The Lichtenstein inguinal hernia repair: applicability, antibiotic prophylaxis and complications
Aufenacker, T.J.
What is the quality of an unfunded multicenter randomized trial in general hospitals?
An audit.

Chapter 8
Abstract

Objective: To determine whether a randomized clinical trial in general hospitals can be performed in a reliable way without financial support.

Methods: The Lichtenstein Antibiotic Trial performed in 4 hospitals between 1998-2003 was analyzed. The results state that antibiotic prophylaxis is not indicated in low-risk patients during inguinal hernia surgery. This audit analyzed the patient charts and study forms of 98 random patients on several quality criteria and was performed by independent researchers.

Results: In all participating clinics approval of the MEC was obtained. From 63/98 (64%) of patients a proper informed consent was acquired. The last (third) follow-up was missed in 23/98 (23%) audit patients. These patients were contacted by telephone which was successful in 98% of cases. The documentation of data in patient charts and at the same time in the study forms was successful in 90% of the, during the operation used, randomisation forms and in 75% of the follow-up registration forms. The trial protocol was pursued on almost every point.

Conclusion: This audit demonstrates a number of flaws which appeared more frequently than expected. Due to a relative simple study objective, the simplicity of the study endpoint and many accessory efforts adjacent to the protocol the study’s crucial data could be gathered and an adequate conclusion drawn. In a study with a more complex objective this could not have been the case. Therefore it is almost impossible to perform a reliable unfunded multicenter randomized trial with a complex objective.
'Evidence based medicine' is nowadays a solid base for good clinical practice and several aspects have been highlighted in the past. The randomized controlled trial (RCT) is one of the best methods for answering clinical questions about diagnostics, therapy and prognosis. Usually a good RCT must include several hundreds of patients to reach adequate power. Performing a large RCT is not easy and often must frequently has to be performed in a multicenter setting to include the patient within a reasonable time. The protocol must be reviewed and approved by a medical ethical committee (MEC). Furthermore firm regulations must be followed when performing RCT for example 'good clinical practice' (GCP) for clinical research on medication and ISO14155 for research on clinical instruments. Correct documentation of study methods, data processing and results in an article is performed according to the CONSORT statement and is based on the original data of the RCT. The correctness and completeness of these original data is essential. Safe guarding the correct execution of a trial and implementing the various regulations takes more and more time and attention. It is because of these points that a good RCT almost always needs support of a study coordinator who constantly protects the quality of the trial and adequately processes the data. Many studies nowadays are supported by fulltime researchers and/or research agencies with special scientific skills and they ensure the quality and completeness of the data source. In this article the quality of an unfounded prospective randomized multicenter trial is analyzed by a research agency (Factory, CRO for medical devices) specialized in managing clinical studies. The study under evaluation was performed in four general hospitals by doctors performing science as a supplement to their daily patient related work. In none of the hospitals researchers were available with structural time to check the data and preserve the quality. All follow-up of the patients was performed during regular consulting hours by a group of surgeons and residents. The question for this audit was: can an unfunded randomized clinical trial be performed in a general hospital with the essential quality?
Patients and methods

Study characteristics and results

The original study (Lichtenstein Antibiotics Trial) was performed in four general Dutch hospitals (one teaching hospital, three at that time nonteaching hospitals) between 1998-2003. The study was double blind, randomized and involved 1040 patients undergoing Lichtenstein inguinal hernia repair (correction with a polypropylene mesh, first choice according to the Dutch Guidelines on inguinal hernia repair). Patients were randomized between a single dose of antibiotics (1500 mg Cefuroxim) and placebo to analyse the effect on the prevention of wound infections. Primary endpoint was the percentage wound infections within three months after surgery. There were eight infections (1.6%) in the antibiotics group and nine (1.8%) in the placebo group (p=0.82).

Statistical analysis revealed an absolute risk reduction (ARR) of 0.19% (95% CI: -1.78% - 1.40%) and a 'number needed to treat' (NNT) of 520 for the total number of infections. The results show that antibiotic prophylaxis is not indicated in Lichtenstein inguinal hernia repair involving low-risk patients.

Audit description

The data for this audit was collected by three researchers from the independent research agency in the years 2001, 2002 en 2003 during on site visits of the four hospitals involved. The patients, around 26 per hospital, were selected from the total population of patients in each hospital by the researchers. During the audit the official patient records and study forms of included patients were compared. The quality criteria analyzed are displayed in table 1.

