Macchiarini Fallet
Investigation of the activities of transplantation of synthetic trachea
Karolinska University Hospital

Report 2016-08-31

Glossary

The following definitions are taken from the Medical Dictionary (1) or Merriam-Webster's Medical Dictionary (2). When defining these sources, is the definition of our own.

Term	Definition	Ref.
Bioengineering	Tillämpningen av biologiska tekniker för att skapa modifierade versioner av en organism; i fråga om luftstrupar har termen används för modifiering av de biologiska egenskaperna av ett organ.	(2)
Biokompatibel	Förenlig med levande vävnad eller levande system genom att inte vara toxisk, skadlig eller fysiologiskt reaktiv och inte skapa immunologisk reaktion.	(2)
Bronk	Luftrör (avgreningar från luftstrupen ut i lungorna).	(1)
ECMO	Syresättning utanför kroppen genom ett membran med syfte att låta lungor och/eller hjärta få vila och läka; "konstgjorde lunga".	(1)
Epitel	Yttersta cellagret i hud och slemhinna.	(1)
Fistel	Onormal kanal i kroppen.	(1)
In vitro-studier	Studier utanför den levande kroppen.	(2)
In vivo-studier	Studier i den levande kroppen.	(1)
Nekrotrakea	Luftstrupe från avliden person.	Egen
Regenerativ kirurgi	En del av den regenerativa medicinen (se nedan) där kirurgiska tekniker också är involverade.	Egen
Regenerativ medicin	En gren av medicinen som utvecklar behandlingar som ersätter vävnad som drabbats av skada eller sjukdom med ny vävnad. Behandlingarna kan röra tillväxt av de celler som redan finns på plats eller transplantation av celler, vävnader eller organ som preparerats utanför kroppen.	(2)
Stent, stentning	Rörformig protes som håller gångar eller kärl öppna, respektive användning av en sådan protes.	(1)
Trakea	Luftstrupe.	(1)
Translationell forskning	Medicinsk forskning som syftar till att underlätta övergång från vetenskapliga upptäckter till utveckling och implementering av nya sätt att förebygga, diagnosticera och behandla sjukdom.	(2), något modifierat

References

1. Medicinsk ordbok. http://medicinskordbokse/.
2. Merriam-Webster's Medical Dictionary. http://www.merriam-webster.com/dictionary/.

Forward

In consultation with the Stockholm County Council decided hospital director Melvin Samsom at Karolinska University Hospital February 12, 2016 to give a mandate to an external investigators to investigate and clarify the circumstances of the surgeries with synthetic trachea which was conducted at the Hospital 2011-2013. Based on the facts investigation concluded, the investigator would give recommendations on improvements.

For investigators appointed Kjell Asplund, Professor Emeritus of Medicine at Umeå University, former Director General of the National Board. He appointed a working group consisting of Nils Blom, former General Counsel at the National Board of Health and the Public Health Agency, Katarina Johansson, Chairman patient organization Network against cancer as well as Jesper Persson, chief physician of internal medicine and former head doctor at Skåne University Hospital.

Pernilla Östlund, Project Manager at the Swedish Council for medical and social assessment (SBU) was hired March 1, 2016 as a research assistant. Clara Wahren, Stockholm County Council, assisted by providing administrative support. The County Council has set the premises available.

We have hired two external reviewers of chapters 11 and 12, Professor Ingemar Petersson, Head of Research at Skåne University healthcare (SUS) and Professor Jack Lysholm, head of the Register Centre Norr, Umeå. Two external experts, Lars Ek, chief of pulmonary medicine at Skåne University Hospital and associate professor Jan Nyman, Chief of Oncology at Sahlgrenska Hospital in Gothenburg, have contributed their views on the two first-transplanted patients' diagnosis and forecast. Responsibility for the final report texts is however on the investigation.

We have the working group consistently met with great willingness to provide material and their own interpretations the event itself. None of them we wished to interview declined. We would like to warmly thank all those who stood up for interviews and contributed material to the investigation.

The inquiry report is hereby completed.

Stockholm 2016-08-31
Kjell Asplund

Contents

Summary Contents

We present here a summary of our report "The Macchiarini Case - Investigation of the synthetic trachea transplantations at Karolinska University Hospital". The complete report is available at www.sll.se. This summary focuses on shortcomings that were exposed during the investigation and on areas where improvements may be needed. For a more intricate illustration – including issues that were properly managed – we refer the reader to the complete report.

Brief summary of the course of events

Paolo Macchiarini was employed at the end of 2010 as a professor at Karolinska Institutet ("KI") and a senior physician at Karolinska University Hospital ("the hospital"). In 2011, he performed the world's first transplant of a synthetic trachea prepared with bone marrow cells, an event that evoked extensive attention in both professional circles and the mass media. In 2011-2013, he performed synthetic trachea transplants on another two patients at the hospital, one of these on two occasions.

The first of the three transplant patients died 30 months after the procedure following severe complications from the synthetic trachea. The second patient died after four months from an unknown cause. The third patient suffered very severe complications that have required continuous hospital care since the transplant in 2012. In May 2016, this patient underwent a lung, trachea and oesophagus transplant from a deceased donor at a U.S. hospital.

When the unfavourable results and other circumstances surrounding the surgical procedures became clear to clinic and hospital management, Macchiarini's employment at Karolinska University Hospital was terminated in November 2013.

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In August 2014, four physicians reported Macchiarini to the Vice- Chancellor of the Karolinska Institute (KI) for research misconduct. According to the reports, the Macchiarini team's scientific articles contained incorrect clinical information. The Vice-Chancellor appointed an external investigator who found that the accusations against Macchiarini were essentially correct. However, the Vice-Chancellor decided to acquit Macchiarini of the accusations of research misconduct.

In April 2015, the Swedish Medical Products Agency filed a police report against Karolinska University Hospital for violating the Medicinal Products Act. In June 2015, the Health and Social Care Inspectorate (IVO) filed a police report against the hospital for violating the Ethical Review Act. In June 2016, a prosecutor accused Macchiarini of a suspicion of gross criminal negligence causing another person's death and gross criminal negligence causing bodily harm. The prosecutor did not rule out the eventuality that more hospital employees would be accused of suspicion of crime.

Growing criticism of Macchiarini, his research and his transplants culminated in January 2016 in the TV series "Experimenten" (The Experiments). The Vice-Chancellor of KI and his closest colleagues resigned. The Personnel Disciplinary Board at KI decided to dismiss Macchiarini in March 2016.

A number of investigations have been initiated due to the Macchiarini case, some with a direct focus on Macchiarini and his activities, some of a more general nature. The hospital and KI have both appointed external investigations, the hospital with a focus on Macchiarini's clinical activities, especially the trachea transplants (this investigation), and KI with a focus on how the Institute handled Macchiarini's academic activities.

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Macchiarini was recruited to the hospital despite warning signs

Macchiarini was recruited as a senior physician at the hospital even though there were strongly critical opinions from his previous employers. We recommend that the hospital should quality assure its recruitment process, especially concerning positions shared with KI.

The employment of Macchiarini at KI and the hospital was a part of a coherent strategy to build a centre for advanced airway surgery at Karolinska University Hospital and KI. In international media, Macchiarini had received attention as a particularly innovative surgeon through the transplant of a specially prepared trachea from a deceased donor. In professional circles, he was considered to be a technically driven surgeon. He himself and his activities were described by a combination of positively charged terms, such as "translational research", "regenerative medicine", "stem cells", "nanotech", "internationally leading" and "star surgeon". It is easy to understand that the collective concept around the recruitment of Macchiarini appeared to be very attractive and visionary. However, at a high level of management, the enthusiasm for Macchiarini appears to have been distinctly greater at KI than at the hospital.

There were expectations that he would very quickly get started with trachea transplants at the hospital. The high expectations may have contributed to decisions being made too quickly when Macchiarini was hired. From the hospitals he previously worked at (in Italy, Germany and Spain), there were signals of inadequacies as a surgeon other than surgical techniques, mainly in terms of indication decisions, in other words what kinds of

operations were performed on which patients. There were also several signals of cooperation difficulties that reached KI and the ear-nose-throat clinic (ENT clinic). In London, where he had research collaboration without being employed, the cooperation problems were nonetheless not considered to be insurmountable.

