Application

Draft **Falconer, Henrik**

Principal investigator: Henrik Falconer

Date of birth: 1973-06-04

Sex: Male

Responsible research body: Stockholm County Council

Project site: Theme: Cancer; Patient area: Pelvic cancer

Doctoral degree: 2008-05-09

Academic title: Associate Professor

Employer: Stockholm County Council

Fee category: Research in which more than one responsible research body is taking part

Fee: SEK 16,000

Project title: Multi-centre study comparing robot-assisted laparoscopic surgery with open surgery in early cervical cancer

Type of research

§ 3a The research will collect sensitive personal data

§ 4.1 The research involves a physical intervention in a research subject

§ 4.3 The research involves studies on biological material that has been taken from a living person and can be traced back to that person

1. General information

1.1 Fee category*

How many responsible research bodies will take part in the study?

Several

Are all of the research subjects directly connected to only one of the responsible research bodies?

No

Does the research relate to a clinical trial?

No

Will only existing personal data be processed in the study?

No

Category of application	Application fee
Research in which more than one responsible research body is taking part	SEK 16,000

1.2 Is an advisory statement required?*

Yes

1.3 Entity principally responsible for the research (responsible research body)*

Responsible research body

Stockholm County Council

Project site

Theme: Cancer; Patient area: Pelvic cancer

1.4 Other responsible research bodies taking part in the project

Name of organisation	Name of contact person	E-mail of contact person
1 Sahlgrenska University Hospital	Lotta Wasser	lotta.wasser@vgregion.se
2 Gynaecology Department, Linköping University Hospital	Ninne Bosendahl Wohlin	ninne.bosendahl.wohlin@regionostergotland.se
3 Västerbotten Centre for Obstetrics and Gynaecology, University Hospital of Umeå (NUS)	Eva Innala	eva.innala@vll.se
4 Skåne University Hospital	Pia Teleman	pia.teleman@skane.se
5 Gynaecology Department, Uppsala University Hospital	Masoumeh Rezapour Isfahani	masoumeh.rezapour.isfahani@akademiska.se

1.5 Chief investigator for the project (contact person):*

1.5 Chief investigator for the project (contact person):

Name*	E-mail address*
Henrik Falconer	henrik.falconer@sll.se
Telephone number*	**Mobile telephone number***
0851776303	0707742146

1.6 Does the chief investigator have a PhD?*

Yes

1.7 Co-investigators

Name	Professional title	Organisation	Qualifications etc
1 Pernilla Dahm Kähler	Consultant	Gynaecological Cancer Surgery Unit, Sahlgrenska University Hospital, Gothenburg	Associate Professor
2 Evelyn Serreyn Lundin	Consultant	Gynaecology Department, Linköping University Hospital	Specialist in Obstetrics and Gynaecology
3 Ulrika Ottander	Consultant	Department of Obstetrics and Gynaecology, University Hospital of Umeå (NUS), Umeå	Consultant
4 Jan Persson	Consultant	Department of Obstetrics and Gynaecology, Skåne University Hospital, Lund	MD, PhD
5 Karin Glimskär Stålberg	Consultant	Gynaecological Cancer Surgery Department, Uppsala University Hospital, Uppsala	Associate Professor

2. Type of research

2.1 In what way(s) will the project deal with research as defined in Sections 3-4 of the Swedish Ethical Review Act?*

§ 3a The research will collect sensitive personal data

§ 4.1 The research involves a physical intervention in a research subject

§ 4.3 The research involves studies on biological material that has been taken from a living person and can be traced back to that person

2.2 State what type of sensitive personal data will be processed in the project

5. Health

7. Genetic information

3. Aims and objectives

3.1 Title of the project:*

Multi-centre study comparing robot-assisted laparoscopic surgery with open surgery in early cervical cancer

3.2 Write a lay summary of the research project*

Cervical cancer is the fourth commonest cause of cancer-related death among women worldwide, with around 500,000 new cases a year. Fewer women in the industrialised world are affected and mortality is also lower there. Around 1400 women a year develop this disease in the Nordic region and the total 5-year survival rate is 58-67%. In Sweden around 550 women a year succumb, with a median age of 48 years. Furthermore, half of them develop symptoms at an early stage, when the disease can be treated surgically and 5-year survival is good (>90%).

