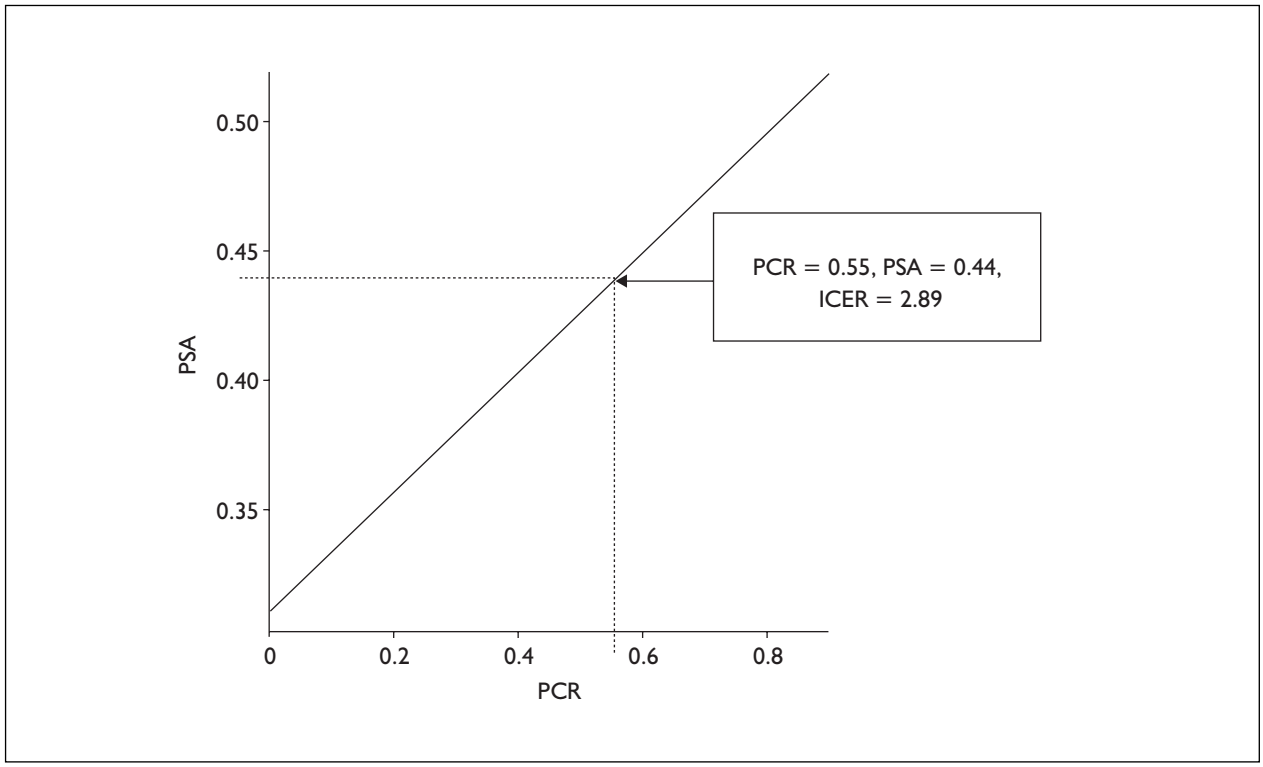


FIGURE 19 *Plot of probability of SA and probability of cryotherapy values yielding equal ICERs. The dashed line approximately indicates the estimate of cryotherapy in the model.*