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Before Macchiarini was employed, he performed a "test operation" where his Stockholm colleagues were impressed by his technical skills. The hospital took no references of its own on Macchiarini's clinical qualifications until a very late stage in the recruitment process. The warning signs that arose then were suppressed. Pressure from KI and some time pressure appear to have contributed to Macchiarini being employed as a senior physician despite the strongly negative signals from his former clinical colleagues.

Macchiarini is a thoracic surgeon, but it was decided that he would have his academic and clinical activities placed with the ear-nose-throat division (ENT unit) at KI and the ENT clinic in Huddinge (the thoracic clinic is in Solna). It is our impression that the KI management was the driver of this decision. The fact that Macchiarini was employed at the ENT clinic in Huddinge, but came to locate most of his surgical activities at the thoracic clinic in Solna contributed to unclear responsibility circumstances, which gave an independent person like Macchiarini an opportunity to move between the two clinics too freely. Even if we in this report find multiple faults in the system that may have contributed to the Macchiarini case developing as it did, we believe that this particular case cannot be taken as a reason to more generally rule out the ambition to recruit international, high-calibre talent for clinical research in Sweden.

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The patients' condition was not immediately life threatening

There was no immediate threat to the life of any of the three transplant patients before the operations. Progressing cancer in two of the patients would very likely have led to death on the longer term. In the third patient, complications of her tracheal injury, especially severe infections, entailed a significant threat to life.

Patient 1 was a 36-year-old man who had undergone surgery and radiation treatment in Iceland for a rare form of tracheal cancer in 2009. Due to clinical symptoms, a relapse into cancer was suspected. Examination showed a constriction of the trachea. An external assessment was obtained from the U.S.; the treatment possibilities were considered to have been exhausted and palliative care was proposed. The patient's physician in Iceland then contacted Karolinska University Hospital which offered to assess the patient and potentially perform a tracheal transplant.

The operation was performed at the ENT clinic in Huddinge in June 2011. There was no cardiopulmonary machine at the clinic, which meant that the patient's life was put at risk. During the operation, it became clear that the material in the synthetic trachea was not optimal. The patient recovered, however, and after just over four weeks' care at Karolinska University Hospital, he was able to return to Iceland for continued rehabilitation. He resumed his doctoral studies and completed his PhD in 2012.

In November 2011, he was referred back to Karolinska University Hospital on the grounds of growing bronchial symptoms. He then came to be treated at the hospital on a large number of occasions between December 2011 and his death in January 2013. His general condition declined, fistulization was confirmed and he was struck by constantly

recurring infections. In the autopsy, the transplanted trachea was found to have come loose. A chronic infection in the chest and a clot in the right pulmonary artery were also found. There was no remaining cancer, however.

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Patient 2, a 30-year-old man from the U.S., had a rare form of cancer in the trachea that was diagnosed in 2009. There were no metastases. He had been treated with chemotherapy and radiation. After having heard of the first tracheal transplant at Karolinska University Hospital, he contacted the hospital through his physician for a possible transplant. He underwent the transplant with a synthetic trachea in November 2011. Microscopic analysis showed that not all cancerous tissue had been removed. After eight weeks' care, he was able to return to the U.S. He died suddenly in March 2012. No autopsy appears to have been performed. There has been speculation regarding various causes of death, both those related directly to the transplant and those that were due to his underlying cancer.

Patient 3 was a 22-year-old Turkish woman who had suffered a severe tracheal injury in 2011 in conjunction with hand sweat surgery to cut the nerve pathways from the spinal cord to the hands. Her right lung was non-functional and there was a fistula between the trachea and the pleura on the right side. She suffered from a constant cough and phlegm formation. In surgery in July 2012, Macchiarini removed the right lung and the trachea was replaced with a pipe to the large windpipe to the left lung.

Two weeks later, the transplant with a synthetic trachea was performed. Postoperative complications arose and she underwent ECMO treatment ("artificial lung") for one month. There were signs of air leakage between the trachea, oesophagus and out through the surgical wound. When the transplanted trachea began to collapse, a second transplant with a synthetic trachea was done in July 2013. The patient suffered a number of severe postoperative complications, including clot formations and kidney failure that demanded dialysis. Due to fistulization, her oesophagus had to be removed.

Ever since the transplant, she has been hospitalised and required constant clean-up of the respiratory passages, but has been partially ambulatory. In May 2016, she underwent a multiple organ transplant in the U.S., including the trachea, with material from a human donor. In August 2016, she is still hospitalised, but is partially ambulatory.

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Many inadequacies before, during and after the transplants

There were clear weaknesses in how the informed consent was obtained, how the multidisciplinary conferences before the operations worked and in the continuity in the contact between patient and treating physician after the transplants. The synthetic material had inadequacies. The pharmaceutical treatment deviated from what is acceptable. Not enough information was gathered about the progression of the first transplant patient when the decisions were made to perform surgery on both of the others.

Informed consent.

The three patients were fully capable of making decisions. Before the operations, they were informed by Macchiarini or his colleagues. That the patients had to provide written informed consent was unconventional for Swedish medical care, but in principle a good initiative and in agreement with international guidelines. We have only been able to find

that patient 1 signed an informed consent. However, the written information contained texts that neither made it possible for the patient to understand the content or refrain from the procedure. If the information had been presented to an ethical review board, it would not have been approved. The patients were not given any possibilities to discuss the operation decisions with an independent expert.

Multidisciplinary conferences.

Prior to the decisions to transplant, multidisciplinary conferences were held for two of the three patients. No conference was held prior to either of the transplants the third patient underwent. In our judgement, the initiative for multidisciplinary conferences was highly motivated, especially as it concerned an entirely new kind of surgical procedure with unknown risks. However, at the conferences, the crucial issues were not discussed regarding what scientific foundation there was and what risks the transplants could conceivably entail for the patients. Important expertise was missing. The conferences came to pro-

vide support to the transplant activities and meant that the responsibility relationships could be perceived as ambiguous. However, the ultimate responsibility for the trachea transplants being performed rested with the operating surgeon (Macchiarini).

Clinical information prior to making a decision. Prior to the operations of patient 2 and especially patient 3, not enough information was gathered about the progress of patient 1, or adequate consideration was not taken to the information on hand.

Synthetic material.

In the four transplants, three different synthetic materials were used. There seems to have been several reasons for the material changes, including that the material was difficult to sew, it was too stiff to be able to replace the human trachea, and material failure (collapsing trachea). We believe that the material changes indicate that too little was known about the material in order for it to be able to begin to be used in patients. Moreover, the diameter of the synthetic trachea was not always optimal.

Medication.

In connection with the first two transplants, growth-stimulating drugs were used. For the third patient, we have not been able to find any information in the medical record that growth-stimulating drugs were applied. In other documentation received by the investigation, it looks, however, as if patient 3 had received the same kind of medication.

There was no permit from the Swedish Medical Products Agency to use the growth stimulants for this purpose and in the doses provided. All three patients were struck by large clot formations and it cannot be ruled out that the drugs may have contributed to this.

Patient-doctor continuity.

As the operating surgeon, Macchiarini was the physician responsible for the patient and thereby responsible for the care of the patients after the operations. He appears to have initially taken this responsibility for patient 1 and possibly patient 2. But Macchiarini was active at several other hospitals. This meant that he was often difficult to get a hold of

when the patients were struck by complications – the patient-doctor continuity was not maintained. This became especially clear during the very long and complicated course of care for patient 3, but was also true of later phases of the care of patient 1.

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The scientific foundation was inadequate prior to the transplants

Our collective assessment is that there was not an adequate scientific foundation for a human transplant of a synthetic trachea seeded with bone marrow cells, combined with the application of growth-stimulating drugs. The concept conflicted not only with scientific and proven experience; it was also too early to conduct a scientific study on humans.

The transplantation of trachea has long been discussed as a treatment alternative if the trachea must be removed due to a tumour or severe injury or if the cartilage is so weak that the trachea is at risk of collapsing. The two main lines of research on trachea transplantation have concerned (a) trachea or other structures that are taken from deceased donors (necrotrachea, so-called biological scaffold) and (b) trachea made of synthetic material.