The surgical treatment of cervical cancer consists of a procedure known as radical hysterectomy, where the uterus, cervix, its supporting tissue and also the upper vagina are removed, together with pelvic lymph nodes. This has traditionally been performed by open surgery; in other words an incision is made in the abdomen to gain surgical access. Since the 1990s, however, keyhole surgery has become increasingly common in the treatment of cervical cancer and almost standard practice in many parts of the world. Robotic surgery, which is an advanced form of traditional keyhole surgery, has over the past 15 years or so become an established method of advanced pelvic surgery, including operations for cervical cancer. In Sweden and the other Nordic countries, the majority of patients with early cervical cancer nowadays undergo robotic surgery.

Previous observational studies have shown that the way in which access is obtained to the abdominal cavity (keyhole technique or open surgery) makes no difference to the oncological outcome (survival and disease recurrence), but that keyhole surgery does have advantages in the form of shorter hospital stays, less bleeding and complications, plus faster post-surgical recovery.

In 2018, however, results were published from an international comparative study started in 2007, which investigated differences in disease recurrence following surgery for cervical cancer depending on whether traditional keyhole surgery or open surgery was used (the LACC study) (1). Contrary to expectations, the results showed that women who underwent keyhole surgery had a higher risk of recurrence (after a median follow up of 30 months). All of the relapses were concentrated in 13 of the >30 participating centres. Thus the LACC study evaluated traditional keyhole surgery and not robotic surgery. Unpublished data from Swedish (and Danish) quality registries in which the majority of patients undergo robotic surgery do not show this difference (after a median follow up of 44 months).

There are, at present, no randomised trials comparing robotic surgery and open surgery with recurrence and survival as the primary outcome measure for the majority of diagnoses in which robotic surgery is used (and is, moreover, already an established method).

As robotic surgery has established itself as the surgical technique of choice in the Nordic region for surgical treatment of early cervical cancer, it is extremely important that we should now, without delay, assess its oncological safety, so that women receive the surgical technique that is safest.

1. Ramirez PT, Frumovitz M, Pareja R, et al. Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer. The New England Journal of Medicine 2018; 379(20): 1895-904.

3.3 What is the scientific aim of the project?*

This is an open-label, prospective, randomised, multinational, multi-centre study based at Karolinska University Hospital, in which the Nordic countries are the main participants. The trial aims to establish whether there is any difference in disease recurrence depending on whether the surgery is performed using a robotic or open technique. Thus the surgical intervention does not actually differ between the groups.

It is planned that 768 women will take part over a 5-year period, with a follow-up 3 years later. A detailed study protocol is attached as an appendix.

Patient selection: Women with early, operable cervical cancer in Sweden (and other participating countries) in hospital departments that fulfil the quality requirements that have been set for participating centres and individual surgeons (see study protocol).

In everyday clinical practice a patient with cervical cancer is assessed in a multidisciplinary case conference in order to decide on suitability for surgical resection, then a clinical examination is performed to determine the disease stage. If the patient is at an early stage of disease, she subsequently meets a surgeon at an outpatient visit for definitive assessment and information/planning. At this appointment the patient is invited to take part in the study provided that the inclusion/exclusion criteria are fulfilled. If the patient agrees to take part, an informed consent has been signed and quality-of-life questionnaires have been answered, the patient is randomised to either open surgery or robotic surgery. (Randomisation takes place centrally at Karolinska University Hospital's Centre for Clinical Cancer Studies.) See the Information for Research Subjects and Consent Form in the appendix.

Further care is then provided in accordance with normal clinical practice, except that the patient comes for an additional study-specific follow-up visit 1 month after surgery. At four routine check-ups and one study-specific check-up after surgery three validated quality-of-life questionnaires are also completed: EORTC QLQ C30 with the cervical cancer addendum CX24, LYMQOL and EQ 5D-3L (see appendices).

3.4 What are the scientific objectives?*

The primary outcome measure is recurrence-free survival at 5 years.

Secondary outcome measures are total survival, quality of life, complications, sensitivity and negative predictive value of pelvic sentinel lymph node biopsy, plus healthcare costs.

4. Method

4.1 Explain the methodology, including the procedure, techniques or treatment*

This is an open-label, prospective, randomised, multinational, multi-centre study based at Karolinska University Hospital, in which the Nordic countries are the main participants. The trial aims to establish whether there is any difference in disease recurrence depending on whether the surgery is performed using a robotic or open technique. Thus the surgical intervention does not actually differ between the groups.

It is planned that 768 women will take part over a 5-year period, with a follow-up 3 years later. A detailed study protocol is attached as an appendix.

