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IMPACT OF PARTICIPATION IN RANDOMISED TRIALS ON OUTCOME FOLLOWING SURGERY FOR GASTRO-OESOPHAGEAL REFLUX

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Key words: Laparoscopic fundoplication, Gastro-oesophageal reflux, Randomised Controlled trial, Surgical Outcomes
ABSTRACT

Introduction
Patients are unwilling to participate in clinical trials if they perceive risks. To identify how trial participation impacts on outcome, outcomes were evaluated following surgery for gastro-oesophageal reflux in patients recruited to randomised trials vs. patients not in trials.

Patients and Methods
From 1994 to 2009, 417 patients entered 6 randomised trials evaluating surgery for reflux, and 980 underwent surgery outside the trials. The choice of procedure outside the trials was according to surgeon or patient preference. Clinical outcomes were determined 1 and 5 years after surgery using a standardised questionnaire, including analogue scales to assess heartburn and dysphagia, and overall satisfaction with the outcome. Subgroup analysis was undertaken for those aged < 75 yrs undergoing laparoscopic Nissen fundoplication.

Results
The trial group contained a higher proportion of men, were younger, more likely to have Barrett’s oesophagus, and have undergone a Nissen fundoplication. Reoperations within 5 years were more common in the trials group. At one year patients in the trials had slightly lower heartburn scores, and less abdominal bloating, but otherwise similar outcomes to those not in the trials. At five years there were no differences except a slightly higher dysphagia score for liquids in the trials group. For the subgroup analysis demographic data were similar for both groups, and at one year there were no differences. At 5 yrs patients enrolled in the trials had higher scores for dysphagia for liquids. The magnitude of all statistically significant differences were unlikely to be clinically significant.
Conclusion

Participation in a randomised trial assessing surgery for reflux does not impact outcomes.
INTRODUCTION

Whilst randomised controlled trials are often undertaken, and the data obtained from such studies underpins the evidence base for current clinical practice, not all patients who meet inclusion criteria for such trials are willing to participate. There might be significant barriers which prevent enrolment in clinical trials, one being the perception held by some individuals that participation makes them a “guinea pig”, and consequently participating might lead to harm. Whilst there could be some truth in this perception, particularly for early phase pharmaceutical trials, an alternative view is sometimes proposed that patients enrolled in clinical trials have better outcomes, irrespective of whether they are in a treatment or control arm, and this might be due more intensive treatment or more careful follow-up\(^1\). If this is correct, participation in a clinical trial might actually be beneficial. Hence, it is important to know whether participation in a randomised clinical trial is advantageous to participants, or whether it is detrimental, and the answer to this question should influence whether clinicians encourage or discourage their patients to participate in trials.

The answer to this question will be influenced by the context of specific trials. This has been addressed to some extent within the setting of clinical trials of cytotoxic agents used for the treatment of cancer\(^1\). Several systematic reviews have addressed this question by pooling data from published trials\(^1,2,3\), but these reviews have not demonstrated any outcome differences between patients in trials vs. outside trials. These analyses might be criticised, however, for not analysing raw data sets which have been structured to specifically address this question. Further, there are no published studies, which have addressed this issue by comparing patients from a single centre, or studies which have evaluated the question within the context of a
Since 1994, we have conducted a series of randomised controlled trials to evaluate variations in surgical procedures for the treatment of gastro-oesophageal reflux\textsuperscript{4,5,6,7,8}, and concurrently we have prospectively followed all patients undergoing surgery for reflux using a similar clinical protocol, irrespective of whether or not they were enrolled in one of the trials\textsuperscript{9}. This now provides an opportunity to determine whether enrolment in a randomised trial impacts on outcome following antireflux surgery. We have done this by comparing the outcome for patients who were entered into a randomised trial with those individuals who concurrently underwent similar surgery outside of these trials.
PATIENTS AND METHODS

