

**COMPARING THE EFFICACY OF BECLOMETHASONE,  
FLUTICASONE AND MOMETASONE NASAL SPRAYS IN  
A SAMTER'S POPULATION**

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## List Of Abbreviations

CRS = chronic rhinosinusitis

CRSsNP = chronic rhinosinusitis without nasal polyps

CRSwNP = chronic rhinosinusitis with nasal polyps

AERD = Aspirin-exacerbated respiratory disease

NSAIDs = non-steroidal anti-inflammatory drugs

CAST = cellular activation stimulation test assay

Cys-LT = cysteinyl leukotriene

## **Abstract**

### **Statement of problem**

Topical corticosteroids nasal sprays remain first line of treatment for patients with chronic rhinosinusitis (with or without nasal polyps). The main aim of treatment is to improve nasal symptoms by reducing or eliminating the nasal polyps<sup>[1]</sup> and preventing polyp recurrence post-operatively<sup>[2-6]</sup>. Our aims were to determine if the type of corticosteroid nasal spray used post operatively influences polyp recurrence rate and if there were any subsequent economic implications as we only have beclomethasone available for prescription in our state hospital.

### **Methods**

Retrospective case note review of all Samter's patients who underwent fronto-spheno-ethmoidectomy by a single surgeon (2000 – 2014).

### **Results**

58 patients were included in our study, divided into 3 study groups. When compared to patients using beclomethasone; patients using fluticasone had an 80% reduced risk of polyp recurrence and patients using mometasone a 90% reduced risk. This rose to 88% and 96% respectively when adjusted for age.

### **Conclusion**

Fluticasone and mometasone are both statistically significantly more effective at reducing polyp recurrence than beclomethasone in our population group.

Mometasone appeared more effective than fluticasone, but this difference was not statistically significant.

# PART A: RESEARCH PROTOCOL

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# **Comparing the efficacy of various corticosteroid nasal sprays in a Samter's population**

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## Introduction

The exact aetiology for chronic rhinosinusitis with nasal polyposis (CRSwNP) is largely unknown, possibly because a single, unified cause may not exist<sup>[7]</sup>.

Samter's triad, also commonly referred to as, Aspirin-exacerbated respiratory disease (AERD) is an acquired chronic inflammatory disease characterised by CRSwNP, asthma and airway reactivity to aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs)<sup>[8]</sup>. The disorder is caused by an anomaly in the arachidonic acid cascade, which causes overproduction of leukotrienes, a series of chemicals involved in the body's inflammatory response. Patients typically present in their 20's to 30's and often require multiple operations for nasal polyposis which are notoriously aggressive and have a tendency to recur<sup>[9-13]</sup>.

Topical corticosteroids in the form of nasal sprays remain the first line of treatment of patients with chronic rhinosinusitis with or without nasal polyps<sup>[1,14,15]</sup>. The main aim of treatment is improve nasal symptoms by reducing or eliminating the nasal polyps<sup>[1]</sup>. They also have an essential role in preventing polyp recurrence should surgical intervention be required<sup>[2-4]</sup>. Numerous different corticosteroid nasal spray preparations are available but there is no consensus on which is most efficacious.

## **Justification**

Beclomethasone nasal spray is the only corticosteroid nasal spray available for prescription at Groote Schuur Hospital (state funded). We set out to compare the efficacy of beclomethasone to other available corticosteroid nasal sprays (fluticasone and mometasone).

We conducted a retrospective case-note review of all Samter's patients undergoing fronto-spheno-ethmoidectomy; documenting the time taken to notice endoscopically visualised polyp recurrence and the nasal preparation used.

Our hypothesis is that beclomethasone nasal spray is less effective at reducing the polyp recurrence rate in Samter's patients when compared to other nasal sprays and should be replaced by more efficacious preparations on the state formulary.

## **Aims & Objectives**

### **Aims**

1. To compare the efficacy of various steroid nasal sprays at reducing polyp recurrence
2. To compare the efficacy of generic versus non-generic nasal sprays
3. To determine any cost implications

## **Objectives**

- To determine whether nasal polyps had recurred on nasal endoscopy following fronto-spheno-ethmoidectomy at post-operative visits
- To determine which nasal spray had been used post-operatively

## **Research Design & Methods**

### **Study design**

Retrospective case note review of all patients identified as Samter's patients who had undergone fronto-spheno-ethmoidectomy for polyposis by a single surgeon in both her private and public health practices.

### **Inclusion criteria**

- Confirmed hypersensitivity reaction to Aspirin or other non-steroidal anti-inflammatories, asthmatic with nasal polyposis
- Undergone fronto-spheno-ethmoidectomy
- Single surgeon
- Minimum of 6 months follow-up post-operatively (unless polyps noted to recur within 6 months)

### **Exclusion criteria**

- Less than 6 months follow-up (unless polyps noted to have recurred)
- Non-compliance with nasal spray
- Changed nasal spray between post-operative follow-up visits

## Data collection

- Age
- Gender
- Number of previous FESS surgeries (all surgeons)
- Date of fronto-spheno-ethmoidectomy by single surgeon
- Hospital
- At post-operative follow-up visits:
  - Date of visit
  - Have nasal polyps recurred (on nasendoscopy)
  - Nasal spray used and compliance
  - Change of nasal spray
  - Sense of smell present

## Analysis

Using the data collected; the time taken to notice polyp recurrence could be calculated for each nasal spray and documented as a treatment failure. If no recurrence is noted on endoscopy, then the time is calculated since surgery and documented as a non-failure for that nasal spray. Stata12 was used for statistical analysis of Kaplan-Meier survival.

## Population

All patients with a confirmed hypersensitivity reaction to Aspirin or other non-steroidal anti-inflammatories, who are asthmatic and have nasal polyposis (Samter's patients) who underwent fronto-spheno-ethmoidectomy by a single

surgeon at either Groote Schuur Hospital or Panorama Hospital between 2004 and 2014 and had at least 6 months post-operative follow-up period (unless their polyps recurred within 6 months).

### **Sampling**

The folder numbers of all Samter's patients who underwent fronto-sphenoidectomy at Groote Schuur Hospital and Panorama Hospital between 2004 and 2014 were obtained from surgery logbooks. Their medical records were then recalled and analysed.

### **Sample size**

58 patients

## **Ethical Considerations**

### **Confidentiality**

The identity of the patients in the study were protected during the collection, analysis and reporting of data by making use of the hospital folder numbers. Only the principle investigator and other investigators on the study had access to the medical records and collected data.

**Beneficence**

The study will serve as an audit of the efficacy of various steroid nasal sprays. This will enable patients to be accurately informed of the relative risk of their nasal polyps recurring post-operatively and by implication the risk of future potential sinus surgery. The study will also widen the scope of epidemiological research in that the results can be used to modify policy on which steroid nasal sprays are available for prescription at Groote Schuur in the future.

**Non-maleficence**

The study will not result in any harm to the patients involved.

**Process of obtaining informed consent and assent**

Retrospective telephonic consent was obtained.

**Stakeholder and reporting**

The results of the study will be reported back to the Division of Otolaryngology at Groote Schuur Hospital in the format of a formal report.

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## PART B: LITERATURE REVIEW

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## Literature Search Strategy

A literature search was undertaken of the PubMed, Medline and Cochrane databases for articles in journals that are listed on Index Medicus. The following keywords were used: “Corticosteroid nasal sprays”, “Corticosteroid comparison”, “Beclomethasone”, “Fluticasone” and “Mometasone”.

## Summary Of Literature

### ***Efficacy of corticosteroid nasal sprays***

Topical corticosteroid nasal sprays are well-established first line therapy for chronic rhinosinusitis patients with or without nasal polyps<sup>[3-5]</sup>. They act by inhibiting the liberation of histamine, inhibiting the degranulation of basophils by reducing their cellular activity and circulating number<sup>[6]</sup>.

The primary clinical benefits of topical nasal steroid preparations are produced by reducing nasal mucosal inflammation. They inhibit phospholipase in the arachidonic acid pathway. This effectively reduces the cell-mediated inflammatory response (basophils, mast cells, eosinophils and neutrophils), in addition to decreasing inflammatory mediator levels in nasal mucosa and nasal secretions. These actions inhibit both the early as well as late allergic responses<sup>[1]</sup>.

Controlled studies have shown that topical steroids can delay the recurrence of polyps after surgery and with that postpone the need for revision surgery<sup>[2]</sup>.

### ***Comparing corticosteroid nasal sprays***

Some feel there is no difference in the efficacy between the various preparations<sup>[2]</sup>, but that is not the authors' opinion.

Beclomethasone dipropionate was introduced in 1970; fluticasone propionate and mometasone furoate were introduced later. Systemic absorption for these preparations is insignificant; less than or equal to 0.1% for fluticasone and mometasone and less than 10% for beclomethasone<sup>[6]</sup>.

The efficacy of beclomethasone, fluticasone and mometasone nasal sprays in reducing polyp size and rhinitis symptoms has been shown in several randomised, placebo-controlled trials<sup>[3]</sup>, but little work has been done to compare the various preparations to each other. The European position paper on rhinosinusitis and nasal polyps (2012) looked at 39 RCTs evaluating intranasal corticosteroids for CRSwNP. Of these 34 trials compared topical steroid against placebo; 8 trials compared low dose to high dose of topical steroid; 3 trials compared topical steroid to no intervention; and 3 trials compared steroid agents, fluticasone propionate and beclomethasone dipropionate<sup>[4]</sup>.

Meta-analysis of the 34 RCTs comparing topical steroid against placebo analysed in EOPS 2012 showed significant benefit in the nasal steroid group for pooled

data analyses of symptoms, polyp size, polyp recurrence and nasal airflow compared to placebo<sup>[4]</sup>.