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In everyday clinical practice a patient with cervical cancer is assessed in a multidisciplinary case conference in order to decide on suitability for surgical resection, then a clinical examination is performed to determine the disease stage. If the patient is at an early stage of disease, she subsequently meets a surgeon at an outpatient visit for definitive assessment and information/planning. At this appointment the patient is invited to take part in the study provided that the inclusion/exclusion criteria are fulfilled. If the patient agrees to take part, an informed consent has been signed and quality-of-life questionnaires have been answered, the patient is randomised to either open surgery or robotic surgery. (Randomisation takes place centrally at Karolinska University Hospital's Centre for Clinical Cancer Studies.) See appendix for Information for Research Subjects and Consent Form.

Further care is then provided in accordance with normal clinical practice, except that the patient comes for an additional study-specific follow-up visit 1 month after surgery. At four routine check-ups and one study-specific check-up after surgery three validated quality-of-life questionnaires are also completed: EORTC QLQ C30 with the cervical cancer addendum CX24, LYMQOL and EQ 5D-3L (see appendices). It takes around 15 minutes to answer these on each occasion.

We will keep a cell sample from the cervix (which is taken in connection with the operation when the patient is under anaesthetic) and blood samples that are taken before the operation and 1 month, 1 year and 2 years after the operation in a biobank. (The blood samples are taken in connection with follow-up visits to the clinic, in other words no significant additional time is required for the participant.) The total amount of blood that may be collected will not exceed 20 ml.

4.2 Explain how the methodology differs from routine clinical measures or the standard treatment

The surgical treatment of cervical cancer consists of a procedure known as radical hysterectomy, where the uterus, cervix, its supporting tissue and also the upper vagina are removed, together with pelvic lymph nodes. This has traditionally been performed by open surgery, in other words an incision is made in the abdomen to gain surgical access. Since the 1990s, however, keyhole surgery has become increasingly common in the treatment of cervical cancer and almost standard practice in many parts of the world. Robotic surgery, which is an advanced form of traditional keyhole surgery, has over the past 15 years or so become an established method for advanced pelvic surgery, including operations for cervical cancer. In Sweden and the other Nordic countries the majority of patients with early cervical cancer nowadays undergo robotic surgery.

Both of these surgical techniques have been used in clinical practice for more than 10 years.

4.3 Outline previous experiences (your own and/or others') of the procedure, technique or treatment in question

Both of these surgical techniques have been used in clinical practice for more than 10 years.

5. Timeframe

5.1 Expected project start-date*

2019-03-28

5.2 Expected project end-date*

2027-12-15

5.3 Timeframe for the different components included in the project

5 years of recruitment followed by 3 years of follow-up, total 8 years, with the first Swedish centre starting in March 2019. It is planned that the study will have started at all centres in Sweden by 1 July 2019.

6. Data collection

6.1 Explain the data collection and the nature of the data*

Patient selection: Women with early, operable cervical cancer in Sweden (and other participating countries) in hospital departments that fulfil the quality requirements that have been set for participating centres and individual surgeons (see study protocol). The women have signed an informed consent, which is documented in the patient records.

For these patients data will also be collected about surgery and treatment, diagnostic assessment of the sentinel lymph node biopsy, disease recurrence (depending on surgical method), any complications during and after the operation, quality of life and personal data of relevance to the study (e.g. age, disease stage).

Information is obtained from patient records and information about quality of life is obtained from the patients themselves, who fill in questionnaires.

6.2 Explain the statistical basis for the size of the study population/experimental material

A clinically relevant non-inferiority margin for robotic surgery was assessed to be 7.5% (the same margin as in the recently published LACC study). With 80% power and a one-sided risk of false-positive results of 5%, it is reckoned that 127 'events' are required. In order to achieve this number of events 768 patients need to take part in the study. It is reckoned that this could happen over 5 years with a follow-up period of 3 years (see study protocol).

It is reckoned that around 200 patients a year can be recruited from Sweden and around 30 patients a year from Karolinska University Hospital.

6.3 How will the investigational procedures be documented?

Examinations and interventions are documented in patient records. Data of relevance to the study will be entered in the study database (eCRF).

6.4 How will collected data be handled and stored?*

Personal data from the present study are recorded in a database (eCRF), which is monitored by the clinical trials officer (CTO) at the Centre for Clinical Cancer Studies, Karolinska University Hospital, Solna, Sweden. The personal data processed are those that are of relevance to the study, such as age, disease stage, surgical outcome, complications, recurrence, etc. Collection of personal data relating to patient records is undertaken by registered physicians (listed in sections 1.5 and 1.7) and the relevant study nurse. All of the data recorded are coded and the patient's personal identity number and name are replaced with a study code. Only participating investigators and the study nurse have access to login data, which is received after training, so as to record data in the database (eCRF).