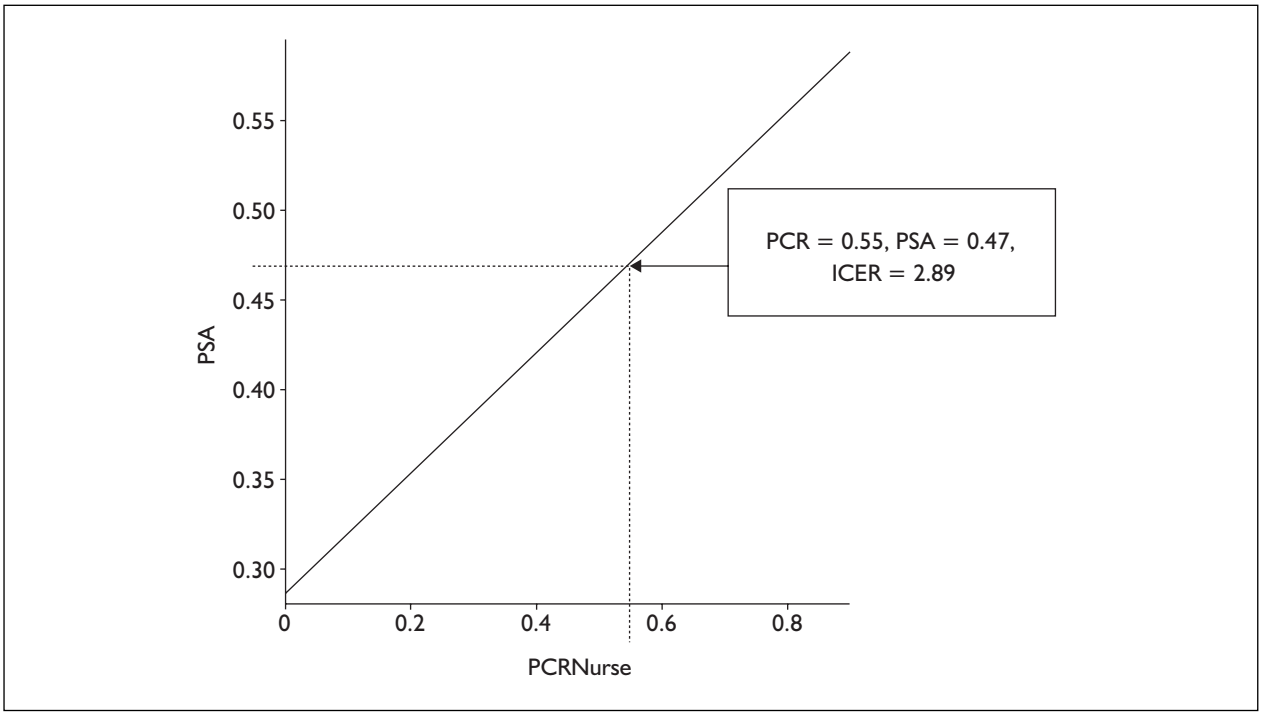


FIGURE 20 *Equal ICER of SA and CRNurse. The dashed line indicates the estimate of cryotherapy cure used in the model.*

relation to SA is very small. To compete with SA treatment values, such as the PSA = 0.57 used in the model, the probability of nurse-administered cryotherapy cure (PCR) would need to be 0.85 to exceed the ICER of OTC SA. Therefore, even in its cheapest form, cryotherapy does not appear to be cost-effective by comparison with topical treatments obtained OTC.

Duct tape

A similar method of sensitivity analysis can be used to compare duct tape with cryotherapy and SA. The plots for equal ICER are shown in *Figures 21* (SA) and *22* [SA and the cheaper form of cryotherapy, CRNurse (administered three times by a nurse)].

The cost and effectiveness values by themselves are sufficient to show that, under the assumptions used in the model, neither SA nor cryotherapy can compete with the cost-effectiveness of duct tape, since duct tape is both cheaper and more effective than these treatments and therefore dominates the cost-effectiveness analysis. However, this estimate of duct tape's effectiveness is only based on a single trial, which could be misleading. Since the costs of duct tape, SA and cryotherapy are known, the sensitivity analysis enables us to calculate how inaccurate the estimate of duct tape's effectiveness would need to be for the more traditional treatments to be comparable.

This analysis shows that, under the current model, even if PSA = 1 (100% cure), duct tape's cure probability would need to be just 0.39 in order to be favourable to SA. Similarly, if cryotherapy cured 100% of patients, duct tape would need to be just 0.33 to compete with CR3 and 0.34 to compete with CRNurse. In practice, it is unlikely that a treatment offering 100% would be rejected in favour of a treatment offering less than 50% cure. However, this sensitivity analysis suggests that, from the available evidence, duct tape is a very effective treatment and its low cost makes it a very attractive option worthy of further investigation.