Several placebo-controlled studies have shown the efficacy of corticosteroid sprays for reducing polyp size and CRS symptoms (obstruction, rhinorrhoea, post nasal drip and anosmia/hyposmia):

- i. Beclomethasone: Bross-Soriano (2004), Holmberg (1997), Lund (1998), Mygrind (1975) and Karlsson (1982)<sup>[7-11]</sup>.
- ii. Fluticasone: Lund (1998), Olsson (2010), Aukema (2005), Bross-Soriano (2004), Holmberg (1997), Masterlerz (1997) and Rowe-Jones (2005)<sup>[7-9,12-15]</sup>.
- iii. Mometasone: Small (2005), Stjarne (2006, 2006b, 2009)<sup>[16-19]</sup>.

When comparing the differences between the modern corticosteroids: fluticasone (15 trials), mometasone (6 trials) versus the first-generation corticosteroids: beclomethasone (7 trials), betamethasone (1 trial) and budesonide (9 trials); they found no significant difference between the two groups<sup>[4]</sup>. Only three trials compared the agents directly however.

Bross-Soriano (2004) compared beclomethasone, fluticasone and mometasone; concentrating on their effects in the intraocular pressure compartment rather than their efficacy at alleviating CRS symptoms. The author found discreet elevations in the beclomethasone and mometasone groups; however, these variations were within normal limits<sup>[6]</sup>. In a separate paper by the same author (2004),

beclomethasone, fluticasone were compared to control (saline lavage) post polypectomy. The findings showed 44% recurrence rate in the control group, compared to 26% in the beclomethasone group and 15% in fluticasone group<sup>[7]</sup>.

Lund (1998) compared the efficacy beclomethasone and fluticasone to placebo in patients with severe polyposis listed for surgery. The author found a significantly decreased polyp score in the fluticasone treatment group; significantly increased nasal cavity volume as measured by acoustic rhinometry and decreased nasal obstruction in both the beclomethasone and fluticasone groups compared to placebo. The study showed some evidence that the fluticasone group responded more quickly and that the magnitude of the response was greater than in the beclomethasone group<sup>[9]</sup>.

These findings were supplemented by Holmberg (1997) who also compared beclomethasone and fluticasone to placebo and found that both were effective at treating the symptoms of nasal polyps, with some evidence that fluticasone has a faster onset of action. No other statistically significant results were found between the two active compounds<sup>[8]</sup>.

### ***Efficacy at reducing polyp recurrence post-operatively***

In 2004, Dijkstra's study showed no difference between fluticasone and placebo in controlling recurrent polyposis 1 year post FESS<sup>[20]</sup>. These findings are by far in the minority.

Besides shrinking intranasal polyps, corticosteroid nasal sprays also have an important role in preventing recurrence post-operatively. Karlsson (1982) found a

reduced polypectomy rate<sup>[11]</sup> and Virolainen (1980) a reduced symptomatic recurrence in patients using beclomethasone post-polypectomy.<sup>[21]</sup>

Dingsor (1985) and Drettner (1982) studied Flunisonide and found it significantly more effective than placebo in preventing polyp recurrence, treating chronic rhinosinusitis symptoms and reduced operation rate after polypectomy<sup>[22,23]</sup>.

Hartwig (1998) found similar results with budesonide<sup>[24]</sup>. Thus, topical corticosteroid sprays are considered invaluable for long term maintenance post-operatively<sup>[3]</sup>.

Stjatne (2009) found a significant longer time to relapse after FESS for patients using mometasone nasal spray compared to placebo<sup>[18]</sup>.

The literature confirms that intranasal corticosteroids are the first line therapy for reducing polyp size; chronic rhinosinusitis related symptoms as well as reducing polyp recurrence rates post-operatively (and thereby reducing the number of polypectomies). All the steroid preparations included in our study have been found to be effective, but which is most efficacious?

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## PART C: ARTICLE MANUSCRIPT

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# **Comparing the efficacy of beclomethasone, fluticasone and mometasone sprays in a Samter's population**

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***Keywords:***

Beclomethasone, fluticasone, mometasone, nasal polyps, nasal sprays

## Summary

### Statement of problem

Topical corticosteroids nasal sprays remain first line of treatment for patients with chronic rhinosinusitis (with or without nasal polyps). The main aim of treatment is to improve nasal symptoms by reducing or eliminating the nasal polyps<sup>[1]</sup> and preventing polyp recurrence post-operatively<sup>[2-6]</sup>. Our aims were to determine if the type of corticosteroid nasal spray used post operatively influences polyp recurrence rate and if there were any subsequent economic implications as we only have beclomethasone available for prescription in our state hospital.

### Methods

Retrospective case note review of all Samter's patients who underwent fronto-sphenoidectomy by a single surgeon (2000 – 2014).

### Results

58 patients were included in our study, divided into 3 study groups. When compared to patients using beclomethasone; patients using fluticasone had an 80% reduced risk of polyp recurrence and patients using mometasone a 90% reduced risk. This rose to 88% and 96% respectively when adjusted for age.

### Conclusion

Fluticasone and mometasone are both statistically significantly more effective at reducing polyp recurrence than beclomethasone in our population group. Mometasone appeared more effective than fluticasone, but this difference was not statistically significant.

## Introduction

Chronic rhinosinusitis (CRS) is defined as the presence of two or more symptoms, one of which should be either nasal blockage/obstruction/ congestion or nasal discharge (anterior/posterior nasal drip), with or without facial pain/pressure or reduction/loss of smell. These symptoms must be present for 12 weeks or more. It can be further classified as with polyps (CRSwNP) or without polyps (CRSSNP)<sup>[7]</sup>.

Many theories as to the aetiology for nasal polyposis exist but the exact mechanism remains largely unknown. Regardless of aetiology, the increased presence of inflammatory mediators is prominent and consistent in nasal polyps<sup>[1]</sup>. There is an established connection with asthma and aspirin hypersensitivity (Samter's triad)<sup>[8]</sup>. The pathophysiology for this is only partially understood. The underlying respiratory disease is thought to be activated by an unknown mechanism<sup>[9]</sup>. In 1988, Szczeklik proposed that this trigger may be a chronic respiratory viral infection<sup>[10]</sup>. This results in an intense infiltration of mast cells and eosinophils into the entire respiratory mucosa<sup>[9]</sup>. Samter's patients are characterised by extensive nasal polyposis which responds well to functional endoscopic sinus surgery (FESS), but the polyps have a tendency to recur post-operatively<sup>[11–16]</sup>.

Intranasal corticosteroid nasal sprays remain the well established first line of treatment for chronic rhinosinusitis patients with or without nasal polyps<sup>[1,7,17]</sup>. They act by inhibiting the liberation of histamine and inhibiting the degranulation of basophils by reducing their cellular activity and circulating numbers<sup>[18]</sup>. The efficacy of beclomethasone<sup>[2,19–22]</sup>, fluticasone<sup>[19–21,23–26]</sup> and mometasone<sup>[4,27–29]</sup> nasal sprays in reducing polyp size and chronic rhinosinusitis symptoms (obstruction, rhinorrhoea, post nasal drip and anosmia/hyposmia) has been proven in several randomised, placebo-controlled trials<sup>[17]</sup>. We also know from the literature that they are effective in reducing polyp recurrence post-operatively<sup>[2–4]</sup> but little work has been done to

compare the various preparations to each other. This is especially pertinent in our clinical setting as Beclate™ (beclomethasone) is the only corticosteroid nasal spray available for prescription at our state funded hospital (Groote Schuur). This may appear to be a reasonable as it is the cheapest preparation to purchase, but we feel that once efficacy is factored in, this may not be the best economical choice.

## Material and Methods

We retrospectively reviewed the case notes for all Samter's patients who had undergone fronto-spheno-ethmoidectomy for polyposis between 2004 and 2014. Patients were identified as Samter's if they had had a documented hypersensitivity reaction to Aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) and were asthmatic with nasal polyposis. All operations were by a single surgeon at either Groote Schuur (state) or Panorama (private) Hospitals in the Western Cape, South Africa. The data we collected included age at time of surgery, gender, number of previous FESS surgeries (by any surgeon), CAST (Cys-LT) result (if tested), date of fronto-spheno-ethmoidectomy and date of post-operative visit. At each post-operative visit the presence of nasal polyps on nasendoscopy, the nasal spray used, nasal spray compliance, whether the nasal spray used had changed since their previous visit and sense of smell were all noted. Patients with less than 6 months follow-up period post-operatively were excluded (unless polyps were noted to have recurred within 6 months). Patients that had changed nasal sprays between visits or were non-compliant were also excluded. Using the data collected; the time taken to notice polyp recurrence was calculated for each nasal spray and documented as a treatment failure. If no recurrence was noted on endoscopy, then the time since surgery was calculated and documented as a non-failure for that nasal spray. Stata12 was used for statistical analysis of Kaplan-Meier survival. Our institutional ethics review board approved this study.

Our aims were to compare the efficacy of various steroid nasal sprays at preventing polyp recurrence. To compare the efficacy of generic versus non-generic nasal sprays and to determine any cost implications.