At the time of the trachea transplants at Karolinska University Hospital, numerous animal experiment studies had been done. The results had been mixed. The Macchiarini team had reported partially successful experiments with transplants in pigs with trachea from other pigs. Other research teams had reported on the growth of tracheal epithelium on transplanted synthetic trachea, although made of a material different than what came to be used in the patients Macchiarini operated on. The survival of laboratory animals after transplant with a synthetic trachea had varied widely.

In 2008, Macchiarini and co-workers reported on a transplant performed in Barcelona with a specially prepared trachea from a deceased donor. According to the report, the transplant was successful and a five-year follow- up was later published. A second transplant with a specially prepared trachea from a deceased donor was performed in London in 2010 and two years later was reported as having been successful.

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The transplants that were performed at Karolinska University Hospital in 2011–2013 were the first in the world where synthetic trachea were used in humans. In the scientific literature, there have been strongly divergent opinions as to whether this is a way forward or not. When the transplants were performed, there were no results from experiments on whole lab animals where the specific techniques were used that were applied in the clinical transplants (the combination of the specific synthetic material, the preparation with bone marrow cells and the application of growth factors).

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The transplants should have been subjected to ethical review

A number of circumstances indicate that the transplants concerned clinical research, which according to the Ethical Review Act also refers to scientifically based development. They should have undergone ethical review. It is unlikely that the project would have been approved if so.

In the debate on Macchiarini's transplant activities, the hospital maintained that it was a matter of the medical care of severely ill individuals where other treatment alternatives had been exhausted. In accordance with this, the hospital asserted that it involved compassionate use (treatment for humanitarian reasons) and that it was not a matter of clinical research. Approval by an ethical review board was therefore not required.

On the contrary, KI's investigator Bengt Gerdin, the Swedish Research Council, the Health and Social Care Inspectorate and a number of debaters have been of the opinion that the trachea transplants involved clinical research. We have found a number of circumstances that indicate that the transplants involved clinical research, which according to the Ethical Review Act also refers to scientifically based development. In our judgement, the rules for research should have been followed – then a number of ambiguities regarding ethics permits and permits from the Swedish Medical Products Agency would have been addressed.

There appears to have been a large humanitarian element (compassionate use) when the decisions were made to perform the transplants. But this does not mean that other ethical values can be set aside. Nor can it be used to justify deviations from current regulations, especially in terms of the protection of the patient and patient safety. A humanitarian element does not reduce the need for review under the Ethical Review Act. We find it to be very unlikely that the transplants would have been approved by an ethical review board based on the scientific information that was available in 2011.

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The hospital has (like KI) maintained the opinion that the trachea transplants were not clinical research. We assess that this position, if maintained, can entail a risk of continued shifting in the application of the regulations on clinical research at the hospital.

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Macchiarini and the heads of department were responsible

As the operating surgeon, Macchiarini had a direct responsibility for the transplants being performed. A head of a clinical department has the responsibility for patient safety at his/her clinic. The participants in the multidisciplinary conferences that preceded the transplants had some professional shared responsibility.

The head of the ENT clinic had the formal responsibility for Macchiarini's employment as a senior physician. He took several well-motivated steps to support and control Macchiarini's establishment at the clinic, but these steps proved inadequate for such a difficult-to-manage employee. The head of the department had the formal responsibility for these inadequacies. In the time that Macchiarini was employed at the ENT clinic, he came to carry out three of the four transplants and the majority of his other operations at the department of thoracic surgery. There were inadequacies in the coordination between the departments, which contributed to ambiguous responsibility relationships.

Decisions to perform transplants on patients 1 and 2 were made at multidisciplinary conferences. When the participants in multidisciplinary conferences supported the transplant decisions, they accepted some professional shared responsibility as consultants. This in no way discharges the operating surgeon (Macchiarini) from the ultimate responsibility for the trachea transplants being done. Macchiarini was also the physician responsible for the patients and was thereby responsible for the patients' care

after the operations. He did not take this responsibility for patient 3 or in the latter phases of the care of patient 1. The head of the department has the formal responsibility for the care provided at the department being safe for the patient and in compliance with

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the rules. There were inadequacies here and the heads of the ENT and thoracic surgery departments accordingly have a responsibility for this. We assess that the head at the thoracic surgery department acted adequately once he fully understood the unfavourable results of the three transplants. Macchiarini was no longer permitted to operate. The ENT department wanted to extend his appointment as a senior physician when it expired in November 2013. After intervention by the hospital director and his staff, it was decided, however, to end Macchiarini's employment at the hospital. The hospital withstood pressures from KI to extend the appointment.

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Laws and other regulations were not followed

The conclusion of the investigation based on the occurred events is that the hospital did not maintain a proper approach to the healthcare regulations. Several deviations were made from the regulations.

As previously presented, we deem that the transplants of the synthetic trachea constituted clinical research. The hospital should therefore have applied the regulations of the Ethical Review Act. The lack of a research ethics review was of crucial importance to the course of events. Permits should also have been obtained from the Swedish Medical Products Agency for the use of the combination of a synthetic trachea, preparation with bone marrow cells and the use of non-approved pharmaceuticals. No such permits existed.

The contacts with various permit issuing bodies were handled informally, most often over the phone. This has allowed room for divergent interpretations. We find it to be unacceptable that formally correct ways to assess the extent to which permits were needed for different parts of the transplantation concept were not used.

The regulations for healthcare were partly applicable in these operations. The management system was inadequate to some extent. The regulation regarding information and consent and a second opinion were not handled satisfactorily.

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Multiple problems concerning patient safety

During our investigation, there were signs of inadequacies in the patient safety work at both of the clinics involved, possibly also at the hospital in general. The Macchiarini case may have contributed to there being a risk that patients cared for at the university hospital feel less safe.

We have not had the ambition of shedding light on the whole hospital's patient safety culture and patient safety work. Our impression is nonetheless that the hospital largely appears to have an adequate organisation and works with the tools and models that are needed for suitable patient safety work.

However, the Macchiarini case has exposed inadequacies in the management and governance of the activities. No risk analysis was done before the procedures and there was no systematic follow-up. In our opinion, patient safety must be put first when new methods are introduced.

We are aware that "lex Maria" is not primarily focused on events in healthcare of the nature in uestion here. But we nonetheless believe that a report under lex Maria should have been filed, in any case after the operation of the third patient. A report had in all certainty led to the hospital conducting an event analysis. Even if Macchiarini had already been forced to stop his transplant activities, an event analysis could have identified more general patient safety problems. One might say that our investigation constitutes an unconventional form of event analysis.

Based on our interviews and the measurements of patient safety culture carried out by the hospital, there are numerous indications of inadequacies in the patient safety culture at both of the departments we examined, above all at the thoracic surgery department (even if these measurements should be judged with caution due to a low response rate in the questionnaires).

The lack of critical questions and ignorance regarding the regulations may have contributed to the course of events

Group thinking, bandwagon effects, a very competitive care environment, many informal leaders and deficient knowledge of and respect for rules are some of the factors that may have contributed to the course of events.

In all likelihood, group thinking contributed to warning signs in connection with Macchiarini's hiring not being taken seriously enough. Group thinking may also have contributed to Macchiarini's clinical colleagues not raising objections or asking critical enough questions before the transplantations. The initial view of Macchiarini as a particularly successful researcher and surgeon appears to have created a bandwagon effect, which is to say that once the wagon started moving, it was important to hop on.

In our investigation, we have tried to get a grasp of the environment that made the course of events in the Macchiarini case possible. Here, we present some of our observations, well aware that there are very wide variations in the care culture within the hospital.

• In an environment as strongly competitive as Karolinska University Hospital, culture of silence is found – people are cautious with open criticism upwards so as to not put their position at risk.

• Since a large share of the doctors hold extensive academic qualifications and have their KI positions linked to clinical service at the hospital, there are many informal leaders.

• The knowledge of and respect for the rules appear to vary within the hospital. It is not uncommon to take short-cuts through informal contacts with authorities. There are such examples in the Macchiarini case.

• Hospital management has had ambitions to work against a repressive culture. This work does not appear to have achieved a full breakthrough in the whole hospital.