From April 1994 to December 2009, patients with gastro-oesophageal reflux who presented for primary laparoscopic antireflux surgery were considered for inclusion in a series of randomised controlled trials evaluating different surgical techniques for the treatment of reflux. These trials entailed:

- Nissen fundoplication with vs. without division of short gastric vessels
- Nissen vs. anterior 180° partial fundoplication
- Nissen fundoplication with anterior vs. posterior hiatal repair
- Nissen vs. anterior 90° partial fundoplication
- Anterior 180° vs. posterior partial fundoplication

The full details of these trials and the procedures employed have been reported previously. At the same time identical surgical techniques were used for patients undergoing surgery for reflux outside of these trials. These techniques entailed either a Nissen (360°) or partial (anterior 90°, anterior 180°, or posterior) fundoplication, and the choice of procedure outside the trials was according to surgeon or patient preference.

Following surgery patients enrolled in the trials, as well as those not enrolled, all underwent follow-up using the same standardized clinical questionnaire. The questionnaire was administered by a research nurse at 3 and 12 months following surgery, and then annually thereafter. Information was collected prospectively, and managed on a computerised database (FileMaker Pro, Version 11.0). The presence or absence of heartburn, and dysphagia for liquids and solids, was graded using previously reported 0 to 10 analog scales (0 = no symptoms; 10 = severe symptoms). Patient satisfaction was also measured using an analog scale (0 = unsatisfied, 10 = highly satisfied). The presence or absence of abdominal bloating
was also determined using a yes/no question. For the current study, we analysed outcome data collected at 1 and 5 years follow-up time points to standardise the assessment of outcome.

Patients were excluded from the current study if they underwent surgery before the first randomised trial commenced (April 1994), or if they met exclusion criteria for the randomised trials; i.e. a large hiatus hernia containing more than 50% of the stomach, or the first operation in our Department was a revision procedure. Patients were divided into two groups according to whether or not they were enrolled in a trial: a “trial” group which included all patients entered into a randomised controlled trial, and a “non-trial” group which encompassed all other patients undergoing primary surgery for reflux. The clinical outcomes for the trial vs. non-trial groups were then compared.

To further minimise potential selection and outcome differences between the 2 study groups we undertook a subgroup analysis, in which we excluded all patients who had not undergone a Nissen fundoplication, and all patients over 75 years of age (n=2). Within this cohort, the trial vs. non-trial groups were again compared.

Statistical analysis was undertaken using SAS version 9.2 for Microsoft Windows XP Professional, and Instat version 3.1 (GraphPad Software Inc) software. Categorical variables are presented as n (%). Continuous variables are presented as Mean (standard deviation (SD). For comparison between groups Fischer’s Exact test was used for dichotomous variables and the Chi Square test was used for non-ordered categorical variables. Matel-Haenszel Chi Square test was used for ordered categorical variables and the Mann-Whitney U-test was used for continuous variables. The clinical trials and follow-up undertaken in this study were approved by the Human Clinical Research Ethics Committees at the Royal Adelaide Hospital
and Flinders Medical Centre, in Adelaide, South Australia.
RESULTS

From April 1994 to February 2009, 1397 patients underwent laparoscopic surgery for gastro-oesophageal reflux and met the entry criteria for this study. 417 were enrolled in a prospective randomised trial (trial group), and 981 concurrently underwent surgery outside the trials (non-trial group). Demographic details are summarised in Table 1. The trial group contained a higher proportion of men, were on average 2.5 years younger, were less likely to have Barrett’s oesophagus, and were more likely to have undergone a Nissen fundoplication.

Follow-up is summarised in Figure 1 and Table 2. During the first year of follow up, 2 patients in the trial group died and 38 (9.1%) did not provide clinical follow-up data at the 1 year time point, whereas in the non-trial group 4 patients died in the first year, and 194 (19.8%) did not provide follow-up data at the 1 year time point. No deaths were related to the antireflux surgery procedures. Clinical outcome data was available for 377 (90.8%) patients in the trial group vs. 782 (80.2%) in the non-trial group at the 1 year follow-up point. At 1 year, no differences were seen in the analog scores for dysphagia or satisfaction, although the score for heartburn was significantly lower, and more patients reported symptoms of abdominal bloating in the non-trial group (56.7% vs. 50.3% p=0.0462).