Primary care treatments: sensitivity analysis

A sensitivity analysis of primary care treatments with an advice-only baseline is shown in *Figure 23*. This figure shows the line at which GP SA and CR3 have the same ICER. The point close to the cryotherapy cure probability used in the model is highlighted. At this point the ICER of GP SA and CR3 is 1.79, the cryotherapy cure probability is 0.55 and the SA cure probability is 0.44. This implies that, if CR3 could be shown to be 55% effective, GP SA would be a favourable treatment

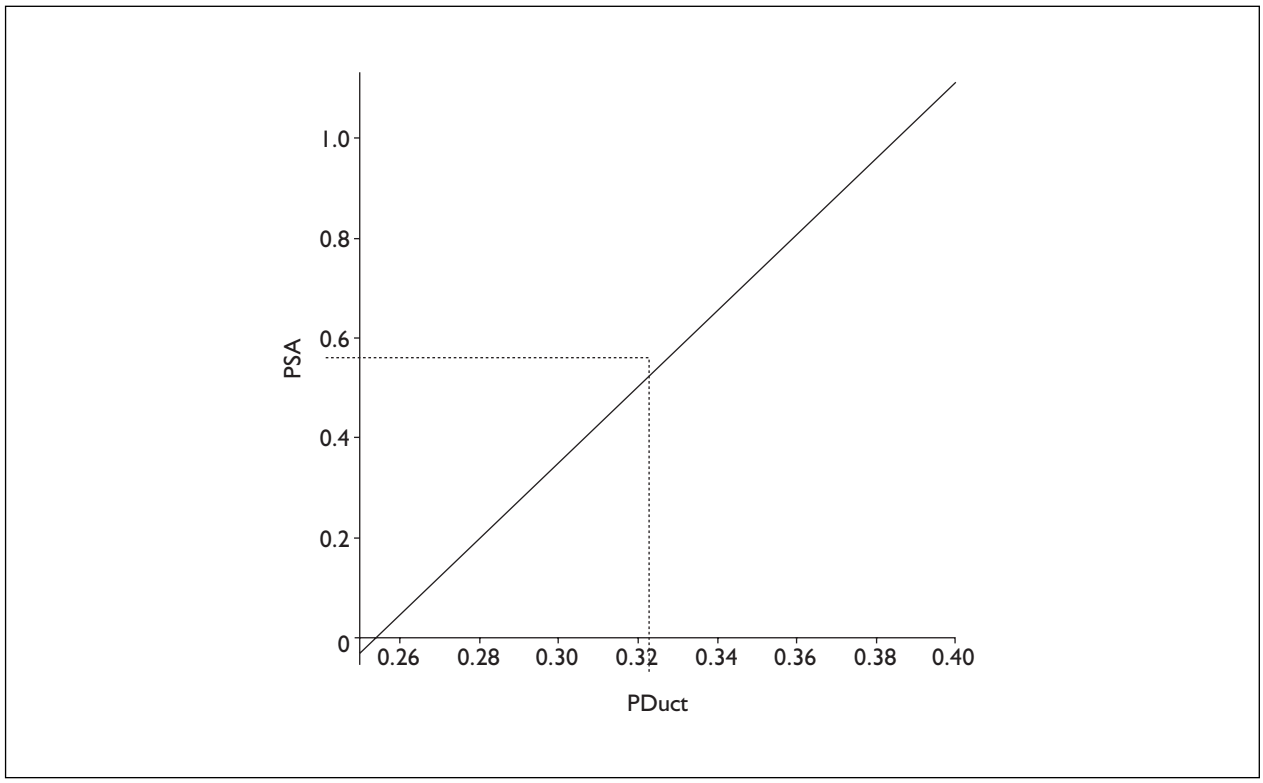


FIGURE 21 *Equal ICER for Duct and SA. The dashed line is the SA probability used in the model.*