• Karolinska University Hospital has a long tradition of being seen as Sweden's leading university hospital in both medical care and research, which is something that entails a risk of inadequacies and shortcomings not coming to light. There may be a need to further develop the hospital's work on core values.

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Complex relationship between the hospital and KI

As a result of different development strategies, management commitment to Macchiarini has been greater at KI than at the hospital. In the Macchiarini case, the hospital has not been independent enough from KI.

KI and the hospital have had different fundamental strategies for how they wanted the hospital to develop. While KI would have preferred to make a stake on excellent researchers and top recruitment of employees with shared positions, hospital management has strived for a system of continuous improvement with the aim of creating a credible and patientsafe organisation. Consequently, KI's backing of Macchiarini was more wholehearted than the hospital's at a high level of management. For better or worse, KI had extensive influence on decisions made within the hospital's organisation, an influence that is probably greater than at other Swedish university hospitals.

When Macchiarini's research activities were criticised by those filing reports and in the media, the hospital, in our opinion, too willingly supported KI's line in the defence of Macchiarini.

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The potential misconduct may have affected the care

Potential research misconduct concerning the first transplant patient may have influenced the care of both of the subsequent patients. Warning signals must be
taken seriously.

When the first report of irregularities in Macchiarini's research were filed with KI, Macchiarini's employment at the hospital had already been ended. In our judgement, potential misconduct in research may have possibly affected the care of the patients by the progress of the first transplant
patient being described too positively. This led to the transplant of patients 2 and 3 not being called into question.

It was unfortunate that focus initially came to rest on the issue of possible unlawful access to medical records instead of on the fundamental issues regarding Macchiarini's activities at the hospital. This can be perceived as a repressive measure towards employees who point out improprieties.

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The Macchiarini case has had serious consequences for clinical research and hospital employees

Restoring the trust in the clinical research demands longterm, wholehearted efforts based on sound ethics, high patient safety and respect for the rules and regulations that exist.

Many employees at the hospital have been harmed by the Macchiarini case. Targeted work-environment efforts are needed.

Macchiarini's transplant activities have damaged clinical research not only at Karolinska University Hospital, but also in Sweden in general. Restoring the confidence in the research requires long-range, wholehearted efforts. We want to emphasise that what happened around Macchiarini in no way in militates against bold and innovative clinical research. Such research presupposes ethical review and can very well be combined with a strong protection of the patient and high patient safety.

It is clear that many of the hospital's employees at various levels were harmed by the Macchiarini case. In the debate, there has been an unforgiving attitude, even bitterness, that many have been very hurt by. This can be seen as a work environment issue. It appears to us to be important that the conflicting views are toned down and a "reconciliation process" is begun.

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The hospital has taken some steps

We find four initiatives on the part of the hospital to be particularly relevant to trying to resolve the problems exposed in connection with Macchiarini's activities:

• A task force will work with issues in the border zone between healthcare and clinical research

• A whistle-blower function has been established

• The chief medical officer recently gathered information on which patients Macchiarini operated on at the hospital in addition to the three transplant patients

• An effort to strengthen patient safety has begun at the thoracic clinic.

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Patient safety and routines need to be improved

Based on our observations, we have compiled a number of recommendations to hospital management on improvement measures.

Our task included making recommendations on improvements that could reduce the risk of events similar to the Macchiarini case. Based on the observations we made, we compiled a number of recommendations. Most of them build on suggestions made by the individuals interviewed, many of whom are hospital employees. Our recommendations are focused on improvement possibilities with regard to patient safety, organisation and routines. Here, we summarise the most important of the recommendations, well aware that they may seem general in condensed form.

Recruitment.

The recruitment process must be quality assured and the hospital must demonstrate greater independence from KI in the recruitment of clinically practising employees.

Rules and guidelines.

Since there are many indications that the knowledge of rules and guidelines is limited in many places within the hospital, extensive training efforts are necessary. It is particularly important to invite the Swedish Medical Products Agency to clarify what rules apply within its field.

Patient safety.

Patient safety must be central. Systematic review of the scientific foundation, risk analysis and systematic follow-up should be regularly done when new methods are introduced in medical care. The staff for quality and patient safety should be given expanded and clearer responsibility for issues of patient safety being put first and for ensuring that the hospital follows and adapts to the research in the patient safety field.

There have been indications that the patient safety culture at the department of thoracic surgery has not been satisfactory. Improvement efforts are under way. Hospital management should carefully monitor this work.

Clinical decision-making.

The working method of the multidisciplinary conference should be quality assured. Group thinking should be prevented, the responsibility for the decisions made needs to be clearer and considerations and decisions must be well documented.

The unit manager has a responsibility for continuity in care, which is something that must be emphasised. This responsibility becomes especially important to maintain with regard to highly specialised care where the expertise is concentrated to one single person or a limited number of people.

Clinical research and introduction of new untried methods.

In the hospital and KI work that has begun on internal guidelines for new untried methods, particular importance should be placed on ensuring compliance to the Ethical Review Act and the regulations on clinical studies. Several of the investigation's recommendations aim to strengthen ethics when new methods are introduced to medical care and thereby preserve the respect for the clinical research.

Special ethical expertise should be tied to the introduction of new methods to medical care (the ethics committee currently at the hospital has a different focus). The room for individual employees to begin applying new untried methods without external review must be minimised.

Employees.

Several recommendations aim to reduce the room for such independence that can lead to inadequate patient safety. Hospital management should continue the work to counter repressive elements, not least in the patient safety work. The hospital should also address the conflicts and work environment problems that the Macchiarini case has created.

Our task and its implementation

In February 2016, the Director of Karolinska University Hospital commissioned an investigation with the directive to answer the following questions surrounding Macchiarini and the trachea transplants he performed at the hospital:

• Under what circumstances and under what conditions was Paolo Macchiarini hired at the hospital and what were the circumstances surrounding the termination of his employment.

• What did the decision-making process and documentation look like prior to the decisions to operate?

• Was the choice of measures correct based on available knowledge, applicable legislation and guidelines? This pertains to both the surgical procedures and the subsequent care.

• What ethical assessments were made before the operations and later during the course of illness?

• What guidelines and other steering documents existed at the time the operations were performed and were they complied with?

• What roles did decision-makers at various levels in the hospital have regarding the decisions on the operations and care? What later steps were taken due to Macchiarini's activities?

• Have there been other circumstances of direct relevance to a specific assessment of Macchiarini's activities at Karolinska University Hospital?

The task also included making improvement recommendations based on the facts that came forth in the investigation.

The task was assigned to Kjell Asplund, Professor Emeritus in Medicine at Umeå University, Chairman of the Swedish Council on Medical Ethics (Smer) and former Director-General of the National Board of Health and Welfare. To help him, he appointed a workgroup consisting of Nils Blom, former Senior Legal Counsel at the National Board of Health and Welfare and the Public Health Agency of Sweden, Katarina Johansson, Chair of the patient organisation Network against Cancer, and Jesper Persson, Senior Physician and former Chief Medical Officer

at Skåne University Hospital. Pernilla Östlund, with the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) as her ordinary place of employment, served as the investigation secretary.

The focus of the investigation was on patient safety issues in a broad sense. We examined the circumstances surrounding the three patients' trachea operations and shed light on issues concerning the patient safety culture that existed in connection with the three patients' operations and continued care. Processes, documentation and decisions were checked against the steering documents and guidelines that applied during the period in question.

To be able to learn lessons from the Macchiarini case, we strived to describe not only

what happened, but also attempted to gain insight into how it could happen.

There was a clear risk that our analyses and assessments would be characterised by hindsight. We therefore, to the furthest extent possible, worked based on the state of knowledge and regulations that applied at the time that various decisions were made in the Macchiarini case.

A large amount of written materials were gathered during the investigation, including:

• the medical records of the three patients

• other documented considerations and decisions

• scientific publications

• local steering documents

• steering documents from authorities and national and international professional organisations

• relevant legislation

• correspondence

• the hospital's patient safety reports and quality reports 2011-2014

• the hospital's patient safety culture measurements 2010-2013

During the investigation, more than 60 people were interviewed. Most of them had a direct connection to Macchiarini's activities at the hospital.