389 patients in the trial group and 714 in the non-trial group (total = 1003) underwent surgery 5 or more years before the data analysis was conducted. At 5 years follow-up, 4 more patients in the trial group had died, and 11 (2.8%) of the trial group provided no follow up data. Hence, an outcome was available from 378 (97.2%) patients at 5 years. In the non-trial group 18 further patients had died by 5 yrs, and outcome data was not available for 45 (6.3%) of the non-trial group. Hence, an outcome was available for 669 (93.7%) (Figure 1). At five years
symptom scores were similar for both groups, except for dysphagia for liquids which was higher in the trial group (Table 2). Both groups reported similar satisfaction scores at five years follow up. There were no differences in bloating symptoms for the 2 groups, with 49.2% of the trial group and 51.8% (P=0.524) of the non-trial group reporting this symptom at 5 years.

Reoperative antireflux surgery within the first 5 years of follow-up was similar for the 2 groups, with 37 (8.9%) of the trial group and 67 (6.8%) of the non-trial undergoing revisional surgery (P=0.183). Within the trial group, 7 underwent revision for recurrent reflux, 23 for dysphagia, 5 for post-operative hiatus hernia and 2 for other reasons (postoperative bleeding - 1, bloating symptoms - 1), compared to 20, 33, 9 and 5 (bloating – 2, non-specific pain -1, oesophageal perforation -2) respectively in the non-trial group.

The results of the subgroup analysis in the patients aged less than 75 years who underwent a Nissen fundoplication are summarised in Tables 3 and 4, and Figure 2. The trial vs. non-trial groups within this subgroup were well matched for gender, age, BMI and presence of Barrett’s oesophagus. Completeness of follow-up at 1 and 5 years for the subgroups is summarised in Figure 2. In the first year of follow-up one patient from each group died. An outcome was available at 1 year from 302 (90.4%) of patients in the trial group and 429 (78.3%) in the non-trial group. There were no significant differences between the 2 groups for the heartburn, dysphagia and satisfaction scores. 62% patients in the trial group and 68% of the non-trial group reported bloating symptoms at 1 year (p=0.151).

At 5 years follow-up, 3 further patients died in the trial subgroup, and 5 in the non-trial subgroup. Clinical follow-up at 5 years was available for 324 (97.0%) patients from the trial
group and 407 (93.1%) from the non-trial group for the subgroup analysis. At 5 years the mean analog scores for heartburn and dysphagia for liquids were slightly higher in the trial group. Scores for dysphagia for solids and satisfaction were similar for the 2 groups. The number of patients reporting bloating symptoms at 5 years was also similar; 65% in the trial group vs. 64% in the non-trial group (p=0.846).
DISCUSSION

In our departments we have conducted a series of randomised controlled trials which evaluate outcomes following antireflux surgery, and we have applied similar standardised questionnaires to the prospective assessment of reflux symptoms and other postoperative outcomes in all of the patients enrolled in these trials, and have concurrently used the same questionnaire for prospective follow-up of patients who concurrently underwent surgery outside of these trials\textsuperscript{4,5,6,7,8,9}. This has provided a unique opportunity to evaluate the impact of trial participation on clinical outcomes for a surgical procedure, laparoscopic fundoplication.

Our results demonstrated that the trial vs. non-trial groups were similar preoperatively for most parameters, except sex, age, and the balance of fundoplication types performed. A larger proportion of patients underwent a Nissen rather than a partial fundoplication within the clinical trials, probably due to standardisation to a Nissen fundoplication in 2 of the first 3 trials conducted\textsuperscript{4,6}, as well as a tendency to construct a partial fundoplication more often outside the trials once we were satisfied with the longer term outcomes for anterior 180\textdegree partial fundoplication\textsuperscript{10}. Standardisation of the selection criteria and operation type for the non-trial vs. trial groups, removed all of the preoperative differences, providing well standardised groups.

