Clinical Study Protocol

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Radiation Induced Cystits treated with Hyperbaric Oxygen – A Randomized controlled Trial

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The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date:	Administrative Change No.	Date:
2 Blood samples	2013-01-15		
3 Re-screening	2013-03-27		
4 New inclusion criteria added (number 6) – "Radiation cystitis is the most probable cause for the patient's symptoms". Genèva added. Updated contact information for Copenhagen. Clarification of subject and screening number. Instructions for cystoscopy in App E. Addition of inclusion criteria number 6. Clarification that AE only will be collected during HBOT-period. Clarification regarding study-specific blood-test. The study's estimated end-date has been changed (+1y). App B, C and D had been updated. App E has been added.	2014-05-01		

PROTOCOL SYNOPSIS – 1 MAY 2014/4

Radiation Induced Cystits treated with Hyperbaric Oxygen – A Randomized controlled Trial

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Study period

Estimated date of first subject enrolled: June 2012

Estimated date of last subject completed: March 2016

Objectives

The primary objective of this study is to assess the relief of symptoms after HBO therapy in patients with late radiation cystitis by having EPIC symptom estimation scale as primary variable.

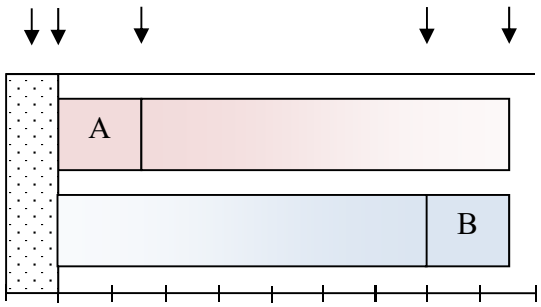
The secondary objectives are

- To assess health related quality of life before and after HBO therapy having SF-36 as the variable
- To investigate the mucosa with respect to functionality by assessment of inflammation activity, quantification of fibrosis, vascular density and the presence of stems cells having biopsies for histological analysis as variables
- To assess the severity of radiation injury having the RTOG-scale as variable.

Study design

This is a prospective, randomized, controlled, parallel-group, multicenter study in Sweden, Norway and Denmark to evaluate the effects of hyperbaric oxygen therapy in 80 subjects suffering from radio-

therapy induced cystitis. Study includes 5 visits and has a total duration of approximately 8 months per subject including treatment periods.



The control group

The control group (n=40) will start treatment 6-8 months after randomization (delayed start) otherwise following the same protocol

Intervention

All 80 subjects will have 40 treatments within 60 days in a mono- or multi-place chamber with 80-90 minutes of 100% O2 at 2.4-2.5 ATA, each time.

Outcome variable(s):

Symptom rating (EPIC), Health-related quality of life (SF36) at baseline (visit 1), visit 3, 4 and 5. Cystoscopy with biopsies and RTOG-grading at baseline and at visit 4.

All patients will be contacted for a post-study long-term follow-up yearly for 5 years regarding symptoms and quality of life.

Safety

Vital signs and standard clinical chemistry and hematology investigations will be taken before and after the study in order to document the health status of the subject. Urologist assessment including, cystoscopy and RTOG-grading. Serious adverse events will be recorded

Statistical methods

A two-sample t-test with a 5% significance level will be used. For each subject, means of measurements from baseline to each of the two measuring points will be calculated. Differences between these means for each subject will be used in the comparison of the two groups i.e. between group A and the control group B (“delayed start”).

Fisher's exact test and logic regression will be used for comparison of other results in the two treatment groups. Jonckheere-Terpstra test will be used for trend analysis.

Patient-reported outcomes and safety data will be summarized descriptively.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Explanation
AE	Adverse event (Appendix B)
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
GCP	Good Clinical Practice
HBO	Hyperbaric oxygen
HBOT	Hyperbaric oxygen therapy
IC	Informed Consent
ICH	International Conference on Harmonisation
ISF	Investigator Study File
OAE	Other Significant Adverse Event (Appendix B)
SAE	Serious adverse event (Appendix B)
SMF	Study Master File
HRQOL	Health-related Quality of Life

STUDY STRUCTURE

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1. INTRODUCTION

1.1 Background

Acute radiation cystitis occurs during or soon after radiation treatment and persists for a short period of time. Late radiation cystitis, on the other hand, can develop from 6 months to 20 years after radiation therapy. Late radiation cystitis becomes chronic and progressive and represents a range of severe and disabling clinical symptoms for which there is as yet no recommended standard management (2, 23).

The chronic phase of radiation cystitis begins approximately 6 months after therapy. However, the period between completion of radiotherapy and the manifestation of late toxicity in the bladder is extremely variable. Ischemia and fibrosis are the main factors responsible for symptoms. The vascular changes include vascular endothelial hyperplasia, vascular occlusion and perivascular fibrosis which ultimately cause tissue hypoxia. Normal smooth muscle is replaced by fibroblasts. The resulting tissue hypoxia and fibrosis can progress to necrosis and fistulation. As the submucosa becomes fibrotic, bladder capacity reduces and vascular telangiectasia develop.

Therefore, clinical presentation can include increased urinary frequency, urgency, pain or difficulty on passing urine, incontinence, hematuria, hydronephrosis, pneumaturia and fecaluria.

Bladder tissue examined histologically during the chronic phase of radiation cystitis shows non-specific submucosal edema and vasodilatation, hemorrhage, acute and chronic inflammation and bizarre stromal cells, blood vessels with myointimal thickening and atypical fibroblasts (21).

Radiation adverse effects appear in about 10-20% of all patients that are exposed for radiotherapy in the pelvic region and are severely affecting patents daily life. The frequency of delayed radiation toxicity in the bladder is about 5-10%. Therapy is primarily aimed at symptoms relief. Surgical options and cystectomy remain when non-surgical interventions fail (2).

Hyperbaric oxygen therapy (HBOT) found early use in the treatment of decompression sickness. More recent research has examined the possibility value for other conditions such as delayed radiation injury (soft tissue and bony necrosis).

HBOT involves the inspiration of a high concentration of oxygen under higher than normal atmospheric pressure. Typically, a patient breathes 100% oxygen at 2 to 3 atmospheres for 1

to 2 hours daily over the course of several weeks. This treatment boosts oxygen levels in deoxygenated body tissue. The oxygen transport in soft tissue is significantly increased. More importantly, this treatment appears to induce angiogenesis in de-vascularised tissue (3, 4, 10). Hyperbar *vs* normobar oxygen (4) have shown in a rabbit model that hyperbar treatment results in marked increased vascularity in previously irradiated tissue. A few clinical studies report the positive healing effects of HBO in patients with chronic radiation cystitis or proctitis.

Recent evidence notes that exposure to HBOT mobilizes stem/progenitor cells from the bone marrow by a nitric oxide (NO) -dependent mechanism (25) This mechanism may account for the patient cases that suggest recovery of damaged organs and tissues with HBOT.

HBO therapy is an established treatment for degeneration of blood vessels in the jawbone as a result of radiotherapy (osteoradionecrosis). In addition, the loss of osseointegrated implants in the maxillofacial bones of these patients could be significantly reduced.

Further indications for HBO therapy include soft tissue necroses, hemorrhagic cystitis and proctitis in tumour patients that have been treated by radiotherapy as part of a multimodality approach (7, 9, 10, 11, 18, 19, and 20). The HBO treatment appeared to be safe, effective and feasible.

The present study intends to investigate the effect of HBOT in patients with symptomatic radio-therapy induced cystitis.

1.2 Research hypothesis

- HBO therapy can reduce or reverse the change or otherwise limit the damage of the bladder function and/or structure, which arose as a result of radiation therapy of cancer in the pelvic region organs.

- The effects of HBOT are associated with relief of symptoms that, at least in part, is related to the reduction of the extent of the radiation damage.

- Vascular density increases, fibrosis prevalence and inflammatory activity are reduced as a sign of an improved function of the mucosa.

- Treatment results of HBOT remains, in whole or in part, during the follow-up (residual effect)

1.3 Rationale for conducting this study

10-20% of all patients receiving radiotherapy to the pelvic region suffer from unwanted side effects such as symptoms of bladder and rectum e.g. bleedings, frequent urination, incontinence and pain (2, 6, 7, 8). The symptoms are chronic, progressive and often disabling.

One of the most significant causes of the symptoms of radio therapy is inflammation and degeneration of blood vessels in the radiated tissue (1, 8). Hyperbaric oxygen therapy involves administration of oxygen at greater than normal atmospheric pressures. A well-documented effect of HBO treatment is the stimulation of angiogenesis. HBO therapy is an established treatment for degeneration of blood vessels in the jaw bone as a result of radiotherapy (3, 4, 10) and several publications have shown good efficacy also when soft tissue is affected (7, 9, 10).

If the method of treatment with HBO means a reduction of the radiotherapy side effect it is thus an obvious importance for the individual patient. There is also significant potential savings for the healthcare and society

1.4 Benefit/risk

Hyperbaric oxygen therapy is a treatment that is associated with low risk (14, 15). Because of the encapsulated nature of these chambers patients occasionally become claustrophobic and therefore refuse treatment. Patients may also develop difficulty in equalizing ear pressure with resultant ear discomfort. Pressure changes can cause a "squeeze" or barotrauma also in the tissues surrounding trapped air inside the body e.g. inside paranasal sinuses or trapped underneath dental fillings which can give rise to temporally pain. Temporarily changed vision, caused by increased fraction in the lens can be perceived which usually resolves in one to two months after termination of HBOT.

The risk of oxygen induced seizures increases with increasing exposure time and pressure. In the present study the dose is adjusted so that the effect is achieved but the risks of side effects are kept to a minimum. In addition some patients will have periodic "air breaks" during which they breathe room air to minimize the risk of oxygen toxicity. The use of air-brakes is applied according to the protocol of the local centre.

Since placebo treatment in the hyperbaric chamber is extremely difficult to achieve, delayed start of the treatment has been chosen in order to create a control group to the group receiving treatment without delay. As deterioration of the cystitis is a slow process patients in the control group are not expected to be progressing on their symptoms to any great extent. It is therefore considered ethical to use “delayed start” as a tool to achieve a control group to the treatment group.

The safety margins in the dose range, (100% O2 80-90 minutes at 240-250 kPa) are considerable. The dose and treatment regimens follow standards and routines.