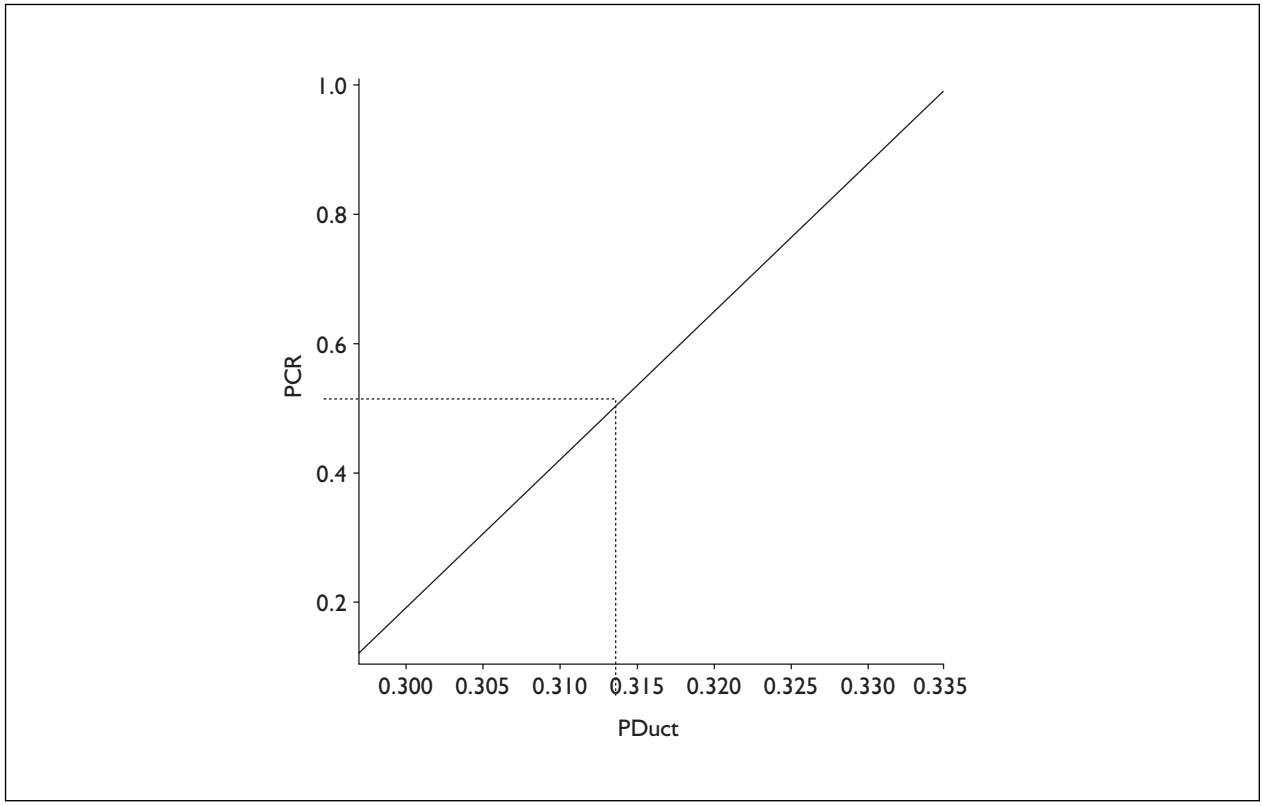


FIGURE 22 *Equal ICER for Duct and CRNurse. The dashed line is the cryotherapy probability used in the model.*

provided that it was at least 44% effective. ICER in this context refers to ICER using advice only as the baseline treatment.

By the same method, GP SA treatment can be compared with nurse-administered cryotherapy. Nurse-administered cryotherapy is cheaper than GP-administered cryotherapy and therefore has a lower ICER regardless of the cryotherapy cure probability.

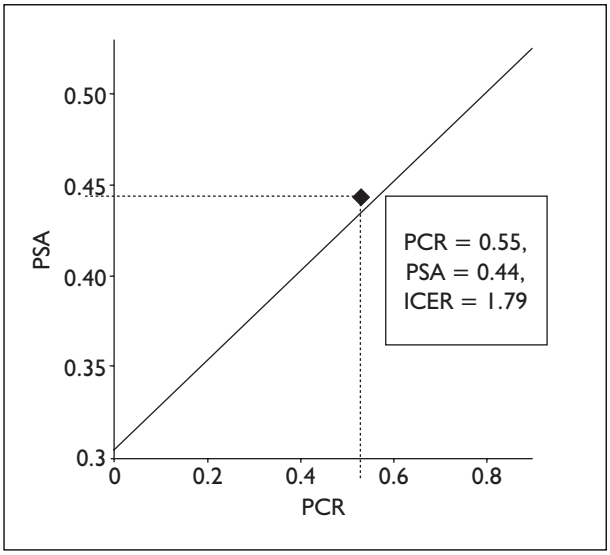


FIGURE 23 *Sensitivity analysis of advice only GP SA versus GP cryotherapy × 3*

Figure 24 shows the sensitivity analysis for GP SA against nurse-administered cryotherapy. Comparing this with *Figure 23*, for a cryotherapy cure probability of 0.55, nurse-administered cryotherapy yields an ICER value of 0.9. This same ICER value would be obtained using GP SA treatment if the SA cure probability was 0.52.