At one year follow-up the only statistically significant difference in symptoms was a slightly higher mean heartburn score in the group not enrolled in the trials. At 5 years follow up the only statistically significant difference was a slightly higher mean dysphagia score for liquids in the group enrolled in the trials. However, neither of these differences are likely to reflect clinically important differences, as the magnitudes of the actual differences were quite small.
In the matched subgroup analysis, the only statistically significant differences were slightly higher heartburn and liquid dysphagia scores at 5 years in the trial group, but again the magnitudes of the differences were very small, and unlikely to be clinically important. Overall, our results suggest equivalent outcomes for patients enrolled in randomised trials vs. those not enrolled, and no disadvantages associated with participation in this type of randomised controlled trial. This should provide reassurance to patients that they can safely enter a randomised trial, at least in the context of antireflux surgery. Further, as our results demonstrate equivalence of outcomes for patients inside and outside the randomised trials, this also suggests that the results from the randomised trials should be generalisable to the whole population of people undergoing surgery for gastro-oesophageal reflux.

In the past, it has been suggested that participants in trials might actually have an improved outcome, compared to their counterparts who do not participate, and this has been used an argument to support trial enrolment. There are various reasons why this might occur, and these include a treatment effect by which the participant benefits from an improved treatment; as well as a participation effect or “trial effect” which can be subdivided in four sub-effects. These include a protocol effect due to improved processes and outcomes, a care effect due to extra follow up and extra nursing care, a “Hawthorne effect” due to changes in patient and clinician behaviour, and a placebo effect due to changes in effects due to informed consent. Other differences between individuals who participate vs. do not participate in trials include confounding factors such as sex, age, ethnic origin, and socioeconomic status. In addition, bias can be introduced, depending on how data is collected and the completeness of follow up. Finally, publication bias can occur due to failure to publish studies reporting negative trial effects. Other literature which has compared outcomes between patients enrolled in clinical trials vs. outside trials derives mainly from the field of oncology, and this has failed to show
better outcomes for patients enrolled in randomised trials compared with those receiving the same or similar treatment outside such trials\textsuperscript{1,2,3}. Our study is the first to evaluate the impact of trial participation on outcome following a surgical procedure, and our data support the conclusion that participation in a randomised clinical trial, at least in the context of antireflux surgery, did not adversely impact the clinical outcome.

There are, however, some limitations to our study. We have only looked at patients undergoing surgery for gastro-oesophageal reflux, and the results might be different for other patient cohorts undergoing different procedures, although we can find no evidence to support any negative benefit associated with enrolment in a randomised trial of any sort. Our outcome measures were standardised clinical scores, and for the current study we did not evaluate the outcome of antireflux surgery using any objective investigations. Nevertheless, objective investigations have been used for follow-up in clinical trials by us and others, and the outcomes of these tests have always been consistent with clinical outcomes reported elsewhere\textsuperscript{4,5,6,11}.

Another risk of bias is “selection bias”, which might generate differences between participants and non-participants in clinical trials. Patients managed outside clinical trials undergo treatment according to their preferences or their surgeon’s preferences, whereas within the context of a trial some treatment choices are determined by randomisation. We tried to minimise the likelihood of this problem by undertaking the subgroup analysis which only included patients undergoing a laparoscopic Nissen fundoplication, and for this analysis the 2 groups appeared well matched. Other forms of bias include “detection bias”, which we minimised in this study by using the same follow up questionnaire, applied in the same way
by the same people, as well as “exclusion bias”, or different rates of follow up. Again, our methodology and high rates of follow-up appear to have minimised this problem.

In conclusion, we have demonstrated no disadvantages for entering a randomised clinical trial in the context of anti reflux surgery, and this outcome is consistent with findings from the domain of oncology. Patients being considered for entry into trials can be reassured that they will not be disadvantaged by entering a trial, and by allowing procedure variations to be determined by randomisation. Confirmation of these findings in other surgical contexts might allow these conclusions to be generalised more widely.