1.5 Ethical assessment

The study will be conducted in compliance with ICH Good Clinical Practice and applicable regulatory requirements and in accordance with the ethical principles in the Declaration of Helsinki. For detailed information regarding ethics and regulatory review, informed consent, data protection and audits and inspections see **Appendix C** (Ethics).

Written approval or favourable opinion must be obtained from the ethics committees (IRB/IEC) prior to commencement of the trial. Regulatory authorities will receive the clinical trial application (CTA) and required documents.

The local investigator (LI) will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. A copy of the signed Informed Consent Form is kept by the subject.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary objective

The primary objective of this study is to assess the relief of symptoms after HBO therapy in patients with late radiation cystitis by having EPIC symptom estimation scale as primary variable.

2.2 Secondary objectives

- To investigate the mucosa with respect to functionality by assessment of inflammation activity, quantification of fibrosis, vascular density and the presence of stems cells having histological analysis from biopsies as variable
- To assess the severity of radiation injury having the RTOG-scale as variable
- To assess health-related quality of life before and after HBO therapy having SF-36 as the variable

2.3 Primary endpoint

The primary endpoint of this study is symptom rating after HBO therapy using the self-administrated EPIC-questionnaire original score as the primary variable at baseline and visit 4.

2.4 Secondary endpoints

- Severity of radiation injury having the RTOG as the variable at baseline and visit 4

- Histological analysis of inflammation activity, degree of fibrosis, vascular density and the presence of stems cells at baseline and visit 4.
- Health-related quality of life (SF36) at baseline visit 3, 4 and 5
- Post-study long-term follow-up follow up with Symptom rating (EPIC) and Health-related quality of life (SF36)

3. STUDY DESIGN AND PROCEDURES

3.1 Overall study design and flow chart

This is a prospective, randomized, controlled, parallel-group, multicenter study in Sweden, Norway and Denmark to evaluate the effects of hyperbaric oxygen therapy in 80 subjects with symptomatic radio-therapy induced cystitis.

All 80 subjects will have 40 treatments within 80 days in a mono- or multi-place chamber with 100% O2 at 2.4-2.5 ATA, 80-90 minutes each time. The control group (n=40) will start treatment 6-8 months after Group A otherwise following the same protocol. Recruitment will continue until 80 subjects have concluded visit 4 according to protocol.

Subjects will be given full and adequate verbal and written information about the study prior to any study procedures. Informed consent will be signed by the patient and the study physician. The original IC will be stored at the study site. A copy will be given to the patient.

Adverse events (AE) including serious adverse events (SAE) will be recorded during the HBO-treatment period. Ongoing AE and SAE at the end of the HBO-treatment period will be followed up within three months from end of HBO-treatment.

Any questions or concerns that arise related to the study protocol should be directed to the RICH-ART principle investigator.

Figure 1 and Table 1 show the study overview and activities.

Figure 1 Study overview

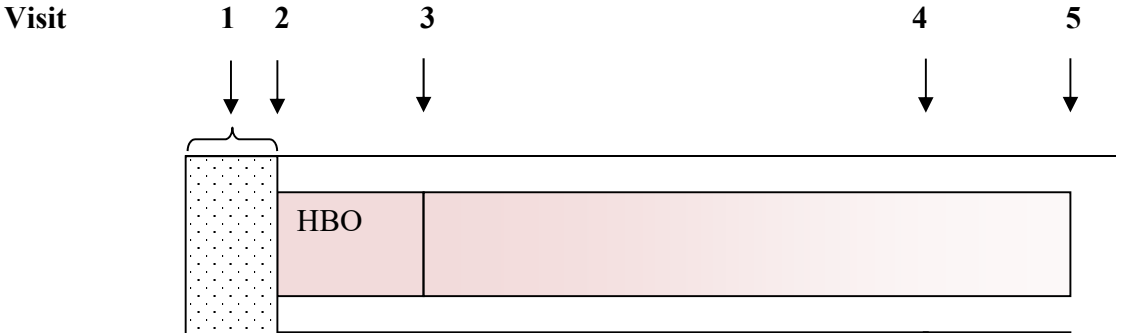

Table 1 Study Activities

Activity	**Visit 1**		**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
	Screening	Biopsy				
	Within 6 weeks					
Informed consent	X					
Demography	X					
Nicotine	X					
Weight, height	X					
Medical history and smoking	X					
Pulse, blood pressure	X			X^{A}		X^{B}
Physical examination	X			X^{A}		X^{B}
Blood for laboratory screen	X			X^{A}		X^{B}
Cystoscopy		X			X	
Biopsy for histologcal analysis		X			X	
Incl/excl criteria	X					
Randomisation	X					
HBO treatment			$\mathbf{X^{A}}$		$\mathbf{X^{B}}$	
EPIC	X			X^{A}	X	X^{B}
SF36	X			X^{A}	X	X^{B}
Concomitant medication	X		X^{A}	X^{A}	X	X^{B}
HBO side effects				X^{A}		X^{B}
SAE	X		X^{A}	X^{A}	X	X^{B}

X^{A} = Group A only X^{B} = Group B only

Visit 1 (screening). All subjects (Group A and B) will undergo a clinical examination including demography, medical, surgical and disease history, tobacco use, physical

examination, blood pressure, pulse, laboratory blood and urine safety screen and pregnancy test (if applicable) within 6 weeks prior to study start. I addition, the disease-specific symptom scale (EPIC) and health-related quality of life survey (SF-36) will be completed.

Cystoscopy including biopsy will be performed by an urologist prior to study start. The urologist will also make an assessment of the patient's medical history and anamnesis in order to establish that radiation cystitis is the most probable cause for the patient's symptoms. At this visit, it is advised that a new appointment should be scheduled for the next cystoscopy investigation at visit 4. The date of the visit 1 cystoscopy will guide the late treatment start of Group B, i.e. 6-8 months later.

Inclusion and exclusion criteria will be checked. Eligible subjects will be randomized to either immediate start of HBO treatment or delayed start.

Start of screening (Visit 1) is the date patient signs "informed consent". End of screening (Visit 1) is the date patient is randomized. Time interval between these two should not exceed 6 weeks. Extra ordinary circumstances might constitute reason to accept a small extension of the time frame, but should always be approved by PI, and documented as a "NoteToFile" in the CRF.

Visit 2 - Group A. Patients randomized to Group A will enter the oxygen pressure chamber day 1 out of 40 for 80-90 minutes each time. A nurse or another observer will monitor the patients and assist with equipment manipulation or emergencies. Patients in a multi-place chamber breathe oxygen via a mask or close-fitting plastic hood. Patient in mono-place chamber breathe ambient oxygen. Standard routines at each hyperbaric unit will be followed.

Visit 3 (Group A). After completing treatment, vital signs and medical examinations will be carried out. EPIC and SF36 will be completed. Concomitant medication and any side effects during treatment period will be recorded in the CRFs.

At visit 4, approximately 6 months later, all patients (group A and B) will undergo cystoscopy including biopsies. All patients will also complete EPIC and SF36. Concomitant medication will be recorded. Group B will start the HBO 40-days treatment within 14 days from the cystoscopy. Standard routines will be followed.

Visit 5 (Group B). After completing treatment, vital signs and medical examinations will be carried out. EPIC and SF36 will be completed. Concomitant medication and any side effects during treatment period will be recorded in the CRFs.

3.1.1 Follow-up

All patients (Group A and B) will receive HBO treatment within the frame of the clinical study. Follow-up of the Group B patients will take place after finalized study. They will be contacted by telephone or via mail for completion of EPIC and SF36 after 6-8 months after the last study visit. All patients (Group A and B) will be contacted for a post-study long-term follow-up yearly the first 5 years after last study visit regarding symptoms (EPIC) and quality of life (SF-36).

3.1.2 Stopping criteria for continuous hyperbaric oxygen administration

Stopping criteria for oxygen administration is development of serious side effects of hyperbaric oxygen therapy such as more than one oxygen-induced episode of generalized seizures, pulmonary barotruma or pronounced deterioration of cardiovascular- or respiratory failure.

3.2 Rationale for study design, doses and control groups

The dose is set to 100% O2 at least 80 minutes at least 240kPa. This exposure is considered to be sufficient to initiate angioneogenesis. The dose is adjusted so that an effect is achieved, but the risks of side effects are kept to a minimum.

Since placebo treatment in the hyperbaric chamber is extremely difficult to achieve, delayed start of the treatment has been chosen in order to create a control group (Group B) to the group receiving direct after randomization (Group A). The usual waiting time for treatment vary between hospitals but is considered relatively short, which means that patients in this group (B) are not expected to be progressing on their symptoms to any great extent.

Patients in the present study will have had their symptoms for a variety of length. It is believed that the longer the changes in the bladder have been, the harder they are to reverse. Despite this fact it has been chosen to allocate all patients despite differences in symptom history to receive the same treatment per protocol. In the statistical analysis it may be possible to make sub-group analysis.

4. SUBJECT POPULATION

A total of 80 male and female patients, treated according to protocol, between 18 and 80 years with clinically verified and symptomatic radio therapy induced cystitis will be included.

The study population will be identified from hospital oncology and urology clinics at participating centers. They can either be referred to the local hypobaric units or to a locally assigned coordinator. Subject population should be selected without bias.

Investigator must keep a record of subjects who entered pre-study screening but were never enrolled (subject screening log). Subjects that do not meet the inclusion/exclusion criteria for a study must not be enrolled into the study.

4.1 Inclusion criteria

For inclusion in the study subjects must fulfil the following criteria.

1. Provision of informed consent prior to any study specific procedures
2. Female or male aged 18-80 years
3. Intended curative radiation of the pelvic region as a treatment for cancer
4. End of radiation therapy more than 6 months ago
5. Radiation cystitis with Urological EPIC < 80
6. Radiation cystitis is the most probable cause for the patient's symptoms

4.2 Exclusion criteria

Subjects must not enter the study if any of the following exclusion criteria are fulfilled

1. Patients with major and ongoing bleedings from the bladder (requiring more than 0.5L blood-transfusion within the last four weeks)
2. Refractory incontinence requiring catheter or surgical intervention
3. Urine bladder capacity < 100ml
4. Fistula in the urine bladder
5. Contraindications for HBO therapy according to the local centres routines
6. Pregnancy
7. Mechanical ventilator support
8. Unable to follow and understand simple commands
9. Not oriented to person, place and time

4.3 Restrictions during the study

- Use effective birth control prior to and during the study (women of childbearing potential only)

- Smoking is strongly discouraged, but local routines may be followed and hence it is ultimately the LIs decision to ban or allow smoking during the study.