Tables 42 and *43* show cure rates at 5% intervals at which GP SA has an approximately equivalent ICER to three sessions of cryotherapy administered by a GP (*Table 42*) and to nurse-administered cryotherapy (*Table 43*).

TABLE 42 *Intervals at which GP SA and CR3 have approximately equal ICER*

GPSA cure	CR3 cure
35%	19%
40%	39%
45%	60%
50%	80%

TABLE 43 *Intervals at which GP SA and CRNurse × 3 have approximately equal ICER*

GP SA cure	CRNurse cure
40%	30%
45%	40%
50%	50%
55%	60%
60%	70%

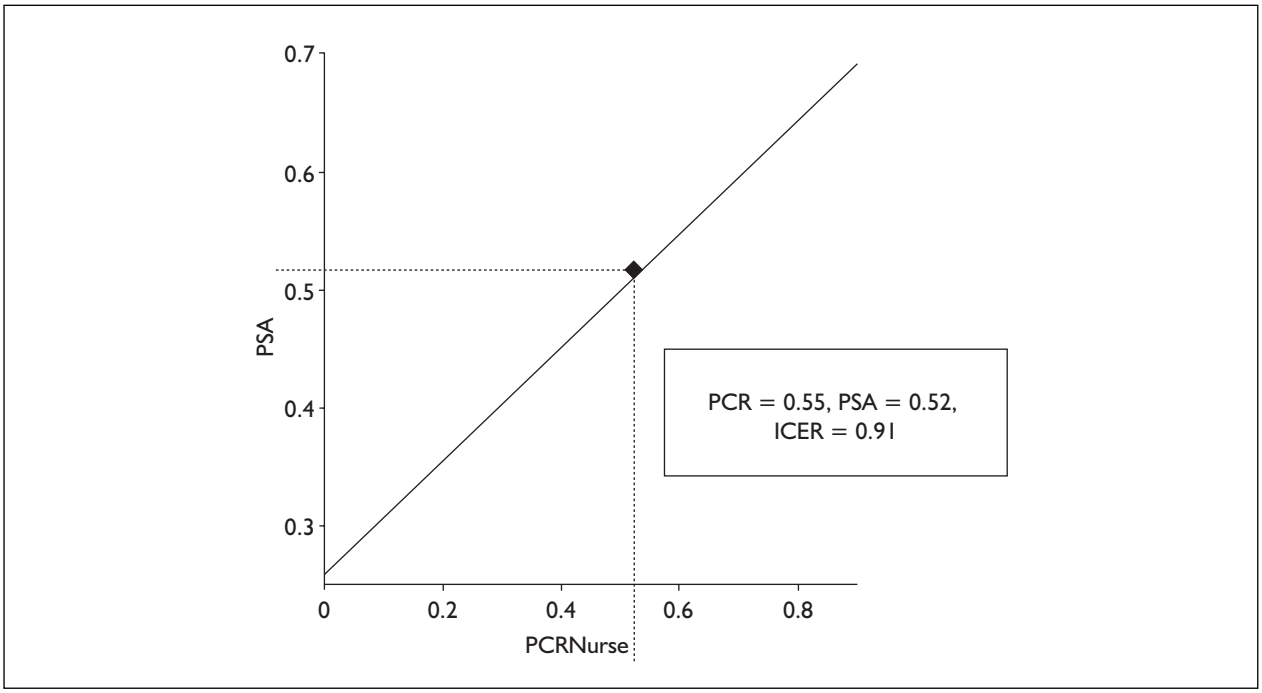


FIGURE 24 *Sensitivity analysis of advice only GP SA versus CRNurse x 3*

Table 42 confirms that the point at which GP SA and GP-administered cryotherapy have equal ICER is at approximately 40% effectiveness. Assuming a similar cure rate between the two treatments, an effectiveness of less than 40% would favour the use of cryotherapy, but an effectiveness greater than 40% would favour SA. The further that these values move from this breakeven point, the greater the difference in cost-effectiveness between the two treatments.

Table 43 shows that the point at which GP SA and nurse-administered cryotherapy have equal ICER is at 50% effectiveness for both treatments. Assuming similar cure rates between the two treatments, an effectiveness value of less than 50% would favour the use of nurse-administered cryotherapy, whereas a value greater than 50% would favour SA. The further that these values move from this breakeven point, the greater the difference in cost effectiveness between the two treatments.