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We also interviewed representatives of authorities, labour unions, patient organisations, individuals who were especially active in the public debate surrounding Macchiarini and people who had more general information in issues concerning new untried methods in medical care. Opinions from Macchiarini were shared with the investigation through an extensive interview, e-mail correspondence and written materials that he sent to the investigation.

During the investigation, four external reviewers were brought in; two made prognosis assessments of patients 1 and 2 and two others reviewed chapters 11 (Analysis and summary assessments) and 12 (Recommendations). Other investigations are addressing issues surrounding Macchiarini's activities at KI and the accusations of misconduct in the Macchiarini team's research.

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1. The Committee's mission and work

1.1 The mission and the mission's content

The management of Karolinska University Hospital (also known as hospital) have wanted to investigate the events before, during and after the luftstrupstransplantationer performed on three patients at the hospital. Hospital Director Melvin Samsom decided 2016-02-12, together with Head doctor Professor Nina Nelson Follin at the headquarters of Quality and Patient Safety and after consultation with the Stockholm County Council, to appoint an external investigation. The contract was awarded Kjell Asplund, professor emeritus, president of the National Council on Medical Ethics (Smer) and earlier Director General of the National Board.

The assignment was to investigate:

• Under what circumstances and conditions Paolo Macchiarini employed at the hospital and what the circumstances were surrounding his employment was terminated.

• How the decision making process and the documentation for the operating decisions looked.

• If the choice of action was correct on the basis of available knowledge, existing legislation and guidelines. This pertains to surgical interventions that subsequent care.

• What ethical assessments conducted for operations and later in the disease.

• What guidelines and other policy documents that existed at the time of implementation of operations and if these were followed.

• What is the role of decision-makers at various levels within the hospital have had when it comes to decisions concerning the operations and management, and the measures taken following the Macchiarinis activity.

• If there were other circumstances directly relevant to a specific assessment of Macchiarinis operations at the Karolinska University Hospital. Based on the facts that emerged from the investigation would formulate recommendations on improvements.

1.2 Project

The investigator has appointed its own working group consisted of:
• Nils Blom, former general counsel at the National Board of Health and the Public Health Agency

• Katarina Johansson, patient representative, chairman of the Network Against Cancer

• Jesper Persson, former head doctor at Skåne University

• Pernilla Ostlund, research assistant

The group has been through Stockholm County Council had access to administrative resources equivalent 20 percent of full time. Stockholm County Council has funded a study and the set premises Working disposal.

1.3 The inquiry's main focus

The focus was on patient safety issues in a broad sense. The study was based on a examination of the circumstances surrounding the three patients who underwent luftstrupstransplantationer, but have also highlighted questions about the patient safety culture prevailing in connection with the three patients' surgeries and continuing care. Processes, documentation and decisions have been checked against the policy documents and guidelines in force during the period in question.

1.4 Limitations

The assignment is limited to Macchiarinis luftstrupstransplantationer at Karolinska University Hospital.

This means that the following issues have been outside of our mission:

• Macchiarinis operations at the hospital regarding other than the three luftstrupsoperationerna

• Macchiarinis operations at other hospitals

• questions about Macchiarinis employment at Karolinska Institutet (KI)

• issues relating to possible misconduct in research

• issues relating to the KI management's handling of Macchiarinifallet.

These issues mentioned in our report if they were of direct relevance to the assessment of Macchiarinis transplant operations at the Karolinska University Hospital, but we have not had the ambition to analyze them more closely.

1.5 Relation to other investigations

It has added several other investigations for the direct or indirect view Macchiarinifallet. The investigation closest to this, "the Karolinska Institute and Macchiarini case An external audit in 2016 ", led by Sten Heckscher with the task of investigating certain matters concerning Macchiarini from a CI perspective. Inquiry appointed by the Senate,

KI University Board.

We have had regular contact with Heckscherutredningen to clarify our boundaries and avoid duplication of efforts and cooperate in cases where it has been possible. We have had, among other some joint interviews and shared some written material that has been of interest to Both investigations.

Other investigations:

- Investigation of Research Misconduct. The Government set this inquiry in October 2015. It will, inter alia, examine the need for a new organization for independent investigations research misconduct. It will be ready on 25 November 2016. Investigators are Margareta Fahlgren, Professor of Comparative Literature.

- Review of the regulatory frameworks for research ethics and the interface between clinical research and health and medical care. This investigation was launched by the government in June 2016, Gudmund Toijer as investigators. The inquiry will report to the Education Ministry by 31 August 2017.

- Ethical aspects of the use of untried new methods of care. The project has been initiated by the National Council on Medical Ethics (Smer) and is about the ethical problems that may arise in the boundary between health care and research, and the need clearer regulations or guidelines. Smers report is expected to be completed in autumn, 2016.

- Clinical guidelines for the use of unproven therapies to seriously ill patients. Collaborative projects between the Swedish Medical Society and the Royal Academy of Science. Published June 16, 2016.

- Reviewing the audit. Universitetskanslersämbetet has requested the investigation of KI so once it is completed, as well as a statement from CI for the action to be taken.

- Misconduct Investigations at KI and the Central Ethical Review Board. KI has re-opened the previous fraud case led by the four doctors report in 2014. In the investigation garnering KI opinion of the expert group on research misconduct at the Central Ethical Review Board (CEPN). Notification was received at CEPN the end of June 2016. For the CEPN submitted three additional cases of Macchiarinianknytning: (a) the animal experimental study of luftstrupstransplantation published by Macchiarinigruppen in Nature Communications 2014 application filed by the four doctors who reported Macchiarini 2014 (b) experimental Article of synthetic windpipe carcass published by Macchiarinigruppen in Biomaterials 2014 Anonymous

notifier, (c) notification of unauthorized use of research data directed against one of the four notifying the doctors, the complaint filed by Macchiarinis German collaborator. opinions on cases (a) and (b) expected to be completed in early autumn 2016. Issue (c)

has recently received to CEPN.

- Legal Council at the National Board. Prosecution Office in Stockholm submitted in January 2016 an request for an opinion from the Council. In late July or August 2016 the case was still Unfinished.

- KI's examination of Paolo Macchiarinis resume. The review confirms that CV includes several inaccuracies.

- Preliminary investigation. Both the Agency for Health Care (IVO) which MPA has Police notified Macchiarinis clinical operations at the Karolinska University Hospital. a preliminary investigation progress of gross negligence manslaughter and grievous bodily harm on the occasion of the operations at the Karolinska University Hospital.

- Local investigations. The attention surrounding Macchiarinis operations at KI and the hospital has meant that in many parts of the country begun to review its regulations on the use of untried new methods of care.

1.6 Inquiry operation

1.6.1 Method

The methodology is based on the fundamental issues that are described in SKL's handbook event analysis, but because of the complexity of the case, the methodology has been modified (1). Compared conventional case analysis, the working group more thoroughly searched for different types of written documentation and conducted far more interviews. This is to illustrate different perspective on the circumstances surrounding Macchiarinis operations at the hospital.

1.6.2 Legal requirements

After consulting the General Counsel at the Stockholm County Council of the Inquiry legal conditions. The members have signed confidentiality undertakings, which collected In the medical director Nina Nelson Follin, Karolinska University Hospital. During secrecy has the Working Group had access to written records and other patient-related information as well as to Patient information obtained in interviews.

The working group has worked independently from the principal. The group's report has been public document if and when it is received by the client.

1.6.3 Written material

A large amount of written material gathered during the investigation, including:

- Three patients' medical records

- Other documented considerations and decisions

- Scientific publications where the patients presented

- Local policy documents

- Policy documents from government agencies

- Relevant legislation

- Professional documents, national and international

- Correspondence Macchiarinifallet

- Protocols and memos

In email correspondence, often written in haste, sometimes occur typo. We have consistently in report chosen to quote without making any corrections.

1.6.4 Interviews

Early in the investigation, made an introductory round of interviews with a small number of key people to identify the persons who should be interviewed. Interviews with the key People have been implemented as personal meetings, primarily with the entire team present, secondly with the investigator and research assistant. Interviews with other individuals have been carried out either by personal meetings or telephone conferences. In all the interviews have at least two members of the group were present. Supplementary questions were asked in phone interviews or through mail.