## Results

74 Samter's patients underwent fronto-spheno-ethmoidectomy between 2004 and 2014 at Groote Schuur and Panorama hospitals. Of these, 16 were excluded from the study due to non-compliance, changing of nasal sprays between follow-up visits or having less than 6 months follow-up period post-operatively (unless their polyps had already recurred). A total of 58 patients were included in the study. There were 34 female and 24 male patients with a mean age of 44 years. On average they had had 3 (1 – 11) previous FESS surgeries (all surgeons). Table 1 lists the different nasal sprays studied and the number of patients in each group. This data was then subdivided by active ingredient of the nasal spray, which left us with 3 study groups: beclomethasone, fluticasone and mometasone. The demographic data and follow-up data for each group are shown in Table 2.

| ALL SPRAYS            |           |    | TOT       |
|-----------------------|-----------|----|-----------|
| <b>Beclomethasone</b> | Beclate   | 19 | <b>19</b> |
| <b>Fluticasone</b>    | Flixonase | 6  | <b>29</b> |
|                       | Flomist   | 12 |           |
|                       | Flonase   | 2  |           |
|                       | Avamys    | 9  |           |
| <b>Mometasone</b>     | Nasonex   | 8  | <b>10</b> |
|                       | Nexomist  | 1  |           |
|                       | Rinelon   | 1  |           |

n=58

*Table 1: All nasal spray preparations; divided by active ingredient*

| SPRAYS                | n  | SEX |    | AGE (y) |     |      | FOLLOW-UP (m) |      |      |
|-----------------------|----|-----|----|---------|-----|------|---------------|------|------|
|                       |    | F   | M  | min     | max | mean | min           | max  | mean |
| <b>Beclomethasone</b> | 19 | 13  | 6  | 16      | 71  | 41   | 2.1           | 33.2 | 11.5 |
| <b>Fluticasone</b>    | 29 | 15  | 14 | 20      | 76  | 47   | 4.6           | 63.5 | 19.3 |
| <b>Mometasone</b>     | 10 | 6   | 4  | 31      | 53  | 41   | 6.9           | 55.4 | 27.6 |
| <b>Combined</b>       | 58 | 34  | 24 | 16      | 76  | 44   | 2.1           | 63.5 | 18.2 |

*Table 2: Summary of demographic data*

Kaplan-Meier survival analysis comparing the time taken to notice polyp recurrence showed a significant difference between the nasal sprays. When compared to patients using beclomethasone nasal spray; the patients using fluticasone had an 80% reduced risk of developing polyp recurrence ( $p=0.000$ ); and those on mometasone a 90% reduced risk ( $p=0.00$ ) (Figure 1). When these figures are adjusted for age (which was found to be an independent risk factor for polyp recurrence) they rise to 88% reduced risk for fluticasone ( $p=0.000$ ) and 95% reduced risk for mometasone ( $p=0.000$ ) when compared to beclomethasone. The apparent advantage of mometasone over fluticasone was not statistically significant ( $p=0.121$ ).

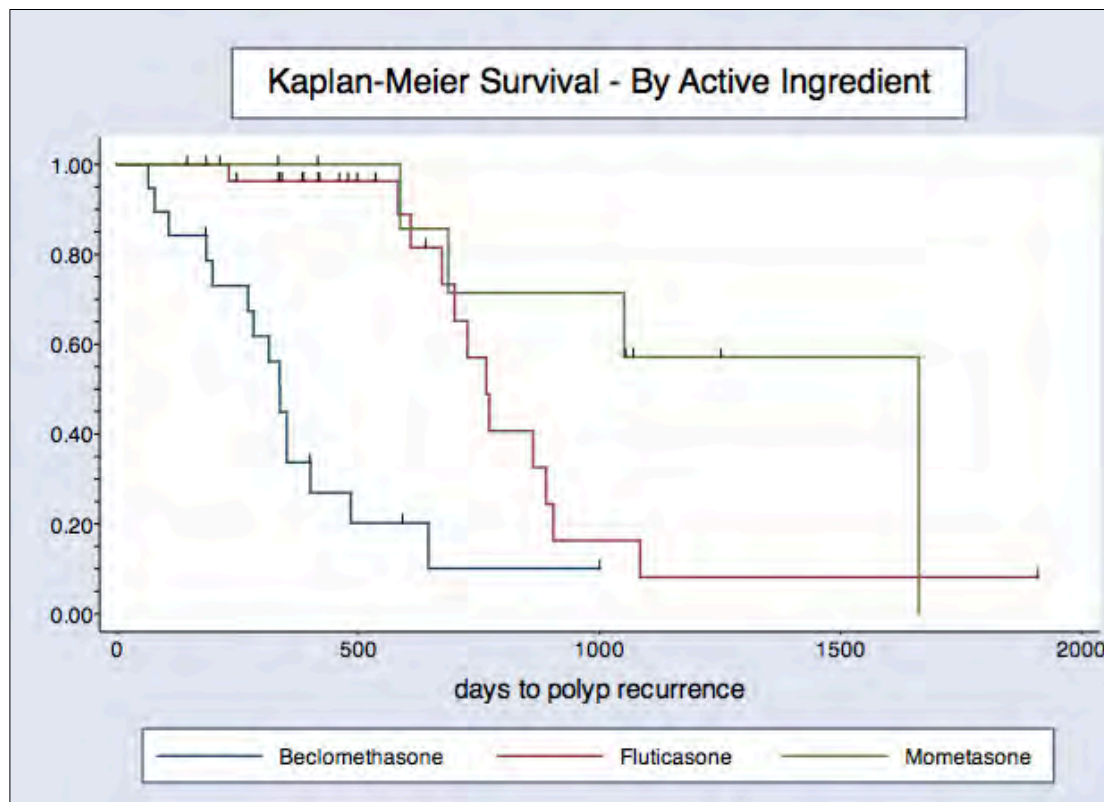
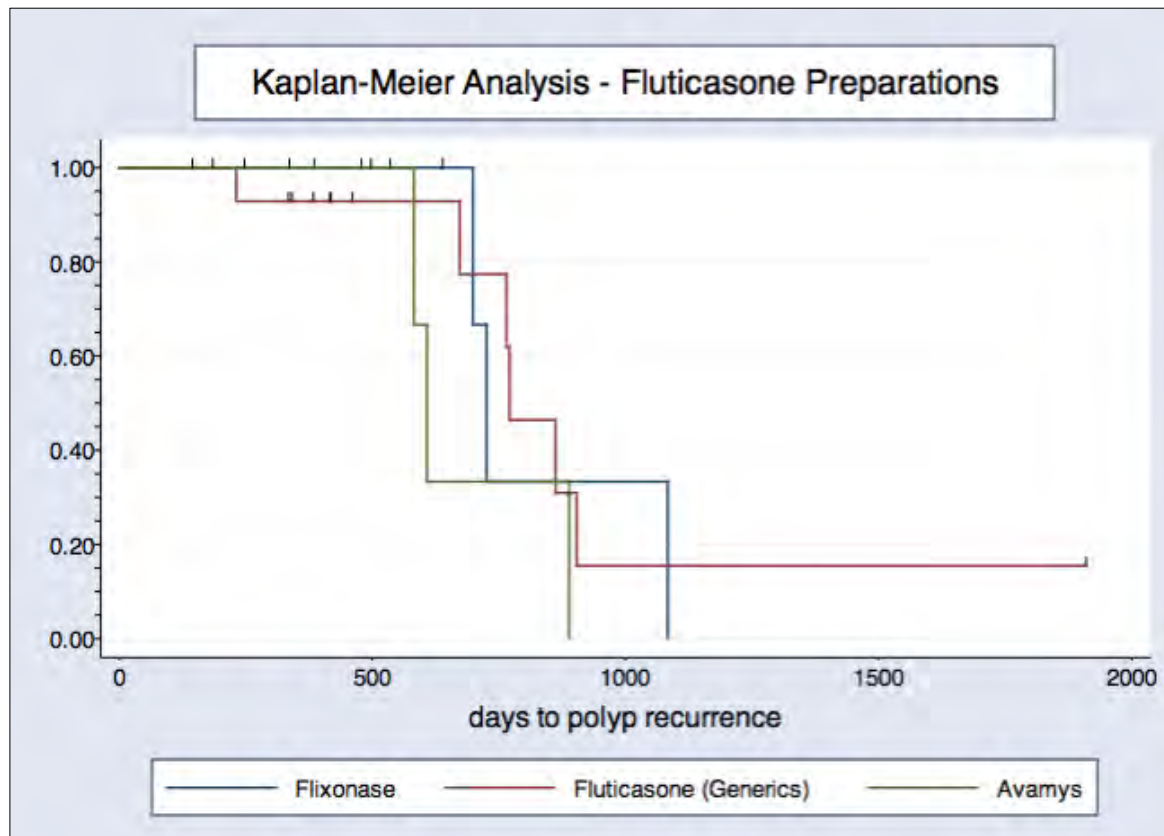


Figure 1: Kaplan-Meier survival analysis comparing time take to notice polyp recurrence for patients using beclomethasone, fluticasone and mometasone

Our study showed no statistical difference in efficacy when comparing fluticasone dipropionate original (Flixonase™), to the various fluticasone dipropionate generics ( $p=0.976$ ) and the newest fluticasone preparation, fluticasone furoate (Avamys™)( $p=0.412$ ) (Figure 2).



*Figure 2: Kaplan-Meier survival analysis of comparing time taken to notice polyp recurrence for the various fluticasone preparations. No statistical difference is noted.*

To ensure that our figures were not being skewed by socio-economic factors; we compared the rate of polyp recurrence in our state and private sector patients using fluticasone. Fluticasone was chosen, as it was the only spray with comparable numbers in both groups. We found no statistical difference between these 2 patients groups ( $p=0.522$ ) (Figure 3).