Appendix 12

Sample Maple worksheet for sensitivity analysis

Sensitivity analysis for cryotherapy versus SA

Set up the upper and lower limits for spontaneous resolution probabilities (weeks 10 and 20)

```
> upySR := PSR + 0.3*(1-PSR);
```

$$upySR := 0.7\ PSR + 3$$

```
> lowySR := PSR;
```

$$lowySR := PSR$$

Calculate the gradient of the line for spontaneous resolution

```
> SRgrad := (upySR-lowySR)/10;
```

$$SRgrad := -0.03000000000\ PSR + 0.03000000000$$

Solve for the intercept

```
> SRc := solve(upySR = SRgrad*20 + c, c);
```

$$SRc := 1.300000000\ PSR - 0.3000000000$$

Declare the line equation

```
> SRline := SRgrad*x + SRc;
```

$$SRline := (-0.03000000000\ PSR + 0.03000000000)\ x + 1.300000000\ PSR - 0.3000000000$$

Do the same for salicylic acid and cryotherapy

```
> upysa := PSA + 0.3*(1-PSA);
```

$$upysa := 0.7\ PSA + 0.3$$

```
> lowysa := PSA;
```

$$lowysa := PSA$$

```
> upycry := PCR + 0.3*(1-PCR) + 0.3*(1-(PCR + 0.3*(1-PCR)));
```

$$upycry := 0.49\ PCR + 0.51$$

```
> lowcry := PCR + 0.3*(1-PCR);
```

$$lowcry := 0.7\ PCR + 0.3$$

```
> crygrad := (upycry - lowcry)/10;
```

$$crygrad := -0.02100000000\ PCR + 0.02100000000$$

```
> sagrad := (upysa - lowysa)/10;
```

$$sagrad := -0.03000000000\ PCR - 0.03000000000$$

```
> cryc := solve(upycry = crygrad*26+c,c);
```

$$cryc := 1.036000000\ PCR - 0.03600000000$$

```
> cryline := crygrad*x + cryc;
```

$$cryline := (-0.02100000000\ PCR + 0.02100000000)\ x + 1.036000000\ OCR - 0.03600000000$$

```
> sac := solve(upysa = sagrad*22+c,c);
```

$$sac := 1.360000000\ PSA - 0.3600000000$$

```
> saline := sagrad*x + sac;
```

$$saline := (-0.03000000000\ PSA + 0.03000000000)\ x + 1.360000000\ PSA - 0.3600000000)$$

Find the solution of SA cure = cryotherapy cure (in terms of both cryotherapy and SA) at week 18

```
> psasoln := solve(subs(x=18, saline = cryline), PSA);
```

$$psasoln := 0.1975609756 + 0.8024390244\ PCR$$

```
> pcrsoln := solve(subs(x=18, saline = cryline), PCR);
```

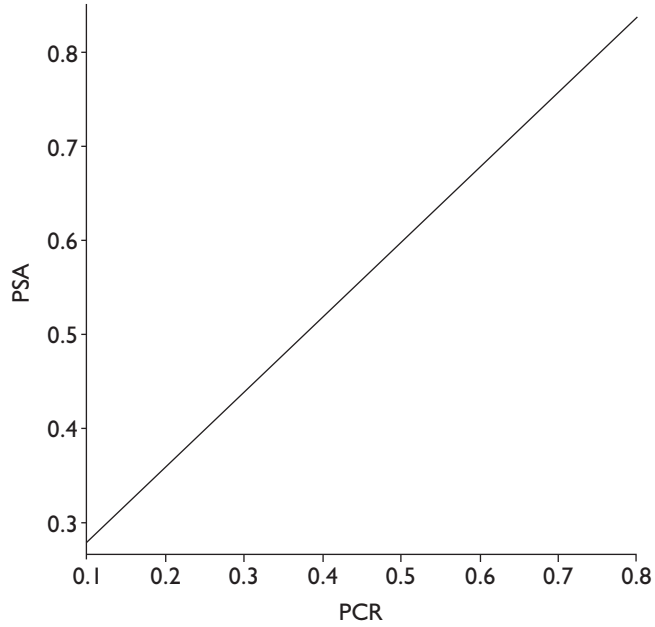
$$pcrsoln := 1.246200608\ PSA - 0.2462006079$$

Substitute the model probability in
> subs(PCR = 0.54, psasoln);