- Coffee or drinks with caffeine may be used according to decision by the LI.

4.4 Withdrawal of subjects

4.4.1 Criteria for discontinuation from the study

Subjects are free to discontinue their participation in the study at any time without prejudice to further treatment. Subjects may be discontinued from the study at any time as judged by the investigator due to risks to subjects, adverse events and severe non-compliance to protocol. Other reasons for discontinuing a subject are incorrect enrolment subjects lost to follow-up, new diagnosis of cancer, significant hyperbaric related complications and HBOT for other conditions given after enrolment. (See Stopping Criteria section 3.1.1).

A subject who discontinues will be asked about the reason(s) for discontinuation and the presence of any adverse events. If possible, they will be seen and assessed by the investigator. Adverse events will be followed up.

4.4.2 Study stop criteria

The Sponsor/Investigator may decide to stop the trial or part of the trial at any time. Furthermore, the manufacturers of the study drugs may revoke their products, which may lead to the entire study may be interrupted.

If a trial is prematurely terminated or suspended, the Investigator should promptly inform the patients and ensure appropriate therapy and follow-up. Furthermore, the Investigator should promptly inform the Ethics committee and provide a detailed written explanation. The regulatory authority should be informed according to national regulations.

4.5 Subject enrolment and randomization

The investigator will obtain signed informed consent from the potential subject before any study specific procedures are performed. The investigator will thereafter determine subject eligibility. Upon entering the subject into the e-CRF, the subject will be assigned a unique *screening number,* which is used during the screening process. This number is unique sequential for all centres.

Upon randomization a *subject number* is assigned to the subject by the e-CRF. These numbers are strictly sequentially and sequential for each centre with a prefix that identifies the centre. Stratification will be made as specified in 4.5.1. If a subject discontinues participation in the

study, his/her screening and subject number cannot be reused. Discontinued subjects that previously have been randomized into the study are not allowed to re-enter the study.

Subjects who discontinue from the study or fail treatment according to protocol will, if possible, be followed according to protocol (intention to treat). These subjects does not count towards the total number of patients included in the study and will hence be replaced. Recruitment ends when 80 patients has completed Visit 4 according to protocol.

This is not a blinded study. The study will use "delayed start" as the control. The analysis of EPIC, SF36 and biopsies will be made by persons blinded to the study randomization.

4.5.1 Re-screeing

Subjects that are screened but have not yet been randomized can be excluded and later re-enter the study. This might be the case if some finding during the screening requires intervention that prevents the subject to receive HBO. The subject shall be excluded from the study and the screening number is blocked. Re-screening must not be made prior to 2 months after exclusion. At re-screening the subject shall be entered as a new subject in the e-CRF and a "NoteToFile" specifying the previous screening number shall be made.

4.5.2 Stratification

Stratification will be made on the basis of gender, time from radiation to inclusion and previous major surgery in the pelvic area. Primary stratification will be made into two groups based on gender; male and female. Secondary stratification will be made into two groups based on time from last day of radiation therapy to inclusion in RICH-ART; 12 months or less and more than 12 months. Tertiary stratification will be made into two groups based on previous major surgery to the pelvic region, as defined below; yes or no.

a. Pelvic surgery for malignant disease
b. Surgery on the lower urinary tract for benign disease

5. TREATMENTS

HBO treatment will be used in the treatment of late radiation cystitis.

5.1.1 Identity of investigational product(s)

100% oxygen (O2)

5.1.2 Doses and treatment regimens

100% oxygen at 240-250 kPa will be delivered to the patents for 80-90 minutes while sitting or lying in a hyperbaric oxygen chamber. Patients will receive treatment once every

day, except week-ends, for 40 days. Both groups will follow the study protocol, however with 6-8 months apart (delayed start for Group B).

The percentage of oxygen being delivered will be checked at start and after the air brake. Notes of any discrepancies from study protocol will be made in the CRFs.

The medical oxygen is obtained from the hospital's gas system. The management and control of oxygen comply with the legislation for delivery, storage, labelling, delivery and returnable and are specified in local protocols at each hospital.

5.2 Concomitant and post-study treatment(s)

Treatment vital for the patient such as transfusion, diathermy etc. is allowed during the study.

Other medication, which is considered necessary for the subject’s safety and well-being, may be given at the discretion of the investigator.

All medications must be recorded in the appropriate sections of the case report form (CRF).

Only one session (30-40 treatments) of HBOT is given for radiation induced cystitis in today’s routine care and support for repeated HBOT is lacking. This applies for both responders and non-responders. Hence, post-study HBOT will not be offered for this condition. However, if an included patient presents with another condition during the follow-up period, where HBOT might be considered, the treatment will not be withheld. In this case, the patient will be excluded from the post-study follow-up as stated in 4.4.1.

5.3 Treatment compliance

When treatment is administered in hospitals, under the supervision of medical staff, there is no uncertainty about compliance. The HBO administration (pressure, treatment time, any air breaks any other specific conditions) must be recorded in the appropriate sections of the Case Report Forms (CRFs).

The 40 treatments should be given within the framework of 80 days. For longer interruption or discontinuation of treatment, patients should not be regarded as treated according to protocol but monitoring will continue (intention to treat). However, the patient should be considered to be treated as per protocol if at least 30 treatments in the hyperbaric chamber have been given within 60 days.

Any discrepancies from study protocol should be commented upon in CRF.

5.3.1 Accountability

The study drug (100% O2 at 240-250 kPa for 80-90 minutes) provided for this study will be used only as directed in the study protocol and according to standard routines at each hyperbaric unit.

The study personnel will account for oxygen equipment dispensed and returned.

6. STUDY MEASUREMENTS AND VARIABLES

6.1 Screening and demography

Each subject will undergo a pre-entry medical examination 1-6 weeks prior to randomization. This will consist of:

- Information and signed consent
- Demographic data – date of birth, sex
- Weight, height (BMI)
- Medical history, current medications, nicotine use
- Cancer-related history including type and localization of cancer and treatment
- Date of radiation tissue injury diagnose
- Pulse, systolic and diastolic blood pressure after 5-10 minutes rest in a sitting position
- Physical examination will include cardiovascular and respiratory systems, general appearance, eyes and ears and neurological examination (reflexes). Specification of abnormalities must be recorded in the CRFs
- Patient self-rating questionnaires: EPIC, Short form (SF)36
- Cystoscopy and biopsies
- Blood for laboratory screen.

6.1.1 A post-study follow-up

The group B patients will be contacted via mail or e-mail for completion of EPIC and SF-36 approximately 6-8 months after visit 5.

All patients will also be contacted for a post-study long-term follow-up every year during 5 years regarding persistent symptom relief and quality of life.

6.2 Efficacy

Efficacy parameters in the study are symptom ratings and health-related quality of life measured by EPIC and SF36 as well as cystoscopy including biopsies for histological analysis.

6.2.1 Patient reported outcomes (PRO)

6.2.1.1 Procedures for administration of questionnaires

Standardization of procedure for administration of the following self-administered questionnaires is important. The questionnaires will be filled in at the study site or at home according to patient's and investigator's discretion. The patients should be allowed to sit alone in a reasonable quiet environment to answer the questions. It will be emphasized that patients complete the questionnaires prior to clinical measurements stated in the study protocol and before meeting a doctor. Questionnaires should be answered by the patient her/himself alone; however, the study staff may advise the patients on how to complete the questionnaires, however without influencing the patients' responses. Ensure the patient confidentiality. Study staff should check the questionnaires for completeness. E-questionnaires are to prefer.

Questionnaires will be completed at visit 1 (Group A and B), visit 3 (Group A), visit 4 (Group A and B) and visit 5 (Group B) as well as during the follow-up.

6.2.2 Expanded Prostate cancer Index Composite (EPIC)

EPIC was developed to measure health-related quality of life among men with prostate cancer (22) modified to enhance sensitivity to therapy effects. It comprises four summary domains; urinary, bowel, sexual and hormonal. The urinary domain is divided into two distinct sub scales; incontinence and irritative /obstructive subscales. Response options for each item form a 5-point Likert scale and scores are transformed to a 0-100 scale with higher scores representing better Health Related Quality of Live (HRQOL).

EPIC has been validated in men with localized prostate cancer who underwent surgery, external beam radiation or brachytherapy with or without the use of hormonal adjuvant. EPIC is sensitive to change (Appendix F).

6.2.3 Short Form Health Survey 36 (SF-36)

SF-36 is a self-administered questionnaire and contains 36 items which measure eight dimensions: Physical functioning (10 items), Role limitation due to physical health problems (4 items), Bodily pain (2 items), General health perceptions (5 items), Vitality (4 items), Social functioning (2 items), Role limitations due to emotional problems (3 items) and General mental health (5 items). There is an additional single item giving information on health change over the past year. Item scores for each dimension are coded, summed and transformed to a scale from 0 (worst possible health state measured by the questionnaire) to 100 (best possible health state). The higher value indicates a better evaluation of health. The SF-36 is well documented in terms of reliability and validity in all available language versions. In this study the acute version of SF-36 reflecting the last four weeks is used.

6.2.4 Radiation Toxicity Grade by Radiation Therapy Oncology Group (RTOG)

RTOG is an internationally well-established research group in the oncology field. They have developed organ specific scales for quantification of both acute and late symptoms after radiation. The scale range is from 0 to 5, where 0 is used for normal function and findings and 5 for death directly related to injuries post radiation. Both subjective and objective findings are used when setting the score.

6.2.5 Cystoscopy and Biopsy

Cystoscopy will be carried through according to routines at the hospitals urology department at visit 1 and 4. More specific instructions are found in Appendix E “Cystoscopy RICH-ART”. Subjective symptoms during the last four weeks will be recorded in the CRF.

Three biopsies will be taken at each cystoscopy. The cold biopsy forceps technique will be used. Biopsies will be stored at room temperature in formalin medium during transport to
Clinical Pathology and Cytology
Att: Dr. Johan Mölne
Gula Stråket 8, SU/Sahlgrenska
413 45 Göteborg

Samples will be labelled individually with pre-printed labels marked with study code, subject number, media, visit number and date.