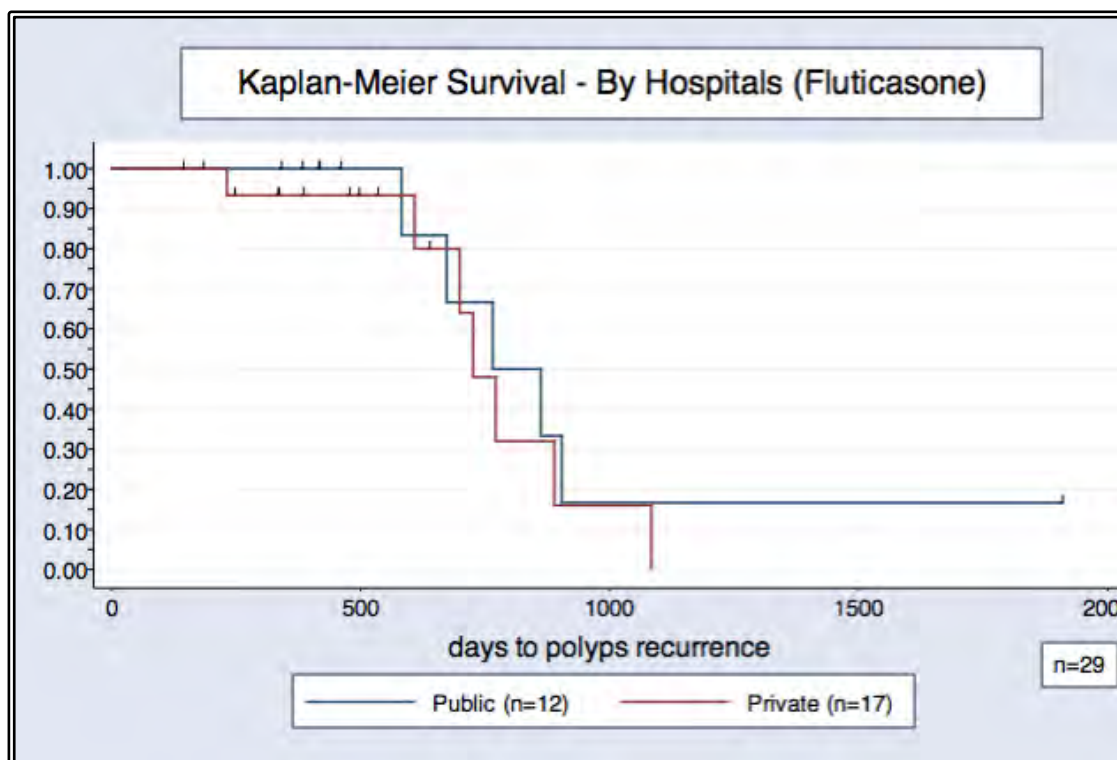


Figure 3: Kaplan-Meier survival analysis comparing the time taken to notice polyp recurrence in patients using fluticasone in the public and private sectors. No statistical difference is noted.

We also collected data on smell recovery post-operatively, but found no difference between the nasal sprays for this variable ( $p=0.6724$ ).

14 of our patients, all of whom had previously documented hypersensitivity reactions to aspirin or other non-steroidal drugs, were sent for CAST (Cys-LT) testing. This is proposed as a safer alternative to aspirin challenge testing. Only 2 of these tests yielded a positive result, a sensitivity of only 14% for this test.

## Discussion

Both fluticasone and mometasone nasal sprays were found to be significantly better than beclomethasone at reducing polyp recurrence post-operatively in our population group. Mometasone appeared more efficacious than fluticasone, but this was not statistically significant in our study.

We found no statistically significant difference in efficacy for the various fluticasone preparations; Flixonase™ (fluticasone propionate), fluticasone generics (fluticasone propionate) and Avamys™ (fluticasone furoate).

These findings are particularly significant in the setting of our public health sector, where only Beclate™ (beclomethasone) is available on state formulary for prescription. Table 3 lists the nasal sprays used in this study and compares the cost of using each preparation if used at maximal dose over a 28-day period. The monthly cost of using Beclate™ (\$4,64) is approximately 30% less than the cost of using fluticasone (\$6,81) or mometasone (\$6,64). This is a significant difference in and on the face of it appears to justify the health department's decision. We know from previous studies, that corticosteroid nasal spray are effective at reducing polyp recurrence as well as re-operation rate<sup>[2-6]</sup>. Thus, it is only when the cost of FESS surgery is considered that an accurate cost assessment can be made. Even in the state sector, the cost of FESS surgery is \$520 (R6000). If this cost is divided by the difference in cost between beclomethasone and mometasone ( $\$520/(\$6.64-\$4,64)$ ), this equates to using the "more expensive" mometasone for 260 months or 21 years. We did not have

enough data in our study to comment on the respective re-operation rates for each nasal spray, but given the significant difference we were able to demonstrate in reduced polyp recurrence, it is not unreasonable to infer that this may result in fewer operations for patients using fluticasone or mometasone. If this resulted in just one fewer operation over a 21-year period for the patients using fluticasone or mometasone compared to patients using beclomethasone, then what initially appears to be the more expensive option actually becomes the more economical option long term. And that is before immeasurables such as increased risk of complications for revision surgery<sup>[30,31]</sup> and work absence, are factored in.

|                       | METERED DOSE (mcg/spray) | DOSES (per bottle) | DOSES per 28 DAYS (@ max dose) | COST (per bottle) | COST (per spray) | COST per 28 DAYS (ZAR) | <b>COST per 28 DAYS (USD)</b> |
|-----------------------|--------------------------|--------------------|--------------------------------|-------------------|------------------|------------------------|-------------------------------|
| <b>BECLAMETHASONE</b> |                          |                    |                                |                   |                  |                        |                               |
| BECLATE               | 50                       | 150                | 112                            | 71,50             | 0,48             | 53,39                  | <b>4,64</b>                   |
| <b>FLUTICASONE</b>    |                          |                    |                                |                   |                  |                        |                               |
| FLOMIST/FLONASE       | 50                       | 100                | 112                            | 69,89             | 0,70             | 78,28                  | <b>6,81</b>                   |
| AVAMYS                | 27,5                     | 120                | 56                             | 177,40            | 1,48             | 82,79                  | <b>7,20</b>                   |
| FLIXONASE             | 50                       | 120                | 112                            | 214,00            | 1,78             | 199,73                 | <b>17,37</b>                  |
| <b>MOMETASONE</b>     |                          |                    |                                |                   |                  |                        |                               |
| NEXOMIST              | 50                       | 140                | 56                             | 191,00            | 1,36             | 76,40                  | <b>6,64</b>                   |
| RINELON               | 50                       | 140                | 56                             | 198,95            | 1,42             | 79,58                  | <b>6,92</b>                   |
| NASONEX               | 50                       | 120                | 56                             | 227,28            | 1,89             | 106,06                 | <b>9,22</b>                   |

*Table 3: Cost comparison for usage of steroid nasal sprays in this study. Cost is calculated if used at maximum prescribed dosage per 28 days.*

All the patients in our study had previously documented hypersensitivity reactions to aspirin or other NSAIDs. Most had bronchospasm requiring admission to hospital, and few required ICU admission.

Although aspirin challenge testing (oral or inhalational) is considered the gold standard for the diagnosis of aspirin hypersensitivity, this can be associated with severe adverse reactions and is not widely available in our setting (nor is desensitisation). The cellular allergen stimulation test assay (CAST) was introduced in the early 1990's as quick, safer alternative to aspirin challenge testing. Evaluation of this test has revealed variable results. Earlier studies showed some promise with good sensitivity (80 – 100%) and specificity (70-100%) results<sup>[32-34]</sup>, but more recent studies confirm our findings with sensitivity below 30%<sup>[35-37]</sup>. Given these findings, we could find no role for this test in the diagnosis of aspirin hypersensitivity.

## **Conclusions**

We were able to demonstrate a significant advantage in efficacy at reducing polyp recurrence for the newer generation corticosteroid nasal sprays (fluticasone and mometasone) over beclomethasone in our Samter's population group. Given this overwhelming advantage, we feel confident that this should translate to reduced operation rates and therefore prove to be more cost effective in the long term. We hope to be able to show this by continuing with this research prospectively and in doing so, change our hospital's prescribing policy.

## **Acknowledgements**

No competing interests to declare. This research was not sponsored by any pharmaceuticals.

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## Tables and Figures

Table 1.

| ALL SPRAYS            |           |    | TOT       |
|-----------------------|-----------|----|-----------|
| <b>Beclomethasone</b> | Beclate   | 19 | <b>19</b> |
| <b>Fluticasone</b>    | Flixonase | 6  | <b>29</b> |
|                       | Flomist   | 12 |           |
|                       | Flonase   | 2  |           |
|                       | Avamys    | 9  |           |
| <b>Mometasone</b>     | Nasonex   | 8  | <b>10</b> |
|                       | Nexomist  | 1  |           |
|                       | Rinelon   | 1  |           |

n=58

Table 2.

| SPRAYS                | n         | SEX       |           | AGE (y)   |           |           | FOLLOW-UP (m) |             |             |
|-----------------------|-----------|-----------|-----------|-----------|-----------|-----------|---------------|-------------|-------------|
|                       |           | F         | M         | min       | max       | mean      | min           | max         | mean        |
| <b>Beclomethasone</b> | 19        | 13        | 6         | 16        | 71        | 41        | 2.1           | 33.2        | 11.5        |
| <b>Fluticasone</b>    | 29        | 15        | 14        | 20        | 76        | 47        | 4.6           | 63.5        | 19.3        |
| <b>Mometasone</b>     | 10        | 6         | 4         | 31        | 53        | 41        | 6.9           | 55.4        | 27.6        |
| <b>Combined</b>       | <b>58</b> | <b>34</b> | <b>24</b> | <b>16</b> | <b>76</b> | <b>44</b> | <b>2.1</b>    | <b>63.5</b> | <b>18.2</b> |