<table>
<thead>
<tr>
<th>Analyzed quality criteria on behalf of the audit of the Lichtenstein Antibiotics Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is the study approved by the medical ethical committee (MEC)?</td>
</tr>
<tr>
<td>2. Does the 'case report form' (CRF) correspond with the protocol?</td>
</tr>
<tr>
<td>3. Is the informed consent form signed by the included patients?</td>
</tr>
<tr>
<td>4. How accurate was the follow-up of patients one week, two weeks and three months postoperatively?</td>
</tr>
<tr>
<td>5. How precise and complete is the registration on the CRF’s?</td>
</tr>
<tr>
<td>6. Does the researcher in the participating hospital adhere to the protocol?</td>
</tr>
</tbody>
</table>
Each case report form (CRF), the registration form for the trial data, was checked on the various pages for missing data. The data needed for final results like the randomisation form with perioperative data including the randomisation code and the postoperative follow-up registration after 1, 2 weeks and three months was controlled. The exact date of each postoperative follow-up was documented and compared with the planned date according to the protocol. In the protocol no time interval was defined for the follow-up only a single date was given. The most important goal of the CRF is to record the endpoint described in the protocol. In this study the occurrence of an infection within three months postoperatively was the endpoint. The infection criteria were defined by the centres for disease control (CDC). An occurring wound infection was classified as superficial or deep according to criteria implemented in the CRF. The data in the original patient charts were also compared to the CRF. Everything registered on the CRF should also be documented in the patient charts. This is called source data verification.

Results

1. Is the study approved by the medical ethical committee (MEC)?
   In all participating clinics approval was given before the start of the study. The report on this was not always available during the visit of the auditors.

2. Does the 'case report form' (CRF) correspond with the protocol?
   In all 4 hospitals the same CRF's are used as described in the protocol. On this CRF the infection criteria are registered according to a list of questions. The interpretation of the answers is not registered on the CRF.

3. Is the informed consent form signed by the included patients?
   Table 2 reports the number of analyzed patients and the quality of the informed consent forms. The total sample size was 105 (11%) of the 940 at that time included patients. The patients were selected by the auditors. Because of study exclusion (7) 98 patients were found suited for the audit. The study exclusion varied between the different clinics but was in line with the data from the complete study. From 63/98 (64%) of the patients a proper informed consent could be found. The other forms were incomplete or empty.
### Table 2

Data from the audit of the Lichtenstein Antibiotics Trial regarding the number of patients analyzed and the quality of the informed consent.

<table>
<thead>
<tr>
<th></th>
<th>Hospital 1</th>
<th>Hospital 2</th>
<th>Hospital 3</th>
<th>Hospital 4</th>
<th>Complete Audit</th>
<th>Complete Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients included when the audit was performed.</td>
<td>300</td>
<td>140</td>
<td>123</td>
<td>377</td>
<td>940</td>
<td>940/1040</td>
</tr>
<tr>
<td>Size of the audit sample.</td>
<td>28/300 (9%)</td>
<td>28/140 (20%)</td>
<td>24/123 (20%)</td>
<td>25/377 (7%)</td>
<td>105</td>
<td>105/940 (11%)</td>
</tr>
<tr>
<td>Patients excluded from the study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did not receive trial medication</td>
<td>1/28 (4%)</td>
<td>2/28 (7%)</td>
<td>0 (0%)</td>
<td>1/25 (4%)</td>
<td>4/105 (4%)</td>
<td>50/1040 (5%)</td>
</tr>
<tr>
<td>No mesh repair</td>
<td>0 (0%)</td>
<td>1/28 (4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1/105 (1%)</td>
<td>4/1040 (0.4%)</td>
</tr>
<tr>
<td>No operation</td>
<td>0 (0%)</td>
<td>1/28 (4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1/105 (1%)</td>
<td>13/1040 (1%)</td>
</tr>
<tr>
<td>Patient withdrew informed consent</td>
<td>0 (0%)</td>
<td>1/28 (4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1/105 (1%)</td>
<td>12/1040 (1%)</td>
</tr>
<tr>
<td>Available and suited for analysis</td>
<td>27</td>
<td>23</td>
<td>24</td>
<td>24</td>
<td>98</td>
<td>-</td>
</tr>
<tr>
<td>Informed consent form</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signed by patient</td>
<td>22/27 (81%)</td>
<td>21/23 (91%)</td>
<td>0/24 (0%)</td>
<td>20/24 (83%)</td>
<td>63/98 (64%)</td>
<td>-</td>
</tr>
<tr>
<td>Signed date missing</td>
<td>4/27 (15%)</td>
<td>1/23 (4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>5/98 (5%)</td>
<td>-</td>
</tr>
<tr>
<td>Form missing</td>
<td>1/27 (4%)</td>
<td>1/23 (4%)</td>
<td>24/24 (100%)</td>
<td>0 (0%)</td>
<td>26/98 (27%)</td>
<td>-</td>
</tr>
<tr>
<td>Form not signed</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>4/24 (17%)</td>
<td>4/98 (4%)</td>
<td>-</td>
</tr>
<tr>
<td>Total number of incomplete IC</td>
<td>5/27 (19%)</td>
<td>2 (9%)</td>
<td>24 (100%)</td>
<td>4 (17%)</td>
<td>35 (36%)</td>
<td>-</td>
</tr>
</tbody>
</table>

*All patients were informed about the study. Informed consent was only obtained by verbal agreement and was frequently (67%) noted in the patient charts.