Analysis of the biopsies will be made when convenient and **no feed-back will routinely be given to the urologist**. Standard procedures at each centre should be followed if the urologist needs the biopsy analysis result in a timely manner i.e. suspects abnormal findings.

6.2.5.1 Immunohistological analysis

All biopsy analysis will be performed by one and the same pathologist and according to standard templates and terminology. Analysis of the fibrosis development, vascular changes and the inflammatory response will be made.

The tissue biopsies will be fixed by immersion into buffered formalin (4%), dehydrated in alcohol and embedded in paraffin. Histological 4µm sections will be cut on a microtome to glass slides. The following parameters will be determined to assess vascular density, number of stem cells and fibrosis:

Determination of vascular density will be done using immunohistochemical staining for CD31 and CD34. Stem cells with hematopoietic differentiation ($CD34^{-/low}$, c-Kit^{+}, Sca-1^{+}) will be visualized using immunohistochemisry. Biopsies will be stained with Massong trichrome staining and fibrosis manually measured. In addition, collagen III immunostains will be used. Additional analysis may be used in order to further investigate findings of the above mentioned.

6.3 Safety

The local investigator is responsible for safety surveillance and for ensuring that procedures and expertise are available to handle medical emergencies during the study. The local investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section. Serious AEs (SAEs) and discontinuations due to AEs must be collected and an assessment of causality of the SAE should be performed. An SAE is an experience that at any dose results in any of the following:

- Death
- A life-threatening experience
- In-patient hospitalization or prolongation of existing hospitalisation
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- Important medical events that may not result in death, be life threatening or require hospitalisation may be considered an SAE - when based on appropriate medical judgement - they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The following terms and definitions are used when assessing the relationship between each AE/SAE and the relevant trial product(s):

- Definite – There is no doubt that the incident is related
- Probably- Good reason and sufficient documentation to assume a causal relationship
- Possible- A causal relationship is conceivable and cannot be dismissed
- Unlikely- The event is most likely related to aetiology other than the trial product
- Unknown/Unclassifiable: a report suggesting an adverse event reaction, which cannot be judged because information is insufficient or contradictory and which cannot be supplemented of verified.

For further details on definitions, reporting and guidelines on safety **see Appendix B**.

Vital signs and standard clinical chemistry and haematology investigations will be taken before and after the HBOT in order to document the health status of the subject. Oxygen exposure and conditions will be monitored by medical staff. Stopping criteria for oxygen administration is development of serious side effects of hyperbaric oxygen therapy such as more than one generalized oxygen-induced seizure or pulmonary barotrauma or pronounced deterioration of cardiovascular- or respiratory failure.
A nurse or other observer will be present during HBO treatments monitoring the patients and assists with equipment manipulation or emergencies.

6.3.1 Pregnancy

Pregnancy test will be carried out at each visit if applicable. The procedures in case of pregnancy are described in **Appendix B**.

6.3.2 Recording and reporting of adverse events

While this is a study with a registered product within the terms of the regulatory approval, serious AEs must be collected, registered in the CRFs and an assessment of causality of the SAE should be performed. Also, discontinuations due to AEs will be collected. Non-serious AEs will be collected in the present study only during the HBOT-period.

All SAEs have to be reported, whether or not considered causally related to the investigational product. The investigator is responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE, as per local requirements. The Clinical Study Serious Adverse Event Report Form will be used together with other relevant supporting documentation (eg. laboratory results, autopsy report) and relevant CRF modules.

6.3.3 Laboratory safety assessment

Blood (20 ml) and urine (10 ml) for laboratory safety screen will be taken at visits 1, 3 (Group A) and 5 (Group B).

Table x Laboratory screen

Clinical Chemistry	**Haematology**
S/P-Creatinine	B-Haemoglobin (Hb)
S/P -Bilirubin, total	B-Leukocytes, total count (LPC)
S/P -Alkaline phosphatase (ALP)	B-Leukocytes diff.absolute count:
S/P -Alanine aminotransferase (ALAT)	B-Basofila
S/P -Aspartate aminotransferase (ASAT)	B-Eosinof
S/P -Albumin	

S/P -Potassium (K)	B-Lymfocyter
S/P -Sodium (Na)	B-Monocyter
S/P -Glucose	B Neutrofila
S/P – C-Reactive Protein (CRP)	
	Study-specific blood samples
Urine	3-5 ml blood in EDTA-tube (ethylene diamine tetraacetic acid)
U-Erythrocytes (U-Ery)	
U-Albumin (U-Alb)	
U-Glucose (U-Glu)	
U-pregnancy-test	
U-culture (bacterial)	

The blood samples will be analysed according to routine standards at the Central laboratories at each hospital. Valid reference values of all routine analyses will be obtained. Laboratory printouts must be dated and signed by the investigator on the day of evaluation and stored in the CRFs. Data from the analysis will be transferred into the study database. Laboratory values outside the reference limit suspected to be of any clinical significance will be followed-up and/or repeated as per local investigator discretion.

6.3.3.1 Study-specific blood sample

Approximately 5 ml blood will be drawn to a tube with EDTA (ethylene diamine tetraacetic acid).

- Centrifuge in approximately 3000 rpm (2000 G) for 10 minutes
- Pipette the plasma into 3 Cryo-tubes
- Store the tubes in -70 to -80°C

The tubes must me marked individually with subject or screening number, date and visit number. The tubes will be sent to Sahlgrenska University Hospital for analysis each year or when convenient. Analyses of immunological activity will be made and the results combined with findings in the biopsies.

7. DATA MANAGEMENT

The study monitoring, data handling, essential documents, auditing and inspections, study drug handling etc are described in detail in **Appendix D**.

7.1 Recording of data

Data will be entered in the Web Based Data Capture (WBDC) system at the study site. Data entered in the WBDC system will be immediately saved to a central database. When the

principal investigator has signed the eCRF electronically as per eCRF instructions, then the subject's data will be locked. The investigator(s) will ensure that all data collected in the study will be provided. He/she ensures the accuracy, completeness, legibility and timeliness of the data recorded in the appropriate sections of the eCRF and according to any instructions provided. There will be paper CRFs in reserve available at each study.

The local investigator shall ensure that the documentation and medical files of study subjects are retained for at least 10 years after the conclusion of the trial.

7.2 Training of study site personnel

The local investigator at each site will ensure that appropriate training relevant to the study is given to all of these staff and that any new information relevant to the performance of this study is forwarded to the staff involved.

The local investigator at each centre will maintain a record of all individuals involved in the study (medical, nursing and other staff).

7.3 Monitoring of the study

An independent body will be appointed for monitoring the study. The monitor will be appropriately trained and informed about the nature of the study, patient written information, GCP and applicable regulatory requirements. Monitor's qualifications will be documented.

The monitor will have regular contacts (in person, telephone and/or e-mail) with the study sites to verify informed consents of participating subjects, to confirm that facilities remain acceptable, that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRF and that therapy accountability is being carried out. The study nurse will also ensure source data verification (comparison of the data in the eCRF with the hospital/practice and other records at the investigational site).

7.3.1 Source data

All patient source data such as analysis results from the hospital central laboratory, cystoscopy reports will be stored at the hospital according to routines. A copy of the eCRF data will be archived at the study site.

The eCRFs serves as the source for demographic data, medical history and physical examination Original scorings of patient-reported outcomes (EPIC and SF36) and biopsy analysis reports will be defined as source data.

7.4 Study agreements

All agreements between the Principal Investigator and laboratory or other technical facilities in which the measurement or assessment of the study evaluation criteria are performed must be in place before any study-related procedures can take place, or subjects be enrolled.

8. STATISTICAL METHODS AND SAMPLE SIZE

This study evaluates the symptoms before and after terminated HBO therapy and between Groups A and B having EPIC symptom estimation scale at baseline and visit 4 as the primary variable.

Secondary variables are RTOG-grading, immunohistological analysis and health-related quality of life (SF36).

All patients will be contacted for a post-study long-term follow-up yearly during 5 years after end of treatment regarding symptoms (EPIC) and quality of life (SF36).

8.1 Description of analysis sets

Calculation is based on an Intent-to-Treat (ITT) and Per Protocol (PP) analysis.

All subjects who received at least 1 dose of HBO and for whom post-dose data are available will be included in the safety population. Throughout the safety results sections, incorrectly treated subjects will be accounted for in the actual treatment group.

8.2 Methods of statistical analyses

The primary endpoint is symptom rating after HBO therapy using the self-administrated EPIC-questionnaire original score as the primary variable at baseline and visit 4.

Secondary endpoints:

- Severity of radiation injury having the RTOG as the variable at baseline and visit 4
- Histological analysis of inflammation activity, degree of fibrosis, vascular density and the presence of stems cells at baseline and visit 4.
- Health-related quality of life (SF36) at baseline visit 3, 4 and 5
- Post-study long-term follow-up follow up with Symptom rating (EPIC) and Health-related quality of life (SF36).

A two-sample t-test with a 5% significance level will be used. For each subject, means of measurements from baseline to visit 4 will be calculated. Differences between these means for each subject will be used in the comparison of the two groups i.e. between group A and the control group B ("delayed start"). Nonparametric methods could also be considered.

Fisher's exact test and logic regression will be used for comparison of other results in the two treatment groups. Jonckheere-Terpstra test will be used for trend analysis.

Other statistical methods might be used in an exploratory fashion but no formal inference will be made. Additional sub-analysis will be made in patients with symptoms for more than 30 months.

Patient-reported outcomes (EPIC, SF-36): Statistical calculations will be made using data obtained from original registrations (questionnaire scores).

Safety and tolerability data will be summarized descriptively by treatment and presented in tabular and/or graphical form. All adverse event data will be listed individually and summarized using MedDRA terminology.

8.3 Determination of sample size

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2.

Using available data from a few similar methodological studies assuming that the symptom reduction has a standard deviation of 23 units and that the expected reduction in EPIC exceeds that of control group by 15%, a parallel group design with 40 patients in each treatment group would have a power exceeding 80% for detecting a statistically difference between the study groups in EPIC (using a two-sample t-test with a 5% significance level).
$N=2x(PIxSD/CL)^2$; $N=2x(2,8x23/15)^2$; N=37. In order to have a safety margin, N is rounded up to 40. In order to secure a statistically sufficient subject population, recruitment will continue until 80 subjects are enrolled and have concluded Visit 4 according to protocol.