0.6308780488

So for equal effectiveness at 18 weeks for PCR=0.54, PSA would need to be 0.63

Plot the line for equal effectiveness
> plot(subs(PCR = y, psasoln), y=0.1..0.8, labels=[PCR, PSA]);



Now want effectiveness of each treatment at week 18
> CRE18 := subs(x=18, cryline);

$$CRE18 := 0.6580000000\ PCR + 0.3420000000$$

> SAE18 := subs(x=18, saline);

$$SAE18 := 0.8200000000\ PSA + 0.1800000000$$

> SRE18 := subs({x=18, PSR=0.3}, SRline);

SRE18 := 0.4680000000

Above are effectiveness values at week 18 for the three treatments

Calculate ICERs for SA and Cryo compared with SR at week 18
> ICERpsa := CSA/(SAE18-SRE18);

$$ICERpsa := \frac{CSA}{0.8200000000\ PSA - 0.2880000000}$$

> ICERpcr := CCR/(CRE18-SRE18);

$$ICERpcr := \frac{CCR}{0.6580000000\ PCR - 0.1260000000}$$

Produce expressions for which ICER values of Cryo and SA would be equal at week 18s effectiveness
> EQICER := CSA/(ESA-ESR) - CCR/(ECR-ESR);

$$EQICER := \frac{CSA}{ESA - ESR} - \frac{CCR}{ECR - ESR}$$

Insert the total cost values for SA and Cryo at week 18, remembering that CSR is zero

```
> totalEQICER := subs({ESA=SAE18, ECR=CRE18, ESR=SRE18, CSA = 20.47,
CCR = 70.67}, EQICER);
```

$$totalEQICER := \frac{20.47}{0.8200000000\ PSA - 0.2880000000} - \frac{70.67}{0.6580000000\ PCR - 0.1260000000}$$

```
>
```

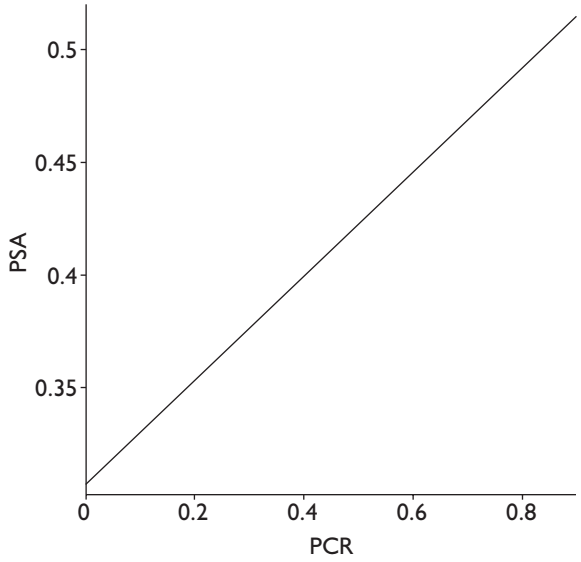
Also find the solution for a cryotherapy cure of 0.54

```
> tEQICERcr55 := subs({ESA=SAE18, ECR=CRE18, ESR=SRE18, CSA = 20.47,
CCR = 70.67, PCR=0.55}, EQICER);
```

$$tEQICERcr55 := \frac{20.47}{0.8200000000\ PSA - 0.2880000000} - \frac{70.67}{0.6580000000\ PCR - 0.1260000000}$$

Produce a plot of the solution of the equal ICERs in terms of PSA against various PCR values. Anything below the line represents an ICER in favour of cryotherapy, anything above the line represents an ICER favouring SA.

```
> plot(subs(PCR=y, solve(totalEQICER, PSA)), y=0..0.9, labels=[PCR, PSA]);
```




```
>
> subs(PCR=0, solve(totalEQICER, PSA));
>
                                0.3067113723
```

The line above shows the intercept with zero on the PSA axis. This illustrates that for SA to have a greater ICER than Cryo, PSA must be at least 0.307. If not, then although cryotherapy would have zero effectiveness, the 12 remaining weeks of spontaneous resolution would be more effective than 12 weeks of SA treatment followed by 6 weeks of spontaneous resolution.

```
>
> subs({PCR=0, x=18}, cryline);
                                0.3420000000
> subs({PSR=0.3, x=12}, SRline);
                                0.3420000000
>
>
>
>
```

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We look forward to hearing from you.

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