4. How accurate was the follow-up of patients one week, two weeks and three months postoperatively?  
The accuracy on the follow-up time intervals is displayed in table 3. The defective follow-up in hospital three is striking. 10/24 (42%) of patients missed their 2nd and 3rd follow-up. They were instructed to come back in case of wound or groin alterations. The 3rd follow-up (after three months) was missed by 23/98 (23%) of the audit patients. In the complete study this was the case in 199/1040 (19%) of the patients. These 199 patients were then contacted by telephone which was successful in 195 (98%). The timing of the follow-up is good on average (8, 16 and 93 days). It is surprising to see the broad time interval of the third follow-up moment (90 days) since this control varies between 30 tot 240 days postoperatively. Most 1st and 2nd check-ups were correctly timed demonstrated by the reported mean and standard deviation (SD).
Table 3
Data from the audit of the Lichtenstein Antibiotics Trial concerning the accuracy of the follow-up time interval.

<table>
<thead>
<tr>
<th>Size of the audit sample</th>
<th>Hospital 1</th>
<th>Hospital 2</th>
<th>Hospital 3</th>
<th>Hospital 4</th>
<th>Complete Audit</th>
</tr>
</thead>
<tbody>
<tr>
<td>(number of patients)</td>
<td>28/300</td>
<td>28/140</td>
<td>24/123</td>
<td>25/377</td>
<td>105/940</td>
</tr>
<tr>
<td>Available and suited for analysis</td>
<td>27</td>
<td>23</td>
<td>24</td>
<td>24</td>
<td>98</td>
</tr>
</tbody>
</table>

**Follow-up 7 days**

<table>
<thead>
<tr>
<th>Number of days</th>
<th>Average (± SD)</th>
<th>1st Follow-up missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of days</td>
<td>Average (± SD)</td>
<td>1st Follow-up missing</td>
</tr>
</tbody>
</table>

5. How accurate and complete is the registration on the CRF's?

The precision accuracy of the registration on the CRF's is reported in table 4. The relevant data needed to judge whether or not an infection was present was almost always correctly noted on the CRF. For source data verification this data should be documented on the CRF and in the patient chart. On this point 90% of randomisation forms and 75% of follow-up forms were correctly filled in. In the other cases the relevant data was only registered on the CRF or sometimes only in the charts. In rare occasion there was a mismatch between the CRF and the chart. This was for instance the presence of swelling but this never compromised the conclusion about a possible infection.

6. Does the researcher in the participating hospital adhere to the protocol?

The trial protocol was followed on nearly all points. Only in the third hospital the informed consent was not registered with a signature of the patient but a verbal consent was acquired and documented in the patients chart in 67% of cases. In all locations the correct version of the protocol with the corresponding CRF and informed consent were used.
Table 4
Data from the audit of the Lichtenstein Antibiotics Trial regarding the accuracy of the filled in case report forms (CRF’s).

<table>
<thead>
<tr>
<th>Size of the audit sample (number of patients)</th>
<th>Hospital 1</th>
<th>Hospital 2</th>
<th>Hospital 3</th>
<th>Hospital 4</th>
<th>Complete Audit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Available and suited for analysis</td>
<td>27</td>
<td>23</td>
<td>24</td>
<td>24</td>
<td>98</td>
</tr>
</tbody>
</table>

**Inclusion form**

- Relevant data noted in chart and on CRF: 24/27 (89%), 22/23 (96%), 23/24 (96%), 19/24 (79%), 86/96 (90%)
- Relevant data only noted in chart: 3/27 (11%), 1/23 (4%), 1/24 (4%), 5/24 (21%), 10/96 (10%)

**Randomisation form**

- Relevant data noted in chart and on CRF: 27/27 (100%), 17/23 (74%), 23/24 (96%), 21/24 (88%), 88/96 (90%)
- Relevant data only noted on CRF or only in chart: 0/27 (0%), 2/23 (9%), 1/24 (4%), 3/24 (12%), 6/96 (0%)

**Incision length and blood loss not documented**

- 0/27 (0%), 4/23 (17%), 0/24 (0%), 0/24 (0%), 4/96 (4%)