9. STUDY TIMETABLE

First Subject In: June 2012. Last Subject Last Visit: March 2016

Final Study Report: December 2016 or within 12 months from end of study.

9.1 Definition of end of study

The end of the entire study is defined as ”the last visit of the last subject undergoing the trial”. The Statistical and Clinical Study Report will be finalized approximately 1 year after last analysed sample.

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Study Protocol Appendix B

Study Code: RICH-ART

Date: 01 May 2014 /4

Appendix B - Definitions of Adverse Events and Procedures in case of Pregnancy

Definitions:

Adverse Events

Serious Adverse Events

A medical emergency usually constitutes an SAE and is to be reported as such

Intensity rating

Causal relationship

Action taken

Reporting in CRF

Adverse Events based on signs and symptoms

Final outcome assessment

Reporting of serious adverse events

Further guidance on Serious Adverse Events:

Life threatening

Hospitalisation

Important medical event or medical intervention

A guide to interpreting the causality QUESTION

Other significant Adverse Events

Procedures in case of pregnancy

Maternal exposure

Overdose

DEFINITIONS OF ADVERSE EVENTS AND PROCEDURES IN CASE OF PREGNANCY

It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The Local Investigator is responsible for ensuring this.

Adverse Events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs

Serious Adverse Events and suspected unexpected serious adverse reactions (SUSAR)

It is important to distinguish between Serious Adverse Events (SAEs) and severe adverse events (AEs). Severity is a measure of intensity whereas seriousness is defined by the criteria listed below. An AE of severe intensity need not necessarily be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

A medical emergency usually constitutes an SAE and is to be reported as such

A serious adverse event is an AE occurring during any study phase (i.e. run-in, Pre-entry, screening, treatment, wash-out), and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following criteria:

- results in death
- is immediately life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital abnormality or birth defect
- is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

For reporting purposes, any suspected transmission via a medicinal product of an infectious agent is also considered an SAE and is reported in an expedited manner. Any organism, virus or infectious particle (for example prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

Definitions for severity rating

0. None – No symptoms

1. Mild - Transient symptoms; awareness of sign or symptom, but easily tolerated. No interference with the subject's daily activities

2. Moderate - marked symptoms; discomfort sufficient to cause interference with normal activities. Moderate interference with the subject's daily activities

3. Severe - considerable interference with the subject's daily activities; unacceptable incapacitating Inability to perform normal activities

N/A Not Applicable

Causal relationship

The causality of (S)AEs (ie, their relationship to study treatment and/or the investigational procedure) will be assessed by the investigator(s), who in completing the relevant case report form must answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the drug/the investigational procedure?"

The following terms and definitions are used when assessing the causal relationship between each AE and the relevant trial product(s):

1. Definite – There is no doubt that the incident is related
2. Probably- Good reason and sufficient documentation to assume a causal relationship
3. Possible- A causal relationship is conceivable and cannot be dismissed
4. Unlikely- The event is most likely related to aetiology other than the trial product
5. Not related – The event is not related to the trail product
6. Unknown/Unclassifiable: a report suggesting an adverse event reaction, which cannot be judged because information is insufficient or contradictory and which cannot be supplemented or verified.

N/A Not Applicable

Causal relationship in cases where the disease under study has deteriorated due to lack of effect will be classified as no reasonable possibility.
For SAEs causal relationship will also be assessed for additional study drug and/or other medication and/or study procedure. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as "yes".

Action taken:

0 None
1 Dose of study drug changed
2 Study drug temporarily stopped
3 Study drug stopped
N/A Not Applicable

Reporting in the Case report Form

The following variables will be recorded in the eCRF for each AE; description of the AE, the date and time when the AE started and stopped, maximum intensity, whether the AE is serious or not, causality rating (yes or no; if yes specify), action taken with regard to investigational product, AE caused subject to discontinue study and outcome.

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: *"Have you had any health problems since the previous visit?"*, or revealed by observation will be collected and recorded in the CRF. When collecting AEs the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Follow-up – Outcome assessment

Any AEs that are unresolved at the patient's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF.

The following terms and definitions are used in assessing the final outcome of an AE:

- Recovered - The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent.

- Recovering - This term is only applicable if the subject has completed the trial or has died from another AE. The condition is improving and the subject is expected to recover from the event.

- Recovered with sequelae - The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.

- Not recovered - The condition of the subject has not improved and the symptoms are unchanged, or the outcome is not known at the time of reporting.

- Fatal - This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as “recovered”, “recovering”, “recovered with sequelae” or “not recovered”. An AE with fatal outcome must be reported as an SAE.

- Unknown - This term is only applicable if the subject is lost to follow-up

Reporting of serious adverse events

For studies in countries implementing the EU Clinical Trials Directive, informing Ethics Committees and Regulatory Authorities will be performed by the local investigator as needed.

All Suspected Unexpected Serious Adverse Reactions (SUSARs) have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The Clinical Study Serious Adverse Event Report Form will be used together with other relevant supporting documentation (e.g. ECG, laboratory results, autopsy report) and relevant CRF modules. All SUSARs have to be electronically reported to the MPA that will further be reported to EMEAs database.

FURTHER GUIDELINES ON THE DEFINITION OF A SERIOUS ADVERSE EVENT

Life threatening

‘Life-threatening’ means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject’s death. ‘Life-threatening’ does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Out-patient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Examples of such events are:

- *Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment*

- *Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine*

- *Intensive treatment in an emergency room or at home for allergic bronchospasm*

- *Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation*

- *Development of drug dependency or drug abuse*

A guide to interpreting the causality QUESTION
The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? A re-challenge would not normally be recommended or supported.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Ambiguous cases should be considered as being a “reasonable possibility” of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Other significant Adverse Events

An expert will identify other significant Adverse Events (OAEs) during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment, will be classified as OAEs. Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment. For each OAE, a narrative will be written and included in the Clinical Study Report.

Procedures in case of pregnancy

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study. All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to PI on the pregnancy outcomes report form.

Part I of this form must be completed in full and returned to PI within 30 days. Part II of the form must be completed when the outcome of the pregnancy is known. Reports of normal outcomes should be sent within 30 days.

Maternal exposure

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

Study Protocol Appendix C

Study Code: RICH-ART

Date: 01 May 2014 /4

Appendix C - Ethics

Ethics and regulatory review

Subject information and written informed consent form

Subject data protection

Audits and inspections

ETHICS AND REGULATORY REVIEW

The final study protocol, including the final version of the Written Informed Consent Form and other information given to subjects eg, advertisements must be approved or given a favourable opinion by an Ethics Committee before enrolment of any subject into the study.

Before enrolment of any subject into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

It is the responsibility of the Local Investigator to apply to the Ethics Committee in writing. The application document should:

- contain the name and address of the Ethics Committee
- clearly identify, by title and date, the protocol and other documents submitted for review
- be dated.

In addition, the Local Investigator should request the Ethics Committee to provide:

- their approval/opinion in a dated document identifying the Local Investigator's application
- Ethics Committee composition for the meeting when the approval was given
- a statement confirming that the Ethics Committee is organised and operates according to GCP and applicable laws and regulations.

The Local Investigator is responsible for informing the Ethics Committee of any modifications and amendments to the protocol as per local requirements.

Progress reports and notifications of serious and unexpected adverse drug reactions will be provided to the Ethics Committee according to local regulations and guidelines

All correspondence with the Ethics Committee should be filed by the Local Investigator in the ISF.

The Local Investigator is also responsible for obtaining approvals from scientific bodies if necessary for the study.

SUBJECT INFORMATION AND WRITTEN INFORMED CONSENT (IC) FORM

The Local Investigator(s) at each centre will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time without prejudice to further treatment. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study-specific procedures.

The Investigator(s) must store the original, signed Informed Consent Form in the Investigator's Study File. A copy of the signed Informed Consent Form must be given to the subject.

If a protocol amendment requires a change to the Informed Consent Form, the Ethics Committee must approve modifications that lead to a revised Informed Consent Form before the revised form is used. Any revision in the Informed Consent Form must lead to an updated version No. and/or date.

SUBJECT DATA PROTECTION

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

Extra precautions are taken to preserve confidentiality and prevent genetic or other study data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic, other study data and the personal identifiers of a subject. For example, in the case of a medical emergency or an investigator might know a subject's identity and also have access to his or her data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

AUDITS AND INSPECTIONS

Authorized representatives of Sponsor (i.e. monitor), a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all or selected study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The "subject information" and IC must contain information and approval of the above mentioned.

Study Protocol Appendix D

Study Code: RICH-ART

Date: 01 May 2014 /4

Appendix D - Study Management Process

Monitoring

Training of study site personnel

Monitoring/Quality control

Data handling

Source data

Data storage

Essential documents

Audits and inspections

Study Drug handling and accountability

Withdrawal of informed consent for donated biological samples

STUDY MANAGEMENT PROCESS

Monitoring

Before the study begins, a representative of Sponsor will visit the investigational site to

- determine the adequacy of the facilities
- discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to study conduct, protocol adherence, and the responsibilities of Sponsor or its representatives.

During the study, a representative of Sponsor will have regular contacts with the investigational site. These contacts will include visits to verify informed consent of participating subjects, confirm that facilities remain acceptable, that the investigational team is adhering to the protocol, that data are being accurately recorded in the Case Report Forms (CRFs) and to provide information and support to the investigator and site team. The representative will also ensure; that drug accountability is being carried out and source data verification (a comparison of the data in the CRF with the hospital/practice and other records at the investigational site) is performed.

A Sponsor representative will be available between visits, should the investigator or the site team need information and advice.

Training of study site personnel

Before the first subject is entered into the study, the Local Investigator will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and systems utilised.

The local investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

Monitoring/Quality control

An independent body will be appointed for monitoring the study. The monitor will be appropriately informed about the study and patient written information. Monitor’s qualifications will be documented.

Monitor will oversee the progress of the clinical trial, and ensure that it is conducted, recorded, and reported in accordance with the protocol, GCP and the applicable regulatory requirements.

Data handling

The investigator ensures the accuracy, completeness, legibility and timeliness of the data recorded in the appropriate sections of the eCRF and according to any instructions provided.