The following individuals and entities have benefited from the interviews:

directly affected
• Paolo Macchiarini

• responsible for Macchiarinis employment at the hospital

• participants in decisions before surgery

• medoperatörer

• responsible for the patients' post-operative care and follow-up

• the doctor who reported Macchiarinis operations at the hospital to KI's Vice-Chancellor and Principal Ethics Committee

• operations managers at the ear, nose, neck and thorax clinics

• chief physician at the time of the operations and then

• hospital development and innovation director

• hospital directors at the time of the operations and then

• responsible for the hospital's external communications related to operations

indirect concerned
• Local President of the Medical Association

• Medicines Agency

• National Board

The study also interviewed external experts and opinion leaders. We have also had meetings with representatives of the following patient groups:

- Mouth & Throat Cancer Association

- Cancer Society pALeMA

- Lung Association ASSISTANCE

- National Association Heart-Lung

The commission has a total interviewed or met with 62 individuals (Appendix 1).

1.6.5 Macchiarinis viewpoints

Comments by Paolo Macchiarini have come to the investigation part through a long interview, followed by email correspondence for some clarifications. Macchiarini also have to put the investigation material in the form of particular description of events, transplantation protocol, scientific literature and its email correspondence especially with employees and managers at Karolinska University Hospital and Karolinska Institutet.

1.6.6 review

We have hired two external reviewers of chapters 11 and 12, Professor Ingemar Petersson, Head of Research at Skåne University healthcare (SUS) and Professor Jack Lysholm, head of the Register Centre Norr, Umeå. Two external experts, Lars Ek, chief of pulmonary medicine at Skåne University Hospital and associate professor Jan Nyman,

Chief of Oncology at Sahlgrenska Hospital in Gothenburg, have contributed their views on the two first-transplanted patients' diagnosis and forecast. Some descriptive texts, however, no patient data, has the support of the relevant authorities.

Reference

1. Manual. Risk analysis and event analysis. Third revised edition: Swedish municipalities and county; 2015.

Report Chapter 2

2. Medical background luftstrupstransplantationer

In this chapter we provide a brief description of the trachea and the diseases where luftstrupstransplantationer could be considered (2.1). In discussing the Macchiarinis transplants Karolinska University Hospital is a central issue was whether there was enough with scientific data to start with transplants of synthetic trachea of humans. We also discuss briefly the scientific literature on luftstrupstransplantationer (2.2) and provides an overview of the growth-stimulating drugs used in connection with transplants (2.3).

2.1 The trachea and its diseases

2.1.1 The trachea

The trachea, the trachea, is a 10-16 cm long pipe connecting the larynx with the lungs. The diameter is in an adult about 2.5 centimeters. It is a seemingly simple hollow organs for transport of air to and from the lungs. But unlike many other agencies where transplant may be appropriate, the trachea is exposed constantly to the environment, which means a high risk of infection.

The trachea is 15-20 horseshoe-shaped elastic cartilage rings (tracheal cartilages) enclosing tube and keeps it open (Figure 2.1). It is located in a vascular area behind the aortic arch and in front of the esophagus and divides into the two main bronchi (airways; primary bronchi), to a each lung.
[figure 2.1 omitted]

In addition to the cartilage found in luftstrupsväggen muscle cells (which contract when coughing), connective tissue, blood vessels which stands for the nutrition and nerve fibers. The inner surface is lined with a mucous membrane with epithelial cells. Some of the epithelial cells produce mucus to keep the trachea moist and protect it, other cells have cilia that transport mucus and particles from the lungs up the pharynx.

2.1.2 trachea diseases

Clearly the most common diseases affecting the trachea are infections and inflammations. In other diseases are the trachea relatively uncommon. The trachea displaceable tumors, both benign and malignant. Cancer that starts from the trachea are rare - in 2014 fostered fewer than ten patients in Sweden with this diagnosis [1]. After injury to the trachea, for example, in connection with traffic accidents or after radiation therapy, scarring with narrowing occur.

There are rare congenital luftstrupssjukdomar, and malformation of one or more cartilage rings constricted as a result, and as pronounced weakening of the cartilage to trachea danger of collapse (tracheomalacia).

2.1.3 Treatment of luftstrupsförträngningar

At strictures, whatever the cause, which is so severe that they cause difficulty breathing, it can constricted section is removed and the ends are sewn together. One condition is that the length of the part of the trachea are removed less than six centimeters. Otherwise stenting is the most common measure - a tube inserted into the trachea and hold it open. The tube may be of synthetic material (absorbable or non-absorbable) or metal.

There are also opportunities to open surgery, laser surgery, other surgical techniques or radiotherapy remove at least part of a tumor or other obstruction. In rare cases, a longer part of the trachea (or all) have to be removed because of a tumor. It is these situations transplantation of the trachea has been updated.

2.2 Luftstrupstransplantationer

Both in literature as in everyday language, the concept of transplantation come to used both in the trachea replacement of organs from human donors (major transplant) and when replacing the trachea with synthetic material. Although compensation with synthetic materials strictly interpreted does not involve the transplantation, we have in this report chosen to use the concept of transplant also in the trachea replaced by a synthetic body, this not complicate terminology (in English sometimes used the concept of replacement that better describes what it concerns).

Transplantation of the trachea has long been discussed as a treatment option if one is forced remove the trachea due to tumor or severe injury or if the cartilage is so weakened that the trachea risk of falling apart. The two main lines of research on luftstrupstransplantation has moved (a) the trachea or other structures taken from deceased persons (nekrotrakea) and (B) the trachea of synthetic materials.

Transplantation of trachea deceased can be implemented as "conventional" transplant. But you can also, like the synthetic trachea, using as a framework nekrotrakea after living cells removed. In experimental trials, the body sometimes inserted without preparation.

But more common is that they tried to dress it with cells, with the aim that these should develop into normal airway cells (epithelial cells) and cartilage cells.

Ideally, the body should be biocompatible, that is not cause rejection reactions. The should be non-toxic and does not contain carcinogens. It must also meet certain mechanical requirements to be of sufficient strength and not be degraded, while it shall be flexible. For a functional trachea is also required to epithelial cells grow firmly and that there is adequate vascular supply [2].

To provide an overview of the research situation that prevailed when luftstrupstransplantationerna was conducted at the Karolinska University Hospital, we summarize here the results of a selection of in vivo studies in experimental animals (studies on whole animals) and people published until 2012, in particular the studies reported longer periods of follow-up. Although we had the ambition to provide a picture of the overall state of knowledge, we make no claim to the case of a systematic literature review. Any irregularities in Macchiarinigruppens research has previously been investigated by KI and

by the expert, Bengt Gerdin, KI engaged. We have stated in the text which studies will from Macchiarinigruppen but has not taken a position on whether they are correct or not, because misconduct issue is now being investigated again, this time by the expert group for the misconduct at the Central Ethics Committee.

2.2.1 Nekrotrakea (trachea from a deceased)

The three patients who luftstrupstransplanterades at Karolinska University Hospital surgery in 2011-2012 (patient 3 underwent a second transplant in 2013). We have therefore chosen to share up this summary overview of what was known at the time of transplantation (even 2012) and what is to come then.

Preclinical studies until 2012. A significant number of experimental studies have been conducted at laboratories around the world with a view to developing a technology that would be adapted for transplantation of donor trachea from a deceased person, called nekrotrakea. Several of these have been published by Macchiarini and his associates.

Trachea from donor animals are usually prepared by removing living cells to eliminate the risk of rejection. The results have been mixed. Macchiarinigruppen has reported that pigs transplanted with nekrotrakea prepared as before transplantation exposed to the epithelial cells on the inside and cartilage cells on the outside ("bio-engineering"), survived in up to 60 days of observation without the emergence of any rejection reaction [3,4]. It is,probably these studies Macchiarini intended when he at information for patients and the The recent debate said that there existed own experimental studies on large animals. In these studies reported Macchiarinigruppen while that in other experimental groups (Pigs) with more limited transplantation preparatory efforts had to

kill the animal prematurely because of severe complications [3]. Although other research groups had reported before 2011 problems in experimental transplantation of nekrotrakea in pigs (for example) [5].