All of the included patients are coded and the code key is kept locked away at the relevant participating centres/clinical trials units at Karolinska University Hospital in Solna (for participants in Stockholm). Access to the code key is only granted to persons taking part in the project and to the study nurse at the relevant clinical trials unit.

Data will be archived for at least 10 years after the study ends and, for source data in Sweden, for the stipulated period after publication of the study results.

7. Ethical considerations

7.1 What risks may participation entail for the research subjects involved in the research project?*

As both of the treatment strategies are standard clinical practice and no other treatment is added, there are no obvious ethical problems from a clinical perspective. The patient's integrity is protected in that as few people as possible have access to the code key and the study nurse keeps it locked away at the clinical trials unit. Furthermore, data will subsequently only be reported at aggregated level, meaning that the patient can never be traced.

7.2 What benefit may participation provide for the research subjects involved in the research project?*

Participation in the study does not bring any added advantage for the individual, but it will help to improve the assessment of treatment strategy for future patients.

7.3 Provide an assessment of the project's risk-benefit ratio*

The advantages and widespread adoption of robotic surgery are based chiefly on minor observational studies and the belief that it ought to be better than open surgery, since the technique facilitates advanced keyhole surgery, causes less surgical trauma and is better at visualising anatomical structures. For other diseases, such as uterine cancer, there are several randomised studies that have confirmed the advantages of keyhole surgery, not least in relation to quality of life and complications. In the Nordic region – and especially in Sweden, where robotic surgery is very well established – the structure of the healthcare system has even been adapted to the technique, resulting in shorter hospital stays and fewer beds.

It is immensely important to investigate which surgical technique is most beneficial to the patient, since a poorer oncological outcome cannot be accepted. The results from this study will provide guidance on which surgical technique should be used in early cervical cancer, irrespective of outcome. If robotic surgery proves to be inferior to open surgery, this will have major implications for how healthcare is organised and, in addition, it requires that other diagnoses for which robotic surgery is used (prostate cancer, urinary bladder cancer, rectal cancer, etc) should also put the technique to the test.

For participating research subjects it is important to emphasise that data from the Swedish quality registry (unpublished data) have not shown the difference in survival that was reported in the international, randomised study (LACC).

7.4 Describe how the project has been designed in order to minimise the risks for the research subjects*

The study is an open, randomised study that clearly shows which treatment options the patient may undergo. In order to ensure that the data are of high quality only hospitals with long experience of the technique are included. Centres participating in the study must pass a quality review (see protocol). An interim analysis is planned and will be conducted by an independent committee consisting of a statistician, an oncologist and a surgeon. The study can then be stopped if any arm shows greater deviation than expected.

7.5 In a broader perspective, identify and specify any ethical problems (advantages/disadvantages) that may arise in connection with the research project*

The advantages and widespread adoption of robotic surgery are based chiefly on minor observational studies and the "belief" that it ought to be better than open surgery, since the technique facilitates advanced keyhole surgery, causes less surgical trauma and is better at visualising anatomical structures.

In the Nordic region – and especially in Sweden, where robotic surgery is very well established – the structure of the healthcare system has even been adapted to the technique, resulting in shorter hospital stays and the need for fewer beds.

It is immensely important to investigate which surgical technique is most beneficial to the patient, since a poorer oncological outcome cannot be accepted. The results from this study will provide guidance on which surgical technique should be used in early cervical cancer, irrespective of outcome. If robotic surgery proves inferior to open surgery, this will have major implications for how healthcare is organised and, in addition, it requires that other diagnoses for which robotic surgery is used (prostate cancer, urinary bladder cancer, rectal cancer, etc) should also put the technique to the test.

8. Research subjects

8.1 How are research subjects selected?*

All patients with early cervical cancer who are candidates for surgery and fulfil the inclusion/exclusion criteria will be invited.

8.2 How many research subjects will be included in the research project?*

It is reckoned that around 200 patients a year can be recruited from Sweden and around 30 patients a year from Karolinska University Hospital.