When data has been entered, reviewed, edited, monitored and signed, the data is declared clean and will be frozen to prevent further editing. Clean File/database lock must be documented. The reason for any excluded data will be described in detail in the report. When the principal investigator has signed the eCRF then the subject's data will be locked and analysis of data can start.

Source data

All patient source data such as analysis results from the hospital central laboratory, readings from the PSGs will be stored at the hospital according to routines.

The eCRF serves as the source for demographic data, medical history and physical examination. Other data stored in the eCRF may constitute source data, but this must then be documented in the source data file.

Data storage

The data collected will be stored in the digital eCRF, without patients name or personal identification number but with a code generated by the system. The physician in charge of the study and his staff will be responsible for the "code key" with which it is possible to connect the data to the patient. All study data and analysis will be filed in the Study Master File (SMF).

Essential documents

All documents which permit evaluation of the conduct of a clinical study and the quality of the data produced should be stored in the Investigator Study File (ISF). Examples of essential documents are: Investigators brochure, signed study protocol, information given to the subjects, financial aspects of the study, insurance statements, signed agreements, approvals of Ethics committee and Regulatory Authorizations, Curriculum Vitae of local and co-investigators, samples of labels, instructions of handling the study drug(s), other records of investigational products, master randomization list, pre-study monitoring report, subject screening logs, audit certificate, any revisions, clinical study report.

Audits and inspections

Authorised representatives of Sponsor, a regulatory authority, an Ethics Committee may visit the centre to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), and any applicable regulatory requirements. The investigator should contact Sponsor immediately if contacted by a regulatory agency about an inspection at his or her centre.

Study Drug handling and accountability

The medical oxygen is obtained from the hospital's gas system. The management and control of oxygen comply with the legislation for delivery, storage, labelling, delivery and returnable and are specified in local protocols at each hospital.

Withdrawal of informed consent for donated biological samples

The local investigator keeps full tractability of collected biological samples from the subjects while in storage at the centre until shipment and keeps documentation of receipt of arrival.

If a subject withdraws consent to the use of biological samples donated the samples will be disposed or destroyed, if not already analysed and documented.

Since collection of the biological samples is a voluntary part of the study, the subject may continue in the study as long as the primary endpoint variable (EPIC) is obtainable.

The local investigator ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed/destructed and the action documented and ensures the laboratory holding the samples is informed about the withdrawn consent immediately and that samples are disposed/destructed and the action documented returned to the study site.

Instructions for cystoscopy and biopsy Appendix E

Study Code: 2012-001381-15 (RICH-ART)

Date: 1 May 2014

Instructions for cystoscopy and biopsy

Copy of the eCRF-form (for reference)

Explanation of the fields

Cystoscopy

Preparations

Measurements

Biopsy

COPY OF THE FORM (ENTER DATA IN E-CRF ONLY)

Date of Cystoscopy

Number of biopsies taken:

Any surgery of urine bladder?

- ☐ Yes
- ☐ No

Any strictures of urethra?

- ☐ Yes
- ☐ No

Digital photography?

- ☐ Yes
- ☐ No

Residual urine

ml

Bladder max capacity

ml

Other clinical findings

Haematuria

- ☐ None
- ☐ Microscopic haematuria
- ☐ Intermittent macroscopic haematuria
- ☐ Frequent macroscopic haematuria
- ☐ Transfusion requiring haematuria

Urine bladder – atrophy

- ☐ Normal
- ☐ Slight epithelial atrophy
- ☐ Coherent macroscopic atrophy

Urine bladder – telangectasia

- ☐ Normal
- ☐ Mild telangiectasia
- ☐ Generalized telangiectasia
- ☐ Severe telangectasia

Urine bladder – other (more than one option possible)

- ☐ Ulceration
- ☐ Necrosis
- ☐ Perforation
- ☐ Fistula
- ☐ None of the above

EXPLANATION OF THE FIELDS

Date of cystoscopy

The date the cystoscopy was performed.

Number of biopsies taken

State the number of biopsies that was sent for analysis. Do not count biopsies taken, but not included in the shipment for analysis. Nor biopsies taken for other purpose i.e. for analysis at a local laboratory.

Strive to take three biopsies as described below. If it impossible to take any biopsied or if it is only possible to take one or two biopsies, please state the reason in the comment field.

Any surgery of urine bladder?

Any previous surgery, including diathermia, should be reported. If "Yes" is marked a comment field will be visible where the year and type of surgery should be entered. Separate several procedures with a comma. Previous cystoscopy without any intervention is not considered surgery and shall not be reported.

Previous surgery to the prostate gland or the urethra is reported elsewhere in the CRF and need not be entered here.

Any strictures to the urethra?

Mark "Yes" if any strictures in the urethra are visualized during the examination and specify what kind of strictures are seen.

Digital photography?

Photography of the urine bladder is NOT mandatory according to protocol. If photos are taken and of interest for the study, please mark "Yes" and state why the photo is of interest, what area is photographed and where the photos are stored.

Residual volume and bladder max capacity

See below for further instructions.

Other clinical findings

This field is optional. Any relevant information should be entered here. This includes, but is not limited to, findings of previously unknown cancer.

Haematuria

Microscopic haematuria are examined using a urine stick.
Intermittent macroscopic haematuria is defined as haematuria at a maximum of two times per week during the last four weeks.
Frequent macroscopic haematuria is defined as haematuria more than two times per week during the last four weeks.
Transfusion requiring haematuria is marked if the patient has received transfusions during the last four weeks due to haematuria.

NB! According to the protocol, the patient should be excluded from the study if more than 500ml blood has been transfused during the last four weeks when examined during screening. This is because randomization to Group B for such a patient is considered un-ethical. The patient is not excluded if the criterion is fulfilled at visit 4A/B.

Urine bladder – atrophy/telangiectasia

Mark ONE option that best describes the WORST findings during the cystoscopy. Further explanation to the findings might be given under “Other clinical findings”.

Urine bladder – other

Mark ALL options that is valid. Further explanation to the findings might be given under “Other clinical findings”.

CYSTOSCOPY

A cystoscopy is performed at two separate times during the study period regardless of which randomization group the patient belongs to.

The first cystoscopy is done during the screening period. The screening period should not exceed six weeks and is calculated from the date when the first examination in the study is performed. (This normally is the same date as when the patient signs the Informed Consent.) The screening period is ended when the patient either is included in the study i.e. is randomized to either group A or B, or is excluded from the study due to findings during the screening process that constitutes an exclusion criteria.

The second cystoscopy is performed at visit 4 (A&B) which should be scheduled six to eight months after the inclusion date.

Preparations and anaesthesia

The RICH-ART protocol does not state that any special preparations of the patient should be made prior to the examination i.e. local procedures are followed for the preparations and execution of the cystoscopy.

Local anaesthesia is preferred over regional (spinal) or general anaesthesia mainly because local anaesthesia constitutes less risk for the patient, but also because it is less time consuming and requires less resources. However, regional or general anaesthesia may be used according to local protocol and patient needs.

Measurements

The methods used for measurements may be adjusted to local standard procedures. If other methods then the blow described are used, a comment in the CRF should be made. This comment should state what alternative method that was used.

<u>Residual volume</u>
Residual volume in the protocol and CRF refers to Post Void Residual (PVR) urine volume.

- Instruct the patient to empty their urine bladder

Method 1:

- Measure residual volume by the use of ultrasonic examination – Bladderscan

Method 2:

- Insert a catheter or cystoscope and empty the bladder completely.
- Measure the volume extracted

Bladder max capacity

Bladder max capacity in the protocol and CRF refers to the maximum volume capacity of the urine bladder.

The preferred method to measure is:

- The patient is under local anaesthesia
- The urinary bladder is emptied completely
- Fluid is slowly infused into the urinary bladder via the cystoscope
- The patient is asked to report when he/she feels a very strong urge to void
- When the patient reports a very strong urge, the infusion is stopped and the volume aspirated and the volume is recorded as bladder max capacity

Alternative methods must be used if the patient is under regional or general anaesthesia since the patient will be unable to feel the urge to void when fluid is infused to the bladder. If this is the case, a note must be made in the CRF. This is done by entering “anaesthetic” in the comment field.

The alternative method to measure is:

- The patient is under regional or general anaesthesia
- The urine bladder is emptied completely via a cystoscopy instrument
- Fluid is infused with a standardized pressure i.e. 60-70 cm above the level of the bladder
- Infusion of fluid is allowed until it stops
- The infused volume is recorded as (anaesthetic) bladder max capacity.

Biopsies

Biopsies are preferably taken with cold forceps, for instance 5mm, technique in order to affect the tissue in the biopsy as little as possible and to minimize the risk of bleeding, fistula formation or other complications. If any other technique is used, please make a comment in the CRF.

The biopsy should at least include the urothelium and some of the underlying lamina propria. It is preferred if at least one biopsy includes some part of the muscle layer, but this is not always possible.

In order to maximize the probability for a good quality of the material, three biopsies should be taken whenever possible. However, if the urologist deems it impossible to take such a number of biopsies or that the quality of the first and/or second biopsy is undisputable, one or two biopsies might suffice.

During screening, biopsies are taken in close proximity to any clinically evident changes in the urine bladder. It is recommended that the urologist makes a note of where the biopsies are taken during screening. Biopsies taken during visit 4A/B should be in close proximity to the previous biopsies, however steering clear of any visible scar tissue. If no evident changes are found it is recommended that the three biopsies are taken at the following locations: one laterally of each ostium and one in the trigonum area.

All biopsies are placed in the same sterile plastic tube filled with formalin. The biopsies can be stored at room temperature during transport to:

Clinical Pathology and Cytology
Att: Dr. Johan Mölne
Gula Stråket 8, SU/Sahlgrenska
413 45 Göteborg

The tubes should be labelled with study code (RICH-ART), subject number, visit number and date.

NB! The biopsies are NOT examined when they arrive to the pathology clinic. They are stored for batch analysis by a blinded examiner at a later date. If the urologist suspects any pathology that needs to be biopsied and examined promptly, separate biopsies should be taken and sent to the local laboratory for analysis.