There was no single report that after transplantation with nekrotrakea in pigs could observe basically normal airway epithelium eight weeks after surgery [5]. In a more complicated animal model (human nasal mucosa was transferred to the trachea in rats transplanted to mice with reduced immune function) were one outgrowth of the human airway epithelium. [6]. Without vascular supply breaks down the cartilage tissue and a variety of methods to stimulate angiogenesis had been launched before 2011 [7-9].

While other organs and tissues in the trachea had been used in experimental luftstrupstransplantationer, for example tissue from the aorta, small intestines, peritoneum and pericardium, with very limited or no long-term success.

Clinical studies until 2012. The first transplantation of the trachea in humans was performed in 1979 [10]. It moved as if a "conventional" transplantation (allo-transplantation) with a trachea from a deceased person. Allo-transplantation of the trachea involves two major problems. The first is common for allo transplants in general - to prevent rejection of the organ requires lifelong immunosuppressive therapy, but even this is no guarantee that the transplanted trachea rejection. The second problem concerns the vascular supply. They have tried different techniques, example, to wrap the transplanted trachea of a piece of it abundantly vascularized mesentery (Omentum). [11] It was also the technology Macchiarini used to try to create vascular supply to the synthetic luftstruparna.

To overcome problems of immune rejection and the need for immunosuppressive drugs (With the risk of side effects) has been working to modify the trachea from a deceased ("Bio-engineering"). In 2004 transplanted Macchiarini and his colleagues a 1.5 x 1.5 cm large tunntarmsbit porcine, which prepared with bioengineeringteknik, to luftstrupsväggen in a patient [12]. It reported early outgrowth of airway epithelium and good vascular supply after six weeks.

The first transplantation in humans with nekrotrakea prepared by bio-engineeeringteknik conducted by Macchiarini and his team in Barcelona in 2008 [13]. The patient was a 30-year-old woman with congenital weakening of the cartilage in the windpipe (trakeomalaci), something that made the trachea in danger of falling apart. The transplanted trachea had pretreated for six weeks to eliminate the living cells that could cause rejection. It had also made a seeding of cartilage cells and cells from the nasal mucosa.

Macchiarini and his colleagues described the surgery as successful in the short term. It reported early growth of airway epithelium (within one month) in the transplanted trachea [13]. In 2012, reported a research team in London transplantation as a treatment

nekrotrakea severe luftstrupsförträngning of a 10 year old boy. A year after the transplant was observed ingrowth of airway epithelium, and two years after the procedure stated that the boy had been functioning airways and that he did not need any medication. [14]

Macchiarini has our investigation submitted a list of nine transplants nekrotrakea which he conducted in the years 2008-2011 due to trakeomalaci (weakening of luftstrupsbrosket) fistula, cancer or congenital severe narrowing [15]. Five patients were at life of 37-67 months after surgery. Four had died after 1-24 months.

Publications after 2012. In the literature that emerged after the transplants at the Karolinska University Hospital have problems in transplantation nekrotrakea in laboratory reported [16,17]. Macchiarini and co-workers published 2014, a 5 year follow up of the patient transplanted in Barcelona in 2008. It described the progress and her condition as satisfactory, albeit not without complications [18]

In a follow-up report four years after the transplantation of nekrotrakea of the boy in London as previously described [14] research group reported that his condition was good - he went in school. He had had to comprehensive treatment and total treatment costs during those first four years was estimated at over half a million dollars [19].

The Belgian ear, nose and throat surgeon Delaere and his colleagues have presented a alternative surgical techniques. Their starting point was the need to secure supply vessels to the transplanted nekrotrakean by first implanting under the skin of the forearm for about four months, this is for capillaries to grow into the implant. They have reported the technology applied in eight transplants in six patients [20]. the research team has in the scientific literature have reported long-term survival in four of the patients [8,21,22]. Delaere told us to hold on to complete a script where long-term survival also described for the remaining 2 patients [23].

2.2.2 Synthetic trachea

At the three luftstrupstransplantationerna at Karolinska University Hospital has used three various synthetic materials. In preclinical studies, a wide range of research groups around the world have studied a variety of synthetic materials.

We describe here only the study of solid or porous polymers ("plastics"), but not studies where they used other materials, such as metals and glass.

Preclinical studies until 2012. There are a number of studies of transplantation of synthetic trachea in laboratory animals (rats, mice, rabbits, dogs). In most of these studies, before transplantation sown implants with cells of different types. Several reports outgrowth of airway epithelium on the synthetic grafts have been published (for example, [2,3,24-27]). mortality after transplantation of synthetic trachea of experimental animals has varied from low (eg [25-27]) to very high (eg [28-30]).

At the first luftstrupstransplantationen at Karolinska University Hospital used a material (POSS-PCU polymer; POSS stands for polyoctahedral silsesquioxanes and PCU poly (carbonate-urea) urethane) as before the operation prepared with bone marrow cells (including another contains stem cells, albeit small portion) to create the outgrowth of epithelial cells on the porous

polymer surfaces. POSS-PCU is usually described as a nanomaterials and since the middle of 2000s investigated as biomaterials in preclinical studies. The material had been tested before 2011 in experimental animals in sterile environments [31,32]. It has created this material including synthetic heart valves, blood and lymph vessels, stents and outer ear, without the material appears to have clinical application. The development of POSS-PCU is mostly made by researchers in London [32,33], which Macchiarini collaborated with [32,33]. Macchiarini and his research team reported in 2012 the results of laboratory studies of other polymers which examined how cells grow on these materials in vitro ("test tubes") [34].

At the time of luftstrupstransplantationerna at Karolinska University Hospital 2011-2012, Macchiarini and / or his associates reported no results from experiments on whole animals that have used the techniques applied in luftstrupstransplantationerna of the three patients, that is, different polymers exposed to bone marrow cells and administration of growth factors.

In the total of four transplants (two in patient 3) they used three different kinds polymeric material. These materials had undergone toxicity and biokompabilitetstetser at second laboratories, but they had not tested the trachea in animal models.

Clinical studies until 2012. The transplant of a synthetic windpipe conducted at the Karolinska University Hospital in June 2011 was the first of its kind in the world (patient 1). The transplant brought already when it was made considerable media attention. In November 2011, published a scientific report in the prestigious journal The Lancet. In Chapter 4 we describe in more detail for this transplant. Lancet article has been cited frequently - 196 citations at the end of July 2016 according to Web of Science. In review articles, it has usually been regarded as a breakthrough study in the field of transplantation by synthetic means (e.g. [2]). It has, however, in the scientific literature also been critical voices as described Macchiarinigruppens methodological approach as unrealistic [20].

The clinical course of patient 2 does not appear to have been reported in the scientific literature. Patient 3 has been mentioned cards (without the clinical course reported) in a work on cell survival 2013 [35].

At a cursory literature search, we have not been able to find that other researchers than Macchiarinigruppen published clinical results from the transplantation of synthetic

trachea in patients (July 2016).

Publications and other experiences after 2012. On the occasion of news interview with Macchiarini in May 2016 [36] wrote the four doctors who notified him of research misconduct a memo in which they commented it Macchiarini said in the interview. This memorandum described the doctors to Macchiarinigruppen began animal experiments with the methodology used in the clinical transplants only after the third patient received its first synthetic windpipe [37].

In Macchiarinigruppens first attempt should be 5-7 rats have been transplanted, half of whom died within two days and the other half survived "several weeks" with increasing luftstrupsförträngningar. These results were not published. Then began a series of transplants of synthetic trachea of 8 rats. results have been published in three articles 2013-2014 [35,38,39]. Two different synthetic materials tested, previously used in transplantation of patient 2 and 3. The synthetic luftstruparna had been sown with mesenchymal stem cells. The research team reported that after a 30-day observation period epithelium observed on the synthetic body and nascent vessel formation. There was no evidence of inflammation or necrosis. The rats were said to feel good with hefty weight gain during follow-up [38]. Two of these articles [35.38] included in the material previously investigated for research misconduct and is now being investigated again.

The Belgian ENT Professor Pierre Delaere (which itself uses nekrotrakea, see above) have review articles 2014 and 2016 in very powerful terms renounced Macchiarinigruppens strategies [20,40]. He says that there is any scientific basis to stem cells could give rise to respiratory tissue when synthetic trachea used.