Table 3.

|                       | METERED DOSE (mcg/spray) | DOSES (per bottle) | DOSES per 28 DAYS (@ max dose) | COST (per bottle) | COST (per spray) | COST per 28 DAYS (ZAR) | COST per 28 DAYS (USD) |
|-----------------------|--------------------------|--------------------|--------------------------------|-------------------|------------------|------------------------|------------------------|
| <b>BECLAMETHASONE</b> |                          |                    |                                |                   |                  |                        |                        |
| BECLATE               | 50                       | 150                | 112                            | 71,50             | 0,48             | 53,39                  | <b>4,64</b>            |
| <b>FLUTICASONE</b>    |                          |                    |                                |                   |                  |                        |                        |
| FLOMIST/FLONASE       | 50                       | 100                | 112                            | 69,89             | 0,70             | 78,28                  | <b>6,81</b>            |
| AVAMYS                | 27,5                     | 120                | 56                             | 177,40            | 1,48             | 82,79                  | <b>7,20</b>            |
| FLIXONASE             | 50                       | 120                | 112                            | 214,00            | 1,78             | 199,73                 | <b>17,37</b>           |
| <b>MOMETASONE</b>     |                          |                    |                                |                   |                  |                        |                        |
| NEXOMIST              | 50                       | 140                | 56                             | 191,00            | 1,36             | 76,40                  | <b>6,64</b>            |
| RINELON               | 50                       | 140                | 56                             | 198,95            | 1,42             | 79,58                  | <b>6,92</b>            |
| NASONEX               | 50                       | 120                | 56                             | 227,28            | 1,89             | 106,06                 | <b>9,22</b>            |

Figure 1.

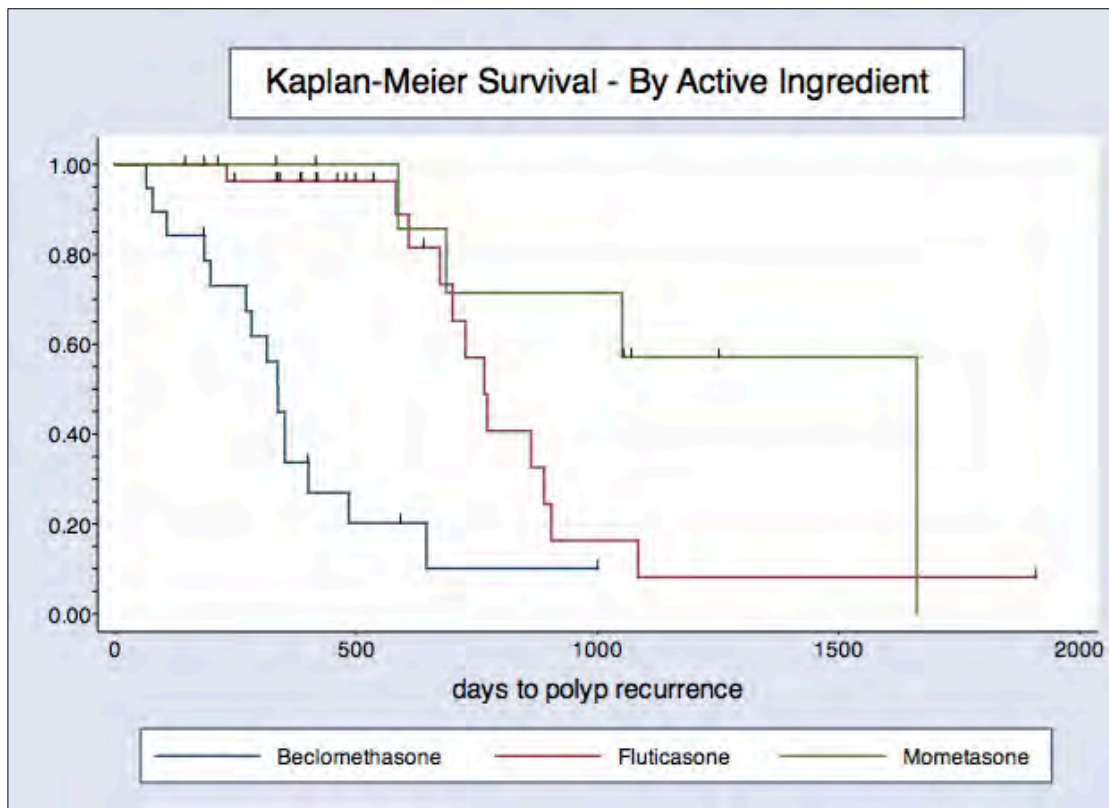


Figure 2.

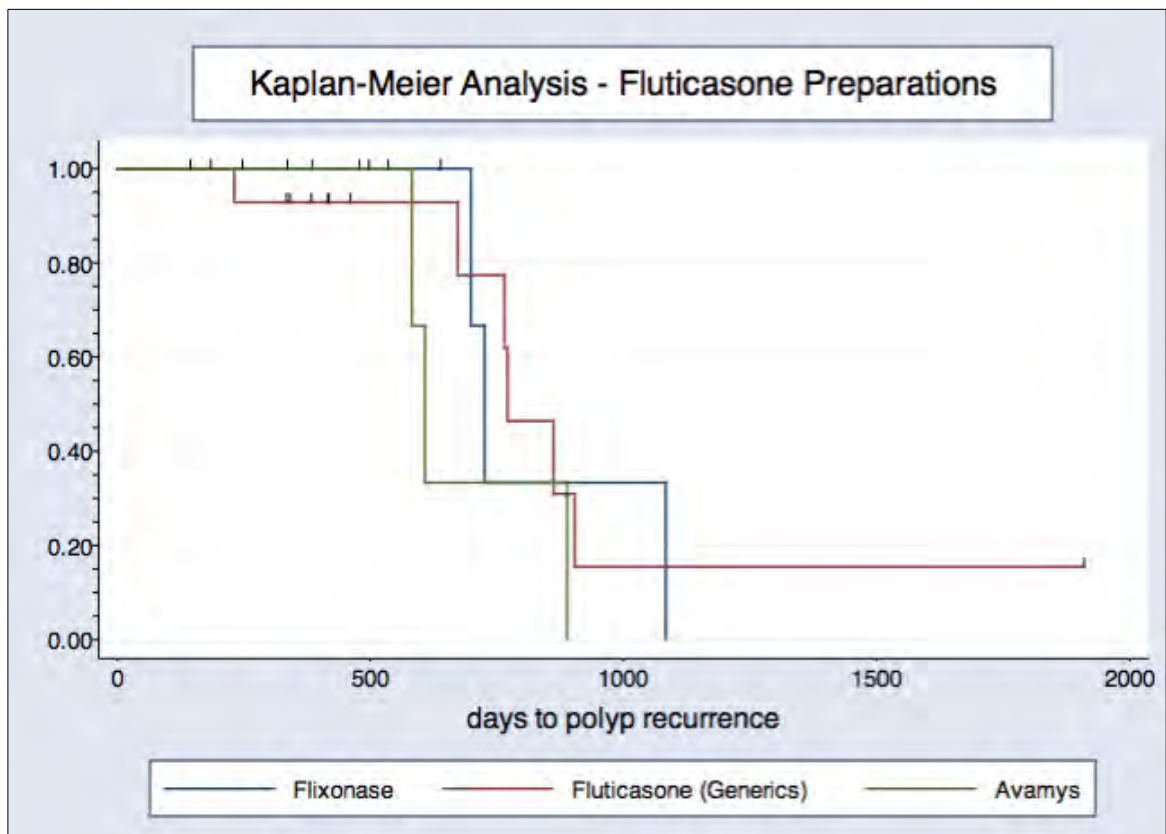
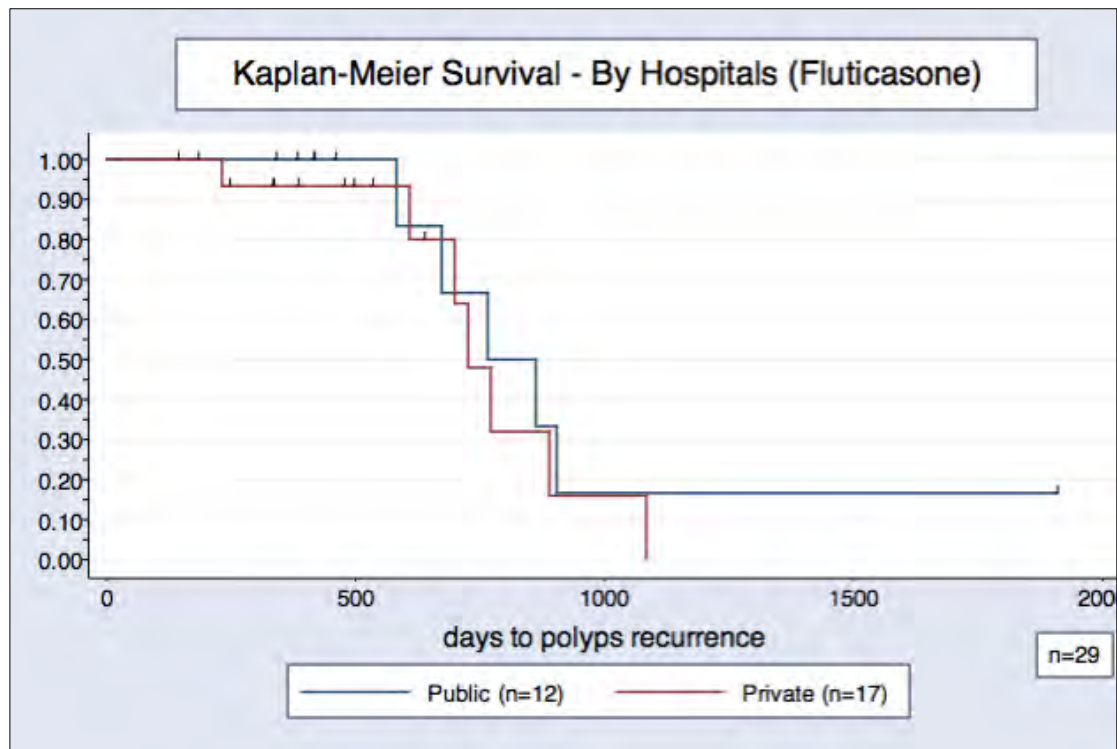


Figure 3.