8.3 What selection criteria will be used for inclusion?*

Inclusion criteria (please see study protocol for detailed list):

- Microscopically verified adenocarcinoma or squamous cell cancer (and adenosquamous carcinoma) of the cervix
- Disease stage IB (IB3 excluded) or IIA1 according to FIGO (International Federation of Gynaecology and Obstetrics)
- Scheduled for Querleu-Morrow type B or C radical hysterectomy
- ECOG Performance Status 0, 1 or 2
- Candidate for surgery
- Consent signed
- > 18 years

8.4 What selection criteria will be used for exclusion?*

Exclusion criteria (please see study protocol for detailed list):

- Histology other than adenocarcinoma, squamous cell cancer (and adenosquamous carcinoma)
- Tumour size greater than 4 cm
- Disease stage II-IV (except IIA1) according to FIGO staging
- Previous history of pelvic or abdominal radiotherapy
- Pregnancy

8.5 State the relationship between investigators and the research subjects*

Treater (doctor) – research subject (patient)

8.6 What insurance cover is available for the research subjects participating in the research project?

Patients treated within this study are covered by patient insurance (just like patients undergoing routine treatment).

8.7 State what preparations have been made to deal with unexpected incidental findings or events during the research process that may compromise the subjects' safety

Monitoring of unexpected incidental findings or events during surgery and for 30 days after surgery is reported on an ongoing basis in the study.

Operations take place in ordinary surgical departments which are equipped to handle any complications.

Further care is then provided in accordance with normal clinical practice, except that the patient comes for an additional study-specific follow-up visit one month after surgery.

8.8 Will financial compensation or other benefits be paid to the research subjects?*

No

9. Information and consent

9.1 Will the research subjects be informed about the research project and asked whether or not they wish to take part?*

Yes

9.1.1 How, when (at what stage) and by whom are the research subjects informed and invited to take part?*

Treating doctors will inform the patient verbally and in writing. Information about the study is given by the recruiting doctor. The patient gives her own consent verbally and in writing after she has received, read and understood the information about the study. She receives her own copy. See appendix. Participation in the study is documented in the patient records.

9.2 Will children under 18 years be included in the research project?*

No

9.3 Will research subjects whose opinion cannot be obtained due to illness, a psychological disorder, debility or some other similar circumstance be included in the research project?*

No

10. Registry data

10.1 Will the project ask for data from an existing registry?*

No

11. Biological material

11.1 Will new biological material be collected for the project?*

Yes

11.1.1 What type(s) of biological material is (are) to be collected?*

Added selection:

11.1.1 What type(s) of biological material is (are) to be collected?

2. Blood

11.1.1 What type(s) of biological material is (are) to be collected?

1. **Tissue**

11.1.2 Will it be possible to trace the origin of the biological material to an individual person, in other words will it be possible to trace or link the biological material to the individual from whom the material was derived?*

Yes

11.1.2.1 State how the biological material will be coded*

A cell sample from the cervix, taken during the operation, will be kept and stored in a biobank and coded. The same applies to the blood samples that are taken before the operation, 1 month, 1 year and 2 years after the operation. Samples are stored in coded form, with only study personnel having access to the code key. Karolinska University Hospital and the clinical trials unit have experience of coding and safekeeping of code keys. Storage of biological material is subject to Karolinska University Hospital's biobank regulations and is done in a separate sample collection within Stockholm Medical Biobank. The entity principally responsible for the biobank is Stockholm County Council.

11.1.2.2 How much biological material do you intended to collect?*

A cell sample from the cervix, which is taken in connection with the operation when the patient is under anaesthetic. Blood samples, approx. 20 ml per collection per patient, are taken on 4 occasions.

11.1.2.3 Give the name of the biobank that will be responsible for collecting the samples. If possible, give the Health and Social Care Inspectorate (IVO) registration number*

914; Stockholm Medical Biobank

11.1.2.4 State the entity principally responsible for the biobank*

Stockholm County Council

11.1.2.5 What analyses will be performed on the biological material?*

It is planned that blood and tissue will undergo DNA sequencing.

11.1.2.6 Where will the analyses be carried out?*

3. Outside Sweden, state country/countries

2. Within Sweden

11.1.2.7 Identify the country (or countries) if you have selected "Outside Sweden"

Denmark, Norway, Finland, USA or Canada

11.1.2.8 How will the biological material be handled once the analyses have been performed?*

1. The material will be destroyed.

11.1.2.9 How long will the biological material be available for the project?

From*

2019-03-28

Until*

2027-12-31

11.1.2.10 State a reason for choosing the period for which the project will have access to the biological material*

Patients will be recruited over a period of around 5 years (until around 2024) and the last blood samples will be taken at the last follow-up (3 years post-op, 2027).