**Follow-up 7 days**

- Relevant data noted in chart and on CRF: 21/27 (78%), 11/23 (48%), 22/24 (92%), 15/24 (63%), 69/96 (70%)
- Relevant data only noted on CRF or only in chart: 6/27 (22%), 11/23 (48%), 0/24 (0%), 9/24 (37%), 20/96 (21%)
- 1st Follow-up missing: 0/27 (0%), 1/23 (4%), 2/24 (8%), 0/24 (0%), 3/96 (3%)

**Follow-up 14 days**

- Relevant data noted in chart and on CRF: 20/27 (74%), 9/23 (39%), 4/24 (17%), 21/24 (88%), 54/96 (55%)
- CRF not used data only noted in chart: 4/27 (15%), 12/23 (52%), 0/24 (0%), 2/24 (8%), 16/96 (17%)
- 2nd Follow-up missing: 3/27 (11%), 2/23 (9%), 20/24 (83%), 1/24 (4%), 26/96 (27%)

**Follow-up 3 months**

- Relevant data noted in chart and on CRF: 19/27 (71%), 9/23 (39%), 14/24 (58%), 10/24 (41%), 58/96 (59%)
- Relevant data only noted on CRF or only in chart: 6/27 (22%), 8/23 (35%), 0/24 (0%), 3/24 (12%), 17/96 (18%)
- 3rd Follow-up missing: 2/27 (7%), 6/23 (26%), 10/24 (42%), 5/24 (21%), 23/96 (24%)

† Source data verification impossible.

* Incision length and length of surgery are frequently missing in the operation reports therefore source data verification is impossible on this point.
Discussion

This audit analyzed 6 quality criteria of an unfunded multicenter randomized trial. For this purpose 105 patients were selected from the 940 patients participating at that time (11%). The audit is a snapshot to judge the quality of the source data essential for a scientific study.

In all reported cases the protocol corresponds with the CRF’s and the MEC approved the study in all participating clinics. In one out of four hospitals the informed consent was verbally acquired after informing the patient according to protocol. The Dutch legislation (WMO) demands however that patients participating in trials sign an informed consent form. In this case this rule was not followed and at least the verbal consent should have been noted in all charts.

In this hospital this was only provided in 67% of cases. Also relatively many 2nd follow-up controls were missed in this clinic. Unfortunately the 3rd control (after 3 months) was not performed in 23 out of the 98 (23%) audit patients. In the complete study this was happened in 199/1040 (19%) patients.

This can lead to an observational error with an under registration of the infections. Fortunately other studies have shown that patients can reliable judge that a wound is not infected.\textsuperscript{9,10} In this study the missing data was completed by a telephonic inquiry which was successful in 195/199 (98%) patients. The timing of follow-up demonstrated a wide interval especially for the third control. In the study protocol no time period for the follow-up was defined so by strictly adhering to the protocol all patients not follow-up on the exact day should be excluded from the analysis. But also on this point no data loss is registered because of the late follow-up. During patient selection, operation and follow-up the administration on patient chart and CRF should both be correct for proper source data verification according to good scientific research. In this audit this administration was complete in 90% of peroperative randomisation form and in 75% of the follow-up registration. This did not result in a reduced quality or different study results. The reason for the missing data can be found in the fact that all scientific work had to be done during routine work like visits to the outdoor patient clinic. Because the study was unfunded there was almost no time for on site visits, training and interim quality control of data. Of course the evidence based principles\textsuperscript{11} were followed in this study. For instance “are the study groups double blind, randomized and correctly analyzed?”, “are the study results relevant for clinical use and applicable for the own patient population?”

These factors have not all been analyzed in the audit because the goal of this audit was to determine if the study was performed according to protocol and to verify the quality of the source data used for analysis. This audit display several shortcomings which occur more frequently than expected. Incomplete gathering of data is difficult to prevent without a study coordinator who can frequently verify the quality of follow-up and adherence to the protocol. In this study due to the relative simple endpoint and many extra efforts the crucial data could be gathered and an adequate conclusion reached. In studies with a more complex
objective this would not have been possible. In such a situation the study would probably not result in evidence based results or the study endpoints would not have been reached. We therefore conclude that for studies (especially RCT) the quality of the source data should be reported. Performing a data-audit by an independent organisation is only one of the ways this can be done. Only after this conditions is fulfilled a level 1B (RCT of good quality) score can be reached. When data gathering has to be flawless more time and therefore money is needed for careful monitoring of the study and strict discipline in every aspect of the protocol must be demonstrated. For studies like the one describe above the individual motivation of the researchers has strong influence on the quality of the gathered data and on the reliability of the results.

Our conclusion must be: It is almost impossible to perform reliable unfunded multicentric randomized controlled trails without proper support during data management in studies with complex objectives.

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Alles moet zo simpel mogelijk
gemaakt worden, maar niet simpeler.

*Albert Einstein*