Acknowledgements
Drs Philip Game, Robert Britten-Jones, Justin Bessell and Sarah Thompson contributed patients to the randomised trials. Bernt Bentsen provided statistical support. The Swedish and Göteborg Medical Society provided a grant to Dr Engstrom, which enabled her to undertake this research in Adelaide, South Australia. The randomised controlled trials were supported by Competing Project grants from the National Health and Medical Research Council of Australia.
REFERENCES


### Table 1  Preoperative demographic data and fundoplication type for all patients in Trial vs. Non-trial groups

<table>
<thead>
<tr>
<th></th>
<th>Trial group (n=417)</th>
<th>Non-trial group (n=981)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male / Female</td>
<td>246 (59.0%) / 171 (41.0%)</td>
<td>506 (51.6%) / 475 (48.4%)</td>
<td>P=0.012</td>
</tr>
<tr>
<td>BMI</td>
<td>28.7 ± 5.7</td>
<td>29.0 ± 5.4</td>
<td>P=0.465</td>
</tr>
<tr>
<td>Age at surgery (yrs)</td>
<td>46.7 ± 12.6 (range 18-74)</td>
<td>49.2 ± 13.0 (range 18-76)</td>
<td>P=0.0007</td>
</tr>
<tr>
<td>Barrett’s oesophagus present</td>
<td>63 (15.2%)</td>
<td>136 (13.9%)</td>
<td>P=0.601</td>
</tr>
<tr>
<td><strong>Fundoplication type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nissen 360°</td>
<td>291 (69.8%)</td>
<td>550 (56.1%)</td>
<td>P=0.0001</td>
</tr>
<tr>
<td>Anterior 180° partial</td>
<td>64 (15.3%)</td>
<td>270 (27.5%)</td>
<td></td>
</tr>
<tr>
<td>Anterior 90° partial</td>
<td>53 (12.7%)</td>
<td>135 (13.8%)</td>
<td></td>
</tr>
<tr>
<td>Posterior partial</td>
<td>9 (2.2%)</td>
<td>26 (2.7%)</td>
<td></td>
</tr>
</tbody>
</table>

Data is mean ± standard deviation, or number of patients (%).
Table 2  Follow-up symptom scores for all patients in Trial vs. Non-trial groups

<table>
<thead>
<tr>
<th></th>
<th>Trial group</th>
<th>Non-trial group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphagia for liquids</td>
<td>1.1 ± 2.0</td>
<td>1.1 ± 2.0</td>
<td>p=0.551</td>
</tr>
<tr>
<td>Dysphagia for solids</td>
<td>2.1 ± 2.7</td>
<td>2.2 ± 2.5</td>
<td>p=0.214</td>
</tr>
<tr>
<td>Heartburn score</td>
<td>0.8 ± 1.9</td>
<td>1.4 ± 2.2</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Satisfaction score</td>
<td>8.4 ± 2.4</td>
<td>8.3 ± 2.4</td>
<td>p=0.244</td>
</tr>
<tr>
<td>5 years follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphagia for liquids</td>
<td>1.3 ± 2.2</td>
<td>1.0 ± 1.9</td>
<td>p=0.021</td>
</tr>
<tr>
<td>Dysphagia for solids</td>
<td>2.4 ± 2.7</td>
<td>2.1 ± 2.6</td>
<td>p=0.127</td>
</tr>
<tr>
<td>Heartburn score</td>
<td>1.7 ± 2.6</td>
<td>1.8 ± 2.6</td>
<td>p=0.236</td>
</tr>
<tr>
<td>Satisfaction score</td>
<td>8.0 ± 2.8</td>
<td>8.0 ± 2.7</td>
<td>p=0.556</td>
</tr>
</tbody>
</table>