Patient Number: Patient's initials:

Patient information regarding:
Hyperbaric treatment of bladder discomfort caused by radiotherapy of cancer in the pelvic region

Project
This is an investigation/study aimed at studying whether oxygen given in a hyperbaric chamber may affect symptoms of the bladder that have occurred due to radiation therapy of cancer in the pelvic region. The study is administered by the Hyperbaric Unit at Sahlgrenska University Hospital/Östra. Several hyperbaric centers in Sweden, Norway and Denmark participate in this study.

Background and purpose
Tissue that has been exposed to radiotherapy can take damage and give rise to a number of adverse symptoms. These may debut in close proximity or long time after the radiotherapy has been given. Often the symptoms become more pronounced over time. Previous scientific studies have shown that oxygen given under pressure in some cases may alleviate the symptoms of the radiation injured tissue and may also reverse some microscopic changes.

The purpose of this study is to investigate whether hyperbaric treatment alleviate the symptoms that have occurred after radiotherapy of the bladder. We shall also examine the appearance of mucous membraine before and after Oxygen Treatment. In this way, we can gain in-depth knowledge about the factors influencing the onset and alleviation of symptoms.

How does the study go?
The first visit takes about 60 minutes. We will ask questions about age, past and current illnesses. Health examination and blood tests, urine tests, blood pressure and heart rate are taken. We also measure height and weight. A pregnancy test will be carried out where appropriate. You can complete the questionnaire on how to experience your quality of life and your symptoms. You will also be informed of certain restrictions that will apply during the study. It is for example that you must not use hairspray, perfume, greasy ointments, etc. before a treatment or bring something flammable into the chamber.

All patients will undergo two cystoscopic examinations with approximately 6-8 months apart. These investigations look for changes in the mucous membrane of the bladder and document it. In connection with these investigations , tissue samples from the mucous membrane of the bladder will be taken. The tissue samples are very small – only a few millimetres. Three tissue samples are taken in local anesthesia at each examination.

After the first cystoscopy you will end up in one of two groups. This division takes place randomly and can not be affected by you or any of the other. Group A, will be offered treatment start as soon as possible. The second group, group B, will be offered treatment

initiation after cystoscopy number 2. This means that group B will have to wait 6-8 months before receiving treatment.

Treatment days: You come to the clinic for a while before and dress up to comfortable and cool cotton clothing. Own underwear can be retained if they are in cotton material. Then you get to enter the hyperberic chamber. There is always a nurse nearby throughout the treatment. When the door is closed, the pressure slowly increases to a pre-determined treatment preassure. You will breathe 100% oxygen in about 90 minutes. In the meantime there is the opportunity to watch movies, listen to music or read a book. Finally, the pressure is slowly reduced and today's treatment is complete. There is no feeling in the body during treatment. It can hit the lid for the ears in the same way as when an airplane lands or a train goes into a tunnel. You will undergo one treatment per weekday for 8 weeks, that is to say a total of 40 treatments.

Once the treatment period is over, you will again have to fill in some questionnaires on how to experience your quality of life and your possible symptoms. A shortened health examination will then also be performed that includes blood tests.

We will contact you once a year for the next five years and ask you to fill in two questionnaires on how to experience your quality of life and your possible symptoms. The Study is completed when the 5-year follow-up is completed.

Biobank
The tissue samples will be examined in a microscope. We will look for the presence of inflammation, damaged cells, fibrosis, and the presence of blood vessels.
One of the blood test tubes is stored together with the tissue sampel in a so-called Biobank registered in the Anesthesia section at Sahlgrenska University Hospital, Sahlgrenska, and is managed by Biobank manager at the Anaesthesia Clinic. The samples are encoded in such a way that they cannot be linked to the individual patient without access to the code key. The code key is managed by the research manager and stored in the locked safe. The samples will be analysed at the Sahlgrenska University Hospital. No samples will be disclosed to any other research group. Saved samples will not be used for other projects without prior review and approval by the Regional Ethical Review Board.You may at any time request that samples be destroyed in an irreversible manner.
If the research samples would be relevant for future yet unplanned research, you will be asked for consent and new ethics application must be made.

Possible side effects, risks and discomfort
The risks of oxygen therapy under overpressure are small and we do not have any support atht it might lead to an increased risk of relapse in cancer. Some patients may experience difficulties in depressurizeing the ears in connection with the pressurization of the chamber. It is important to inform the staff of the House if you experience problems with equializayion so that they can help you and thus avoid damage to the eardrum.
Oxygen given under pressure may in very rare cases give rise to transient seizures. The seizure is terminated soon after the 100% oxygen dilivery is interrupted. Oxygen can, among

other things, give rise to some changes in visual acuity. However, this change nearly almost reverse fully. Visual acuity gradually returns to its previous values over the course of someone to a few months. When taking tissue samples there is always a small risk of a minor bleeding occurring in connection with the small wound that is left behind. The bleeding usually halts by itself.

Are there any advantages to participating?
There is no guarantee that participation in the study will provide any immediate benefits. But the purpose of the study is to investigate whether the effect of oxygen therapy under pressure can affect the symptom image and you may therefore benefit from the oxygen therapy during the treatment period. One advantage of participation may be that you may undergo medical examinations and control of your health several times during the study.

Participation in the study is entirely voluntary.
You can cancel your participation in the study at any time, without reason and without giving reasons, and no one has the right to question your decision.

Processing of personal data (Swedish Personal Data Act SFS 1998:204).
Participation in the study after consent is documented for the patient. All information from patient records are treated with privacy under the Patient Data Act and stored in your study file. Study data will be provided with a code that is specific to you. Your name or social Security number will therefore not be directly accessible to others. The responsible doctor is responsible for the "code key" with which it is possible to link the data to you.
The “Personuppgiftsombud” of Sahlgrenska University Hospital is responsible for the treatment of Personal data. You have the right to request a statement of the information recorded about you and get help for any rectification. You can refer to the contact person below or to the Hospital representative (see below).
The study is controlled by an independent auditor, so-called Monitor. They may request access to collected material to ensure that the data in the study have been collected correctly. The review is subject to the same privacy rules as responsible researchers.

Insurance and compensation
Being involved in the study does not entail any costs for you. No additional compensation will be paid. As always in the in the public healthcare sector, you are covered by the full patient insurance.

Results from the study
The results of the study will be presented in scientific journals and on scientific meetings relevant to this type of disease. Results that directly influences healthcare will also be of importance for the design of health care policies and guidelines. What is presented, you as a patient can take advantage of if desired. You are offered an account of your individual results during the planned follow-up.

Consent form

This form shall be drawn up in duplicate, of which you retain one. The consent form shall be jointly reviewed and signed by you and the physician responsible.

People to contact: If You have questions about the study, you can turn to the principal investigator:
Nicklas Oscarsson , consultant, An-Op-IVA, Sahlgrenska University Hospital
031-343 40 00 (Sahlgrenska gear)

Other responsible persons:
Per Aziz, business consultant, anesthesia and intensive Care Clinic, SU/ÖPer Lodding, Docent, MD, Urol
KLin. SU/S

Personuppgiftsombud:
Sahlgrenska University Hospital
Susan Lindahl 031-343 27 15

Patient Number: ☐ Patient's initials: ☐

CONSENT FORM

For participation in clinical study, as well as for the saving, use and dispensing of tissue samples in biobank prepared for clinical study at the hyperbaric Unit, Sahlgrenska University Hospital.

You are hereby asked if you agree to participate in the study of hyperbaric treatment at the Bladder discomfort that occurred after radiotherapy for cancer in the pelvic region. You are also asked if you agree that tissue samples are taken for storage in Biobank.

The study is approved by the Regional Ethical Review Board in Gothenburg (epn.se). There is a registered Biobank (biobanksverige.se) at the Sahlgrenska University Hospital, Sahlgrenska Clinic. This consent form has been designed in two copies, of which you retain one copy.

I have received oral and written information about the research project hyperbaric treatment at Bladder discomfort that occurred after radiotherapy for cancer in the pelvic region.
I have had the opportunity to ask questions and get the information I think I need. I am aware that participation does not involve any advantages or disadvantages and that my decision doesn't affect other care I receive. I can cancel my participation at any time and without justification.

I have received information about how data is handled and encoded. ALL information from patient notes and protocols are treated with confidentiality according to the Patient Data Act. The study also has a register that been notified to Sahlgrenska University Hospital's representative in accordance
Personal Data Act.

I agree that the tissue samples included in the study are analyzed and stored in a Biobank
I agree to participate in the study after reading the above.

_____ _____
Name Date

Head of research contact, Sahlgrenska University Hospital

_____ _____
Name Date

Project manager for study, specialist Nicklas Oscarsson, anaesthesia and
Intensive Care Clinic, area 2 Sahlgrenska/Östra. Nicklas.oscarsson@vgregion.se 031-343 40 00

A copy of this signed patient information is given to the patient

Patientnummer: | | Patientens initialer: | |

Patientinformation angående:
Tryckkammarbehandling vid besvär från urinblåsan som uppkommit efter strålbehandling av cancer i bäckenregionen

Forskningsprojektet
Detta är en undersökning/studie som syftar till att studera huruvida syrgas givet under övertryck i tryckkammare kan påverka symtom från urinblåsan som uppkommit till följd av strålbehandling av cancer i bäckenregionen. Studien administreras av Tryckkammarenheten på Sahlgrenska Universitetssjukhuset/Östra. Flera tryckkammarcentra i Sverige, Norge och Danmark deltar i denna studie.

Bakgrund och syfte
Vävnad som utsatts för strålbehandling kan ta skada och ge upphov till en rad negativa symtom. Dessa kan debutera i nära anslutning eller långt tid efter det att strålbehandlingen givits. Ofta blir symtomen mer uttalade med tiden. Tidigare vetenskapliga studier har visat att syrgas som ges under tryck i vissa fall kan mildra symtomen från den strålskadade vävnaden och kanske även reversera en del mikroskopiska förändringar.

Syftet med denna studie är att undersöka om tryckkammarbehandling mildrar de symtom som har uppkommit efter strålbehandling av urinblåsan. Vi skall även undersöka slemhinnans utseende i mikroskop före och efter syrgasbehandling. På så sätt kan vi få fördjupad kunskap kring de faktorer som påverkar uppkomsten och lindringen av symtomen.