11.1.2.11 How long does the biological material need to be available after the project has ended?

From*

2027-12-31

Until*

2038-01-01

11.1.2.12 State a reason for choosing the period for which the project will have access to the biological material after the project has ended*

The last blood samples will be taken in 2027 (see explanation under 11.1.2.10). Having access to the biological material will allow time for analysis, interpretation, reanalysis (if necessary) and validation.

11.2 Is it intended that the project will use biological material from one or more existing sample collections?*

Yes

11.2.1 What biological material do you intend to use?*

Added selection:

11.2.1 What biological material do you intend to use?

1. Tissue

11.2.2 How much biological material do you intend to use?*

We wish to have access to resected tumour material that is available in clinical pathology. We would like to have access to original slides that have been used for diagnostic purposes. We also wish to obtain 2 'cores' from formalin-fixed paraffin-embedded (FFPE) blocks in order to produce a so-called tissue microarray.

11.2.3 State the name(s) of responsible biobanks and entities from which the biological material will be obtained*

914; Stockholm Medical Biobank

11.2.4 **State the name of the biobank that will be responsible for this sample collection and, if possible, give the Health and Social Care Inspectorate (IVO) registration number***

914; Stockholm Medical Biobank

11.2.5 **State the entity principally responsible for the biobank***

Stockholm County Council

11.2.6 **State how the material is coded***

Samples are stored in coded form, with only study personnel having access to the code key.

11.2.7 **What analyses will be performed on the biological material?***

Immunohistochemistry and in-situ hybridisation of FFPE tumour material.

11.2.8 **Where will the analyses be carried out?***

1. In our own laboratories

11.2.9 **Identify the country (or countries) if you have selected "Outside Sweden"**

11.2.10 **How will the biological material be handled once the analyses have been performed?***

1. The material will be destroyed.

11.2.11 **How long does the biological material need to be available for the project?**

11.2.11.1 From*

2019-03-28

11.2.11.2 Until*

2027-12-31

11.2.12 **Give a reason for choosing the period for which the biological material will need to be available for the project***

Patients will be recruited over a period of around 5 years (until around 2024) and the last follow-up is 3 years post-op (2027).

11.2.13 **How long does the biological material need to be available after the project has ended?**

11.2.13.1 From*

2027-12-31

11.2.13.2 Until*

2038-01-01

11.2.14 **Give a reason for choosing the period for which the biological material needs to be available after the project has ended***

Last follow-up is 2027 (see explanation under 11.1.2.10). Having access to the biological material will allow time for analysis, interpretation, reanalysis (if necessary) and validation.

12. Results from animal studies

12.1 Are there relevant results from animal studies?*

N/A

13. Reporting of results

13.1 How will the entity principally responsible for the research and co-investigators be ensured access to data?*

Data processing and the first draft of the report for the primary outcome measure will be carried out by persons listed under 1.5 and 1.7.

13.2 Who will be responsible for data processing and written reporting of the results?*

Data processing and the first draft of the report for the primary outcome measure will be carried out by persons listed under 1.7. Please see attached CV for details.

13.3 How and when do you intend to publish the results?*

The results will be reported in peer-reviewed scientific journals and at international/national meetings and scientific conferences.

13.4 How will the subjects' right to integrity be ensured when the material is published?*

All results will be fully pseudonymised for the purposes of statistical processing and official reporting or publication and reported at group level.

14. Financial matters

14.1 Disclose any financial agreements with sponsors or other funders (name(s) and amount(s))

Not relevant.

14.2 Disclose the economic interests of the entity principally responsible for the research, the chief investigator and the co-investigator*

Not relevant.

15. Appendices

15.1 Attach a research protocol that is intended for specialists*

See next page for appendix.

15.2 Will advertising material be used for recruitment of research subjects?*

No

15.3 Will written information be given to the research subjects?*

Yes

15.3.1 Subject information sheet*

See next page for appendix.

15.3.2 Subject information sheet

No file has been uploaded

15.3.3 Subject information sheet

No file has been uploaded

15.3.4 Subject information sheet

No file has been uploaded

15.3.5 Subject information sheet

No file has been uploaded

15.4 Will the project ask for data from an existing registry?*

No

15.5 Does the research relate to a clinical trial?*

Yes

15.6 Will surveys, questionnaires, interview guides or interview questions be used in the project?*

Yes