## Legends for Illustrations

**Figure 1:** *Kaplan-Meier survival analysis comparing time take to notice polyp recurrence for patients using beclomethasone, fluticasone and mometasone*

**Figure 2:** *Kaplan-Meier survival analysis of comparing time taken to notice polyp recurrence for the various fluticasone preparations. No statistical difference is noted.*

**Figure 3:** *Kaplan-Meier survival analysis comparing the time taken to notice polyp recurrence in patients using fluticasone in the public and private sectors. No statistical difference is noted.*

## Legends for Tables

**Table 1:** *All nasal spray preparations; divided by active ingredient*

**Table 2:** *Summary of demographic data*

**Table 3:** *Cost comparison for usage of steroid nasal sprays in this study. Cost is calculated if used at maximum prescribed dosage per 28 days.*

## PART D: APPENDICES

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## Ethics Approval



UNIVERSITY OF CAPE TOWN  
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Human Research Ethics Committee



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Website: [www.health.uct.ac.za/fhs/research/humanethics/forms](http://www.health.uct.ac.za/fhs/research/humanethics/forms)

24 December 2014

**HREC REF: 903/2014**

**A/Prof D Lubbe**  
Otorhinolaryngology  
ENT  
H-53 OMB

Dear A/Prof Lubbe

**PROJECT TITLE: COMPARING THE EFFICACY OF VARIOUS CORTICOSTEROID NASAL SPRAYS IN SAMTER'S POPULATION GROUP (MMed candidate-Dr P Monteiro)**

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

**Approval is granted for one year until the 30<sup>th</sup> December 2015.**

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: [www.health.uct.ac.za/fhs/research/humanethics/forms](http://www.health.uct.ac.za/fhs/research/humanethics/forms))

**Please quote the HREC REF in all your correspondence.**

*We acknowledge that the student, Dr P Monteiro will also be involved in this study.*

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

**PROFESSOR M BLOCKMAN**  
**CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE**

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

## Departmental Research Committee Approval



**UNIVERSITY OF CAPE TOWN**

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### Department of Surgery

#### Departmental Research Committee

**Professor Anwar Suleman Mall**

J-45 Room Old Main Building, Groote Schuur Hospital,  
Observatory 7925, South Africa

Tel (021) 406 6168/6232/6227 Fax (021) 448 6461

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1<sup>st</sup> December 2014

Dr P Monteiro  
Department of Surgery  
Division of Otolaryngology  
Groote Schuur Hospital  
University of Cape Town

Dear Dr Monteiro,

**RE: PROJECT 2014/116**

**PROJECT TITLE: Comparing the efficacy of various corticosteroid nasal sprays in Samter's patients**

The above proposal was reviewed by the Department of Surgery Research Committee and I am pleased to inform you that the committee approved the study.

Please use the above project number in all future correspondence.