All data is mean ± standard deviation
Table 3 – Preoperative demographic data for Trial vs. Non-trial groups for patients aged less than 75 who underwent a Nissen fundoplication

<table>
<thead>
<tr>
<th></th>
<th>Trial group (n=291)</th>
<th>Non-trial group (n=550)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male / Female</td>
<td>168 (57.7%) / 123 (42.3%)</td>
<td>316 (57.5%) / 234 (42.5%)</td>
<td>0.942</td>
</tr>
<tr>
<td>BMI</td>
<td>28.7 ± 5.9 (n=195)</td>
<td>29.5 ± 5.6 (n=147)</td>
<td>0.250</td>
</tr>
<tr>
<td>Age at surgery (yrs)</td>
<td>46.3 ± 11.9</td>
<td>45.6 ± 13.0</td>
<td>0.372</td>
</tr>
<tr>
<td>Barrett’s oesophagus present</td>
<td>44 (15.1%)</td>
<td>84 (15.3%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Data is mean ± standard deviation, or number of patients (%).
Table 4  Follow-up symptom scores for Trial vs. Non-trial groups for patients aged less than 75 who underwent a Nissen fundoplication

<table>
<thead>
<tr>
<th></th>
<th>Trial group</th>
<th>Non-trial group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 year follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphagia for liquids</td>
<td>1.2 ± 2.1</td>
<td>1.3 ± 2.1</td>
<td>P=0.623</td>
</tr>
<tr>
<td>Dysphagia for solids</td>
<td>2.3 ± 2.8</td>
<td>2.5 ± 2.6</td>
<td>P=0.303</td>
</tr>
<tr>
<td>Heartburn score</td>
<td>0.8 ± 1.9</td>
<td>0.01 ± 1.9</td>
<td>P=0.238</td>
</tr>
<tr>
<td>Satisfaction score</td>
<td>8.3 ± 2.5</td>
<td>8.5 ± 2.1</td>
<td>P=0.490</td>
</tr>
<tr>
<td><strong>5 years follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphagia for liquids</td>
<td>1.4 ± 2.3</td>
<td>1.0 ± 1.8</td>
<td>P=0.013</td>
</tr>
<tr>
<td>Dysphagia for solids</td>
<td>2.6 ± 2.8</td>
<td>2.2 ± 2.5</td>
<td>P=0.063</td>
</tr>
<tr>
<td>Heartburn score</td>
<td>1.6 ± 2.6</td>
<td>1.2+/-2.0</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Satisfaction score</td>
<td>7.9 ± 2.9</td>
<td>8.2 ± 2.5</td>
<td>P=0.148</td>
</tr>
</tbody>
</table>

All data is mean ± standard deviation
FIGURE LEGENDS

Figure 1  Flow chart of follow-up for all patients in Trial vs. Non-trial groups.

Figure 2  Flow chart of follow-up for Trial vs. Non-trial groups for patients aged less than 75 who underwent a Nissen fundoplication.
FIGURE 1

n=1397

Trial Grp (n=417)

1 year
Deceased n=2
No follow-up scores n=38
Follow-up completed n=377

5 years
Available for follow-up n=389
Deceased n=6
No follow-up scores n=11
Follow-up completed n=372

Non-trial Grp (n=980)

1 year
Deceased n=4
No follow-up scores n=194
Follow-up completed n=782

5 years
Available for follow-up n=714
Deceased n=22
No follow-up scores n=45
Follow-up completed n=647
FIGURE 2

N=882

**Trial Grp (n=334)**
- **1 year**
  - Deceased n=1
  - No follow-up scores n=32
  - Follow-up completed n=301

**Non-trial Grp (n=548)**
- **1 year**
  - Deceased n=1
  - No follow-up scores n=119
  - Follow-up completed n=428

**5 years**
- Available for follow-up n=334
- Deceased n=4
- No follow-up scores n=10
- Follow-up completed n=320

**5 years**
- Available for follow-up n=437
- Deceased n=6
- No follow-up scores n=30
- Follow-up completed n=401