Hur går studien till?
Första besöket tar ca 60 minuter. Vi kommer att ställa frågor om ålder, tidigare och nuvarande sjukdomar. Hälsoundersökning genomförs och blodprov, urinprov, blodtryck och puls tas. Vi mäter också längd och vikt. Ett graviditetstest kommer att göras i förekommande fall. Du får fylla i frågeformulär om hur du upplever din livskvalitet och dina symptom. Du blir också informerad om vissa restriktioner som kommer gälla under studien. Det är t.ex. att du inte får använda hårspray, parfym, feta salvor etc. före en behandling eller ta med dig något brandfarligt in i kammaren.

Samtliga patienter kommer att genomgå två cystoskopiundersökningar med ca 6-8 månaders mellanrum. Vid dessa undersökningar tittar man efter förändringar i urinblåsans slemhinna och dokumenterar det. I samband med dessa undersökningar kommer vävnadsprover från urinblåsans slemhinna att tas. Vävnadsproverna är mycket små – endast ett par millimeter. Det tas tre vävnadsprov i lokalbedövning vid varje undersökning.

Efter första cystoskopiundersökningen hamnar du i en av två grupper. Denna indelning sker slumpmässigt och kan inte påverkas av dig själv eller någon av annan. Den ena gruppen,

grupp A, kommer att erbjudas behandlingsstart så snart som möjligt. Den andra gruppen, grupp B, kommer att erbjudas behandlingsstart efter andra cystoskopiundersökningen. Det betyder att grupp B kommer att få vänta 6-8 månader innan de får sin behandling.

Behandlingsdagarna: Du kommer till kliniken en stund innan och klär om till bekväma och svala bomullskläder. Egna underkläder kan behållas om de är i bomullsmaterial. Därefter får du gå in i tryckkamaren. Det finns alltid en sjuksköterska i närheten under hela behandlingen. När dörren är stängd ökar trycket långsamt till ett förbestämt maxtryck. Du kommer att andas 100% syrgas i ca 90 minuter. Under tiden finns möjlighet att se på film, lyssna på musik eller läsa en bok. Trycket sänks slutligen långsamt och dagens behandling är färdig. Det känns inget i kroppen under behandlingen. Det kan slå lock för öronen på samma sätt som när ett flygplan landar eller ett tåg åker in i en tunnel. Du kommer att genomgå en behandling per vardag i 8 veckor, det vill säga totalt 40 behandlingar.

När behandlingsperioden är över kommer du återigen få fylla i några frågeformulär om hur du upplever din livskvalitet och dina eventuella symptom. En förkortad hälsoundersökning kommer då även att göras som inkluderar blodprover.

Vi kommer att kontakta dig en gång per år under de kommande fem åren och be dig fylla i två frågeformulär om hur du upplever din livskvalitet och dina eventuella symtom. Studien är avslutad när 5-års uppföljningen är avklarad.

Biobank
Vävnadsprovet kommer att undersökas i mikroskop. Man tittar då på förekomst av inflammation, skadade celler, bindvävsinlagring, samt förekomst av nybildning av blodkärl. Ett av blodprovsrören lagras tillsammans med vävnadsprovet i en så kallad biobank som är registrerad på anestesisektionen vid Sahlgrenska Universitetssjukhuset, Sahlgrenska och som sköts av biobanksansvarig på anestesikliniken. Proverna är kodade på sådant sätt att de inte kan kopplas till enskild patient utan tillgång till kodnyckel. Kodnyckeln sköts av forskningsansvarig och förvaras i låst kassaskåp. Proverna kommer att analyseras vid Sahlgrenska Universitetssjukhuset. Inga prover kommer att lämnas ut till någon annan forskningsgrupp. Du kan när som helst begära att prover destrueras på ett oåterkalleligt sätt. Om forskningsprover skulle bli aktuella för framtida ännu ej planerad forskning kommer du att tillfrågas för samtycke och ny etikansökan måste göras.

Eventuella biverkningar, risker och obehag
Riskerna med syrgasbehandling under övertryck är små och leder inte till ökad risk för återfall i cancer. En del patienter kan uppleva svårigheter att tryckutjämna öronen i samband med trycksättning av kammaren. Det är viktigt att informera personalen vid kammaren om du skulle uppleva problem med tryckutjämningen så att de kan hjälpa dig och på så sätt undvika att det uppstår skador på trumhinnan.
Syrgas som ges under tryck kan i mycket sällsynta fall ge upphov till en övergående kramper. Dessa bryts så snart syrgastillförseln avbryts. Syrgas kan i bland ge upphov till något förändrad synskärpa. Denna förändring består dock nästan aldrig över tid. Synskärpan återgår successivt till sina tidigare värden under loppet av någon till några månader. När man tar

vävnadsprover finns alltid en liten risk för att det uppstår en mindre blödning i anslutning till det milimmeterstora såret som efterlämnas. Blödningen avstannar vanligen av sig självt.

Finns det några fördelar med att deltaga?
Det finns inga garantier för att deltagandet i studien ger några omedelbara fördelar. Men avsikten med studien är att undersöka om effekten av syrgasbehandling under tryck kan påverka symptombilden och du kan därför komma att ha nytta av syrgasbehandlingen under behandlingsperioden. En fördel med deltagandet kan vara att du får genomgå läkarundersökningar och kontroll av din hälsa flera gånger under studien.

Deltagandet i studien är helt och hållet frivillig.
Du kan när som helst, utan anledning och utan att uppge skäl, avbryta ditt deltagande i studien och ingen har rätt att ifrågasätta ditt beslut.

Behandling av personuppgifter (Personuppgiftslagen SFS 1998:204).
Deltagande i studien efter samtycke dokumenteras i patientjournalen. All information från patientanteckningar behandlas med sekretess enligt patientdatalagen och lagras i din patientjournal. Studiedata kommer att förses med en kod som är specifik för dig. Ditt namn eller personnummer kommer därmed inte vara direkt tillgänglig för andra. Ansvarig läkare ansvarar för den ”kodnyckel” med vilken det går att koppla uppgifterna till just dig.

Utförandestyrelsen för Sahlgrenska Universitetssjukhuset är ansvarig för behandlingen av personuppgifter. Du har rätt att begära ett utdrag över de uppgifter som registreras om dig och få hjälp till eventuell rättelse. Du kan vända dig till nedanstående kontaktperson eller till sjukhusets personuppgiftsombud (se nedan).

Försäkring och ersättning
Att vara med i studien medför inga kostnader för dig. Ingen extra ersättning kommer att utgå. Liksom inom sjukvården i övrigt omfattas du av Patientförsäkringen.

Resultat från studien
Resultaten från studien kommer att presenteras i vetenskapliga tidsskrifter och på vetenskapliga möten som är aktuella för denna typ av sjukdom. Resultat som dirket påverkar vården kommer också att få betydelse för utformning av vårdprogram och riktlinjer. Det som presenteras får du som patient ta del av om så önskas.
Du erbjuds en redovisning av dina individuella resultat vid den planerade uppföljningen.

Samtyckesformulär
Detta formulär skall upprättas i två exemplar, varav du behåller det ena. Samtyckesformuläret skall gemensamt gås igenom och signeras av dig och ansvarig läkare.

Personer att kontakta: Har du frågor om studien kan du vända dig till:
Nicklas Oscarsson , specialistläkare, An-Op-IVA, Sahlgrenska Universitetssjukhuset
031-343 40 00 (Sahlgrenskas växel)

Övriga ansvariga personer:
Sven-Erik Ricksten, professor, överläkare Anetesi- och intensivvårdsklinien, SU/S
Per Arnell, verksamhetsöverläkare, Anestesi- och intensivvårdskliniken, SU/Ö
Per Lodding, docent, överläkare, Urolklin. SU/S
Jon Kindblom, överläkare, Onkkliniken, SU/S
Heléne Seeman-Lodding, docent, överläkare, Anestesi- och intensivvårdskliniken SU/S
Ansvarig kontakt **personuppgiftsombud:**
Clare Melin, Sahlgrenska Sjukhuset
Bruna Stråket 21, 413 45 Göteborg
031- 342 00 00 (växel)

Patientnummer: ☐ Patientens initialer: ☐

SAMTYCKESFORMULÄR

För deltagande i klinisk forskningsstudie, samt för sparande, användning och utlämning av vävnadsprov i biobank upprättad för klinisk forskningsstudie vid Tryckkammarenheten, Sahlgrenska Universitetssjukhuset.

Du blir härmed tillfrågad om du samtycker till att delta i studien om tryckkammarbehandling vid
besvär från urinblåsan som uppkommit efter strålbehandling mot cancer i bäckenregionen. Du tillfrågas även om du samtycker till att att vävnadsprov tas för lagring i biobank.

Studien är godkänd av regionala etikprövningsnämnden i Göteborg (epn.se). Vid anestesikliniken Sahlgrenska Universitetssjukhuset, Sahlgrenska finns en registrerad biobank, (biobanksverige.se). Detta samtyckesformulär har utformats i två exemplar, varav du behåller det ena exemplaret.

Jag har fått muntlig och skriftlig information om forskningsprojektet tryckkammarbehandling vid
besvär från urinblåsan som uppkommit efter strålbehandling mot cancer i bäckenregionen. Jag har fått möjlighet att ställa frågor och få den information jag anser att jag behöver. Jag är medveten om att ett deltagande inte innebär några fördelar eller nackdelar och att mitt ställningstagande inte påverkar den vård jag får. Jag kan när som helst och utan motivering avbryta
mitt deltagande i studien.

Jag har fått information om hur data hanteras och kodas. All information från patientanteckningar
och protokoll behandlas med sekretess enligt patientdatalagen. Stuiden har också ett register som
anmälts till Sahlgrenska Universitetssjukhusets personuppgiftsombud i enlighet med personuppgiftslagen.

Jag samtycker till att vävnadsprov ingående i studien analyseras och lagras i en biobank
Jag samtycker till att deltaga i studien efter att ha läst ovanstående.

_____ _____
Namn Datum

Forskningsansvarig kontaktperson, Sahlgrenska Universitetssjukhuset

_____ _____
Namn Datum

Projektansvarig för forskningsstudien, Specialistläkare Nicklas Oscarsson, Anestesi- och intensivvårdskliniken, Område 2 Sahlgrenska/Östra. Nicklas.oscarsson@vgregion.se 031-343 40 00

En kopia av denna signerade patientinformation ges till patienten

Clinical Study Protocol
Study Code: **RICH-ART**
Date: 1 May 2014