Yours sincerely

Signed by candidate

**PROFESSOR ANWAR S MALL  
CHAIRMAN: RESEARCH COMMITTEE**

## Data Capture Sheet

| number | sex | dob        | hospital | asthma | number FESS | aspirin sensitivity | CAST | lys-aspirin | lys-a interpretation | surgery date | follow up  | spray used | polyps present | days to recurrence | days disease free | small recovery |
|--------|-----|------------|----------|--------|-------------|---------------------|------|-------------|----------------------|--------------|------------|------------|----------------|--------------------|-------------------|----------------|
| 1      | f   | 11/12/1946 | GSH      | y      | 4           | y                   | y    | 41          | neg                  | 18/10/2011   | 16/01/2013 | flomist    | n              | no recurrence      | 456               | n              |
| 2      | f   | 07/12/1950 | GSH      | y      | 4           | y                   | n    |             |                      | 13/11/2012   | 15/05/2013 | beclate    | n              | no recurrence      | 183               | u              |
| 3      | f   | 12/08/1948 | GSH      | y      | 3           | y                   | n    |             |                      | 7/02/2012    | 27/03/2013 | flomist    | n              | no recurrence      | 414               | n              |
| 4      | m   | 1/09/1955  | GSH      | y      | 1           | y                   | y    | 43          | neg                  | 27/09/2011   | 26/10/2012 | beclate    | n              | no recurrence      | 395               | n              |
| 5      | m   | 20/05/1956 | GSH      | y      | 8           | y                   | de   | de          | de                   | 17/08/2010   | 31/08/2011 | flomist    | n              | no recurrence      | 379               | n              |
| 6      | f   | 19/02/1949 | GSH      | y      | 1           | y                   | n    |             |                      | 31/05/2011   | 2/05/2012  | flomist    | n              | no recurrence      | 337               | n              |
| 7      | f   | 7/02/1962  | GSH      | y      | 2           | y                   | n    |             |                      | 15/03/2011   | 26/10/2012 | beclate    | n              | no recurrence      | 591               | y              |
| 8      | f   | 20/02/1992 | PH       | y      | 1           | y                   | n    |             |                      | 24/09/2012   | 11/02/2013 | avamys     | n              | no recurrence      | 140               | y              |
| 9      | f   | 20/11/1962 | PH       | y      | 2           | y                   | y    | 75          | pos                  | 21/03/2012   | 15/10/2012 | nasonex    | n              | no recurrence      | 208               | y              |
| 10     | f   | 3/09/1977  | PH       | y      | 4           | y                   | n    |             |                      | 22/05/2009   | 25/10/2012 | rinelon    | n              | no recurrence      | 1252              | n              |
| 11     | m   | 23/05/1966 | PH       | y      | 2           | y                   | n    |             |                      | 13/05/2011   | 25/10/2012 | flixonase  | n              | no recurrence      | 531               | y              |
| 12     | f   | 29/08/1933 | PH       | y      | 2           | y                   | n    |             |                      | 6/08/2010    | 2/05/2012  | flixonase  | n              | no recurrence      | 635               | y              |
| 13     | f   | 31/05/1959 | PH       | y      | 3           | y                   | y    | 0           | neg                  | 7/05/2009    | 26/03/2012 | nasonex    | n              | no recurrence      | 1054              | y              |
| 14     | f   | 26/11/1964 | PH       | y      | 8           | y                   | n    |             |                      | 30/11/2011   | 25/10/2012 | flonase    | n              | no recurrence      | 330               | y              |
| 15     | m   | 9/10/1960  | PH       | y      | 2           | y                   | n    |             |                      | 15/08/2012   | 15/04/2013 | avamys     | n              | no recurrence      | 243               | y              |
| 16     | f   | 3/08/1955  | PH       | y      | 1           | y                   | n    |             |                      | 15/04/2011   | 12/03/2012 | avamys     | n              | no recurrence      | 332               | y              |
| 17     | f   | 11/12/1946 | GSH      | y      | 4           | y                   | y    | 41          | neg                  | 5/08/2008    | 26/01/2011 | flomist    | y              | 904                |                   | n              |
| 18     | f   | 11/12/1946 | GSH      | y      | 4           | y                   | de   | de          | de                   | 11/07/2006   | 16/04/2008 | beclate    | y              | 645                |                   | n              |
| 19     | m   | 20/05/1956 | GSH      | y      | 9           | y                   | y    | 0           | neg                  | 3/06/2008    | 7/04/2010  | flomist    | y              | 673                |                   | n              |
| 20     | m   | 20/05/1956 | GSH      | y      | 9           | y                   | y    | 0           | neg                  | 17/08/2010   | 31/08/2011 | flomist    | n              | no recurrence      | 379               | n              |
| 21     | f   | 18/09/1964 | GSH      | y      | 1           | y                   | n    |             |                      | 18/01/2011   | 4/05/2011  | beclate    | y              | 106                |                   | n              |
| 22     | m   | 19/11/1958 | GSH      | y      | 1           | y                   | n    |             |                      | 22/06/2010   | 31/05/2011 | beclate    | y              | 336                |                   | y              |
| 23     | f   | 01/12/1949 | GSH      | y      | 11          | y                   | y    | 0           | neg                  | 3/06/2008    | 21/08/2013 | flomist    | n              | no recurrence      | 1905              | y              |
| 24     | f   | 15/10/1938 | GSH      | y      | 4           | y                   | n    |             |                      | 24/08/2010   | 16/05/2013 | beclate    | n              | no recurrence      | 996               | n              |
| 25     | f   | 24/10/1947 | GSH      | y      | 2           | y                   | y    | 27          | neg                  | 11/05/2011   | 27/07/2011 | beclate    | y              | 77                 |                   | y              |
| 26     | f   | 24/09/1962 | GSH      | y      | 2           | y                   | n    |             |                      | 31/05/2011   | 26/09/2012 | beclate    | y              | 484                |                   | n              |
| 27     | m   | 06/10/1992 | GSH      | y      | 3           | y                   | n    |             |                      | 11/04/2009   | 18/01/2010 | beclate    | y              | 282                |                   | n              |
| 28     | m   | 06/10/1992 | GSH      | y      | 3           | y                   | n    |             |                      | 13/07/2010   | 15/09/2010 | beclate    | y              | 64                 |                   | n              |
| 29     | m   | 06/10/1992 | GSH      | y      | 3           | y                   | n    |             |                      | 16/10/2012   | 18/09/2013 | beclate    | y              | 337                |                   | n              |
| 30     | m   | 25/05/1979 | GSH      | y      | 3           | y                   | y    | 0           | neg                  | 13/05/2011   | 8/02/2012  | beclate    | y              | 271                |                   | y              |
| 31     | m   | 12/12/1962 | GSH      | y      | 4           | y                   | n    |             |                      | 1/06/2011    | 3/01/2013  | avamys     | y              | 582                |                   | n              |
| 32     | f   | 01/01/1972 | GSH      | y      | 1           | y                   | y    | 45          | neg                  | 29/03/2011   | 29/09/2011 | beclate    | y              | 184                |                   | n              |
| 33     | f   | 11/04/1952 | GSH      | y      | 3           | y                   | n    |             |                      | 7/10/2008    | 16/02/2011 | flomist    | y              | 862                |                   | y              |
| 34     | f   | 21/10/1982 | GSH      | y      | 2           | y                   | n    |             |                      | 23/10/2012   | 8/05/2013  | beclate    | y              | 197                |                   | y              |
| 35     | f   | 21/10/1982 | GSH      | y      | 2           | y                   | n    |             |                      | 19/04/2011   | 4/04/2012  | beclate    | y              | 351                |                   | n              |
| 36     | f   | 14/03/1974 | GSH      | y      | 1           | y                   | n    |             |                      | 17/07/2012   | 21/08/2013 | beclate    | y              | 400                |                   | n              |
| 37     | f   | 10/04/1974 | GSH      | y      | 2           | y                   | n    |             |                      | 2/02/2010    | 13/12/2010 | beclate    | y              | 314                |                   | n              |
| 38     | f   | 12/01/1979 | GSH      | y      | 3           | y                   | de   | de          | de                   | 19/06/2012   | 5/08/2013  | flomist    | n              | no recurrence      | 412               | n              |
| 39     | f   | 12/01/1979 | GSH      | y      | 3           | y                   | de   | de          | de                   | 16/10/2007   | 19/11/2009 | flomist    | y              | 765                |                   | n              |
| 40     | f   | 12/01/1979 | GSH      | y      | 3           | y                   | de   | de          | de                   | 1/08/2006    | 18/07/2007 | beclate    | y              | 351                |                   | n              |
| 41     | f   | 14/06/1963 | PH       | y      | 2           | y                   | y    | ?           | neg                  | 27/07/2012   | 12/08/2013 | avamys     | n              | no recurrence      | 381               | y              |
| 42     | m   | 8/09/1943  | PH       | y      | 4           | y                   | y    | ?           | pos                  | 3/08/2011    | 19/11/2012 | avamys     | n              | no recurrence      | 474               | y              |
| 43     | m   | 7/05/1969  | PH       | y      | 5           | y                   | n    |             |                      | 25/02/2011   | 25/10/2012 | avamys     | y              | 608                |                   | n              |
| 44     | m   | 18/12/1975 | PH       | y      | 3           | y                   | n    |             |                      | 3/11/2010    | 11/06/2012 | nexomist   | y              | 586                |                   | y              |
| 45     | m   | 18/12/1975 | PH       | y      | 3           | y                   | n    |             |                      | 8/12/2008    | 25/10/2010 | nasonex    | y              | 686                |                   | n              |
| 46     | m   | 13/06/1983 | PH       | y      | 4           | y                   | y    | 0           | neg                  | 6/12/2010    | 25/07/2011 | flomist    | y              | 231                |                   | n              |
| 47     | f   | 10/01/1959 | PH       | y      | 3           | y                   | n    |             |                      | 20/04/2012   | 15/03/2013 | nasonex    | n              | no recurrence      | 329               | n              |
| 48     | f   | 28/11/1957 | PH       | y      | 1           | y                   | n    |             |                      | 4/11/2011    | 3/10/2013  | flixonase  | y              | 699                |                   | n              |
| 49     | f   | 16/08/1978 | PH       | y      | 1           | y                   | n    |             |                      | 3/04/2013    | 30/09/2013 | avamys     | n              | no recurrence      | 180               | y              |
| 50     | f   | 1/02/1962  | PH       | y      | 2           | y                   | n    |             |                      | 25/08/2010   | 11/07/2013 | nasonex    | y              | 1051               |                   | u              |
| 51     | m   | 17/06/1966 | PH       | y      | 2           | y                   | n    |             |                      | 19/06/2009   | 24/05/2012 | nasonex    | n              | no recurrence      | 1070              | y              |
| 52     | m   | 30/04/1980 | PH       | y      | 2           | y                   | n    |             |                      | 15/08/2012   | 30/09/2013 | nasonex    | n              | no recurrence      | 411               | u              |
| 53     | m   | 30/05/1968 | PH       | y      | 4           | y                   | n    |             |                      | 2/12/2011    | 8/04/2013  | flixonase  | n              | no recurrence      | 493               | y              |
| 54     | m   | 12/11/1974 | PH       | y      | ?           | y                   | n    |             |                      | 16/11/2011   | 11/11/2013 | flixonase  | y              | 726                |                   | u              |
| 55     | m   | 26/10/1970 | PH       | y      | 5           | y                   | n    |             |                      | 21/05/2010   | 9/05/2013  | flixonase  | y              | 1084               |                   | n              |
| 56     | m   | 12/09/1969 | PH       | y      | 2           | y                   | n    |             |                      | 24/11/2010   | 1/05/2013  | avamys     | y              | 889                |                   | y              |
| 57     | f   | 8/01/1967  | PH       | y      | 3           | y                   | n    |             |                      | 1/02/2008    | 20/08/2012 | nasonex    | y              | 1662               |                   | n              |
| 58     | m   | 7/11/1976  | PH       | y      | 3           | y                   | n    |             |                      | 29/06/2011   | 8/08/2013  | flonase    | y              | 771                |                   | y              |

**STATA**

Nasal sprays by active ingredient:

| spraynew  | person-time       | failures  | rate          | [95% Conf. Interval] |               |
|-----------|-------------------|-----------|---------------|----------------------|---------------|
| Beclome~e | <b>6564.0000</b>  | <b>15</b> | <b>2.2852</b> | <b>1.3777</b>        | <b>3.7905</b> |
| Flutica~e | <b>16815.0000</b> | <b>12</b> | <b>0.7136</b> | <b>0.4053</b>        | <b>1.2566</b> |
| Mometas~e | <b>8309.0000</b>  | <b>4</b>  | <b>0.4814</b> | <b>0.1807</b>        | <b>1.2827</b> |
| total     | <b>31688.0001</b> | <b>31</b> | <b>0.9783</b> | <b>0.6880</b>        | <b>1.3911</b> |

Nasal sprays: Age distribution:

| -> spraynew = Beclomethasone |           |           |           |                 |                 |           |           |
|------------------------------|-----------|-----------|-----------|-----------------|-----------------|-----------|-----------|
| variable                     | N         | min       | max       | mean            | sd              | p50       | iqr       |
| ageyrs                       | <b>19</b> | <b>16</b> | <b>71</b> | <b>41.31579</b> | <b>16.40817</b> | <b>39</b> | <b>28</b> |

| -> spraynew = Fluticasone |           |           |           |                 |                 |           |           |
|---------------------------|-----------|-----------|-----------|-----------------|-----------------|-----------|-----------|
| variable                  | N         | min       | max       | mean            | sd              | p50       | iqr       |
| ageyrs                    | <b>29</b> | <b>20</b> | <b>76</b> | <b>47.96552</b> | <b>13.24355</b> | <b>49</b> | <b>17</b> |

| -> spraynew = Mometasone |           |           |           |             |                 |           |           |
|--------------------------|-----------|-----------|-----------|-------------|-----------------|-----------|-----------|
| variable                 | N         | min       | max       | mean        | sd              | p50       | iqr       |
| ageyrs                   | <b>10</b> | <b>31</b> | <b>53</b> | <b>41.2</b> | <b>8.403703</b> | <b>42</b> | <b>17</b> |

### Nasal sprays: Follow-up:

-> spraynew = Beclomethasone

| variable | N  | min | max | mean     | sd       | p50 | iqr |
|----------|----|-----|-----|----------|----------|-----|-----|
| fupdays  | 19 | 64  | 996 | 345.4737 | 222.5804 | 336 | 216 |

-> spraynew = Fluticasone

| variable | N  | min | max  | mean     | sd       | p50 | iqr |
|----------|----|-----|------|----------|----------|-----|-----|
| fupdays  | 29 | 140 | 1905 | 579.8276 | 348.1099 | 493 | 347 |

-> spraynew = Mometasone

| variable | N  | min | max  | mean  | sd       | p50   | iqr |
|----------|----|-----|------|-------|----------|-------|-----|
| fupdays  | 10 | 208 | 1662 | 830.9 | 461.9566 | 868.5 | 659 |

### Log-rank test for equality of survivor functions:

| spraynew       | Events observed | Events expected |
|----------------|-----------------|-----------------|
| Beclomethasone | 15              | 4.96            |
| Fluticasone    | 12              | 16.32           |
| Mometasone     | 4               | 9.72            |
| Total          | 31              | 31.00           |

chi2(2) = 27.38  
Pr>chi2 = 0.0000

Survival analysis: Crude hazard ratio: Polyp recurrence rate  
(spraycat1=beclomethasone, spraycat2=fluticasone, spraycat3=mometasone)

```

. *** Crude Hazard Ratio *****
.
.   xi: stcox i.spraycat
i.spraycat      _Ispraycat_1-3      (naturally coded; _Ispraycat_1 omitted)

      failure _d: recur
analysis time _t: survivaltime
              id: id

Iteration 0:  log likelihood = -96.462181
Iteration 1:  log likelihood = -87.56107
Iteration 2:  log likelihood = -85.622729
Iteration 3:  log likelihood = -85.582459
Iteration 4:  log likelihood = -85.582455
Refining estimates:
Iteration 0:  log likelihood = -85.582455

Cox regression -- Breslow method for ties

No. of subjects =          58                Number of obs =          58
No. of failures =          31
Time at risk   =         32073
Log likelihood = -85.582455

LR chi2(2)      =         21.76
Prob > chi2     =         0.0000

```

| _t           | Haz. Ratio | Std. Err. | z     | P> z  | [95% Conf. Interval] |          |
|--------------|------------|-----------|-------|-------|----------------------|----------|
| _Ispraycat_2 | .188241    | .0784244  | -4.01 | 0.000 | .0831935             | .4259308 |
| _Ispraycat_3 | .0933182   | .0576794  | -3.84 | 0.000 | .0277872             | .3133926 |

Survival analysis: Age adjusted hazard ratio: Polyp recurrence rate  
(spraycat1=beclomethasone, spraycat2=fluticasone, spraycat3=mometasone)

```
. ** Adjusted Hazard Ratio ****
*
.   xi: stcox i.spraycat ageyrs
i.spraycat      _Ispraycat_1-3      (naturally coded; _Ispraycat_1 omitted)

      failure _d: recur
analysis time _t: survivaltime
      id: id
```

```
Iteration 0:  log likelihood = -96.462181
Iteration 1:  log likelihood = -77.241852
Iteration 2:  log likelihood = -76.910239
Iteration 3:  log likelihood = -76.907694
Iteration 4:  log likelihood = -76.907694
Refining estimates:
Iteration 0:  log likelihood = -76.907694
```

Cox regression -- Breslow method for ties

```
No. of subjects =          58                Number of obs =          58
No. of failures =          31
Time at risk   =         32073

LR chi2(3)      =         39.11
Prob > chi2    =         0.0000

Log likelihood = -76.907694
```

| _t           | Haz. Ratio | Std. Err. | z     | P> z  | [95% Conf. Interval] |          |
|--------------|------------|-----------|-------|-------|----------------------|----------|
| _Ispraycat_2 | .1133354   | .059974   | -4.11 | 0.000 | .0401729             | .3197409 |
| _Ispraycat_3 | .0367538   | .0268661  | -4.52 | 0.000 | .0087719             | .1539958 |
| ageyrs       | .9415158   | .0145691  | -3.89 | 0.000 | .9133897             | .9705081 |

Log rank test for equality of survivors: Fluticasone v Mometasone: Polyp recurrence

| spraynew    | Events<br>observed | Events<br>expected |
|-------------|--------------------|--------------------|
| Fluticasone | <b>12</b>          | <b>8.92</b>        |
| Mometasone  | <b>4</b>           | <b>7.08</b>        |
| Total       | <b>16</b>          | <b>16.00</b>       |

chi2(1) = **2.55**  
 Pr>chi2 = **0.1106**

Survival analysis: Crude hazard ratio: Fluticasone v Mometasone: Polyp recurrence rate  
(spraycat1=fluticasone, spraycat2=mometasone)

```
. xi: stcox i.spraynew
i.spraynew      _Ispraynew_2-3      (naturally coded; _Ispraynew_2 omitted)

      failure _d: recur
      analysis time _t: survivaltime
      id: id

Iteration 0:  log likelihood = -38.586112
Iteration 1:  log likelihood = -37.247876
Iteration 2:  log likelihood = -37.235983
Iteration 3:  log likelihood = -37.235978
Refining estimates:
Iteration 0:  log likelihood = -37.235978

Cox regression -- no ties

No. of subjects =          39          Number of obs =          39
No. of failures =          16
Time at risk   =        25124

LR chi2(1)      =          2.70
Prob > chi2    =          0.1003

Log likelihood = -37.235978
```

| _t           | Haz. Ratio      | Std. Err.       | z            | P> z         | [95% Conf. Interval]    |
|--------------|-----------------|-----------------|--------------|--------------|-------------------------|
| _Ispraynew_3 | <b>.4000967</b> | <b>.2366616</b> | <b>-1.55</b> | <b>0.121</b> | <b>.1255075 1.27544</b> |

Log rank test for equality of survivor functions: Fluticasone preparations

| spraynew3 | Events<br>observed | Events<br>expected |
|-----------|--------------------|--------------------|
| 2         | 3                  | 3.34               |
| 3         | 6                  | 6.91               |
| 5         | 3                  | 1.75               |
| Total     | 12                 | 12.00              |
|           | chi2(2) =          | 1.10               |
|           | Pr>chi2 =          | 0.5768             |

Survival analysis: Crude hazard ratio: Polyp recurrence rate (Fluticasone preparations)  
(spraycat1=Flixonase, spraycat2=fluticasone generics, spraycat3=Avamys)

```
. xi: stcox i.spraynew3
i.spraynew3      _Ispraynew3_2-5      (naturally coded; _Ispraynew3_2 omitted)

      failure_d:  recur
analysis time _t:  survivaltime
      id:  id

Iteration 0:  log likelihood = -23.450105
Iteration 1:  log likelihood = -23.000472
Iteration 2:  log likelihood = -22.973416
Iteration 3:  log likelihood = -22.973397
Refining estimates:
Iteration 0:  log likelihood = -22.973397

Cox regression -- no ties

No. of subjects =      29      Number of obs =      29
No. of failures =      12
Time at risk =      16815

Log likelihood = -22.973397      LR chi2(2) =      0.95
      Prob > chi2 =      0.6208
```

| _t            | Haz. Ratio | Std. Err. | z     | P> z  | [95% Conf. Interval] |          |
|---------------|------------|-----------|-------|-------|----------------------|----------|
| _Ispraynew3_3 | .9786663   | .7034084  | -0.03 | 0.976 | .2392437             | 4.003398 |
| _Ispraynew3_5 | 2.023977   | 1.738077  | 0.82  | 0.412 | .3760468             | 10.89355 |

Log rank test for equality of survivor functions: Hospitals (Fluticasone, polyp recurrence)

| hospital | Events<br>observed | Events<br>expected |
|----------|--------------------|--------------------|
| GSH      | 5                  | 6.11               |
| Panorama | 7                  | 5.89               |
| Total    | 12                 | 12.00              |

chi2(1) = 0.42  
Pr>chi2 = 0.5194

Survival analysis: Crude hazard ratio: Hospitals (Fluticasone, polyp recurrence)  
(hospital1=GSh, hospital2=Panorama)

```
. xi: stcox i.hospital
i.hospital      _Ihospital_1-2      (_Ihospital_1 for hospital==GSH omitted)

      failure _d:  recur
      analysis time _t:  survivaltime
      id:  id

Iteration 0:  log likelihood = -23.450105
Iteration 1:  log likelihood = -23.241784
Iteration 2:  log likelihood = -23.241769
Refining estimates:
Iteration 0:  log likelihood = -23.241769

Cox regression -- no ties

No. of subjects =          29          Number of obs =          29
No. of failures =          12
Time at risk =          16815

Log likelihood = -23.241769          LR chi2(1) =          0.42
          Prob > chi2 =          0.5186
```

| _t           | Haz. Ratio | Std. Err. | z    | P> z  | [95% Conf. Interval] |
|--------------|------------|-----------|------|-------|----------------------|
| _Ihospital_2 | 1.460527   | .8635516  | 0.64 | 0.522 | .4583823 4.653624    |

Log rank test for equality of survivor functions: Smell recovery

| spraynew       | Events<br>observed | Events<br>expected |
|----------------|--------------------|--------------------|
| Beclomethasone | 5                  | 4.13               |
| Fluticasone    | 15                 | 14.03              |
| Mometasone     | 6                  | 7.84               |
| Total          | 26                 | 26.00              |

chi2(2) = 0.79  
 Pr>chi2 = 0.6724

Survival analysis: Crude hazard ratio: Smell recovery  
 (spraycat1=beclomethasone, spraycat2=fluticasone, spraycat3=mometasone)

```
. xi: stcox i.spraynew
i.spraynew      _Ispraynew_1-3      (naturally coded; _Ispraynew_1 omitted)

      failure _d:  smell
      analysis time _t:  survivaltime
      id:  id

Iteration 0:  log likelihood = -79.721678
Iteration 1:  log likelihood = -79.311946
Iteration 2:  log likelihood = -79.30966
Iteration 3:  log likelihood = -79.30966
Refining estimates:
Iteration 0:  log likelihood = -79.30966

Cox regression -- no ties

No. of subjects =          58      Number of obs =          58
No. of failures =          26
Time at risk   =       31688

Log likelihood =    -79.30966      LR chi2(2) =          0.82
                                      Prob > chi2 =          0.6623
```

| _t           | Haz. Ratio | Std. Err. | z     | P> z  | [95% Conf. Interval] |
|--------------|------------|-----------|-------|-------|----------------------|
| _Ispraynew_2 | .8598791   | .4589069  | -0.28 | 0.777 | .3021075 2.447447    |
| _Ispraynew_3 | .5845533   | .3811863  | -0.82 | 0.410 | .1628384 2.098415    |

Kaplan-Meier survival: Smell recovery