As ending to his last article he describes Macchiarinigruppens approach hypothetical and scientifically unfounded. The references he gives for this conclusion are limited: own previous article and an article in the scientific journal Nature about the charges against Macchiarini of research fraud [41].

Macchiarini has submitted to the inquiry a list of the transplants with synthetic trachea he performed in addition to the Karolinska University Hospital. The case of five patients operated in the 2012-2014 period [42]. Four of them were transplanted in Krasnodar (Russia) and a in Preoria (USA). Of the five patients had two omtransplanterats, which means a total seven transplants with synthetic trachea performed elsewhere than in Stockholm. Of the Five patients were at least still alive (July 2016); the latter had the transplant removed after seven months. For one of the patients lacked information about survival. One of the deaths were caused by car accident.

In our interview with Professor Martin Birchall, London, declared him to be inspired by Macchiarinis report on patient 1, performed a transplant of synthetic trachea 2011 or 2012. The patient died shortly after the transplant. This patient has not been reported in thescientific literature.

In the recent public debate, the whole idea of transplantation of synthetic trachea challenged, often ridiculed. It might then be worth recalling that synthetic materials today in fairly large scale in health care, and then you work - in sterile environments. In non-sterile environments, the problems are far greater. The trachea has been shown in experimental studies to be a body means very special mechanical and biological challenges.

Macchiarini contacted in March 2013 operations manager at the Department of Thoracic Surgery of plans for a Clinical trials of synthetic trachea in collaboration with Harvard Bioscience [43]. Since His transplants as had been questioned, was not completed this idea. But in several countries an ongoing preclinical development of synthetic trachea with a view to transplantation in humans. Projects have large research grants from countries including the EU [44]. Clinical trials are planned but there is contradictory information about getting started or not.

2.3 Drugs

In connection with transplants used three drugs in a way that challenged:

• NeoRecoromon (erythropoietin)

• NEUPOGEN (G-CSF, filgrastim, granulocyte colony stimulating factor)

• TGF-β3 (transforming growth factor)

All three substances used in the preparation of the benmärgscellsbesådda synthetic luftstruparna facing operations. NeoRecormon and Neupogen was also given as injections into the first two transplant patients, possibly even to the third, for two weeks after the operations. According to patient records and scientific articles published Macchiarinigruppen used these substances as regenerative boosting therapy, the aim was therefore to stimulate cell formation luftstruparnas on the synthetic surface.

NeoRecormon is a drug that is approved in Sweden. It stimulates the formation of red blood cells and its licensed indication the treatment of various forms of anemia [45,46]. The dose the first two transplant patients had exceeded the recommended initial dose more than 10 times. At the time of transplantation at the Karolinska University Hospital was it is well documented that drug in recommended doses increases the risk of clot formation with an average of 60-70 percent [47,48]. According to the company, the effects and side effects of very high doses of NeoRecormon is not studied [45].

Neupogen is a drug that is approved to stimulate the formation of white blood cells in patients with a deficiency of white blood cells, such as during cancer chemotherapy [49]. It can also mobilize peripheral stem cells in organ donors. The dose of both first transplanted patients were in line with the recommended dose.

The interaction (interaction) between NeoRecormon and Neupogen not studied. According to the treatment protocol used TGF-β3 only during the preparation of the synthetic luftstruparna; it was never given directly to patients. The substance is not approved for use in humans. The manufacturer, the British company Bio-Techne, has stated that the only is intended for research and not for use in humans or animals. [50] The substance is only partly purified, so one can not rule out that it contains, for example, viral components with the contingency effects if used for human purposes. The company has stated that it used for human use as it is against their license agreements with users of the substance [50].

The pharmaceutical company Roche, the company that manufactures NeoRecormon, and Amgen, manufacturers of Neupogen, have both stated that the use as regenerative therapy is boosting foreign for them and that they take away from this unproven use [45,50]. They do not have known to some studies where drugs used for this purpose.

2.4 Summary

When Macchiarini recruited and when transplants were performed at the Karolinska University Hospital (2010-2013) was a small number of preclinical studies that showed encouraging result of transplantation of nekrotrakea. While it was apparent that several problems remain to solve before in the laboratory had fully developed a successful and safe method. MAN had also reported favorable results in the short term from two transplants with nekrotrakea in patients; Macchiarini and his associates accounted for one of these reports.

Regarding the transplantation of synthetic trachea has been greatly among experts divergent opinion, if this is a viable option or not. Several reports outgrowth the airway epithelium of synthetic grafts have been published. The survival of laboratory animals varied considerably between studies. When luftstrupstransplantationerna at Karolinska University Hospital was conducted, there were no results from experiments on whole animals that have used the specific techniques applied for transplants at Karolinska University Hospital. When these luftstrupstransplantationer conducted Macchiarinigruppen had not yet started Animal studies with the transplant concepts that have been used on patients (this except for the second transplantation in patient 3). The therapy with growth-promoting drugs used as the boosting regenerative therapy was largely experimental.

References

1. Socialstyrelsen. Statistikdatabas för diagnoser i sluten vård. http://www.socialstyrelsen.se/statistik/statistikdatabas/diagnoserislutenvard . 2014.
2. Fishman JM, Wiles K, Lowdell MW, De Coppi P, Elliott MJ, Atala A, et al. Airway tissue engineering: an update. Expert Opin Biol Ther 2014;14:1477-91.
3. Go T, Jungebluth P, Baiguero S, Asnaghi A, Martorell J, Ostertag H, et al. Both epithelial cells and mesenchymal stem cell-derived chondrocytes contribute to the survival of tissue-engineered airway transplants in pigs. J Thorac Cardiovasc Surg

2010;139:437-43.
4. Jungebluth P, Go T, Asnaghi A, Bellini S, Martorell J, Calore C, et al. Structural and morphologic evaluation of a novel detergent-enzymatic tissue-engineered tracheal tubular matrix. J Thorac Cardiovasc Surg 2009;138:586-93; discussion 592-3.
5. Remlinger NT, Czajka CA, Juhas ME, Vorp DA, Stolz DB, Badylak SF, et al. Hydrated xenogeneic decellularized tracheal matrix as a scaffold for tracheal reconstruction. Biomaterials 2010;31:3520-6.
6. Dupuit F, Gaillard D, Hinnrasky J, Mongodin E, de Bentzmann S, Copreni E, et al. Differentiated and functional human airway epithelium regeneration in tracheal xenografts. Am J Physiol Lung Cell Mol Physiol 2000;278:L165-76.
7. Chue WL, Campbell GR, Caplice N, Muhammed A, Berry CL, Thomas AC, et al. Dog peritoneal and pleural cavities as bioreactors to grow autologous vascular grafts. J Vasc Surg 2004;39:859-67.

8. Delaere P, Vranckx J, Verleden G, De Leyn P, Van Raemdonck D, Leuven Tracheal Transplant G. Tracheal allotransplantation after withdrawal of immunosuppressive therapy. N Engl J Med 2010;362:138-45.
9. Walles T, Giere B, Hofmann M, Schanz J, Hofmann F, Mertsching H, et al. Experimental generation of a tissue-engineered functional and vascularized trachea. J Thorac Cardiovasc Surg 2004;128:900-6.
10. Rose KG, Sesterhenn K, Wustrow F. Tracheal allotransplantation in man. Lancet 1979;1:433.
11. Klepetko W, Marta GM, Wisser W, Melis E, Kocher A, Seebacher G, et al. Heterotopic tracheal transplantation with omentum wrapping in the abdominal position preserves functional and structural integrity of a human tracheal allograft. J Thorac Cardiovasc Surg 2004;127:862-7.
12. Macchiarini P, Walles T, Biancosino C, Mertsching H. First human transplantation of a bioengineered airway tissue. J Thorac Cardiovasc Surg 2004;128:638-41.
13. Macchiarini P, Jungebluth P, Go T, Asnaghi MA, Rees LE, Cogan TA, et al. Clinical transplantation of a tissue-engineered airway. Lancet 2008;372:2023-30.
14. Elliott MJ, De Coppi P, Speggiorin S, Roebuck D, Butler CR, Samuel E, et al. Stem-cellbased, tissue engineered tracheal replacement in a child: a 2-year follow-up study. Lancet 2012;380:994-1000.
15. Macchiarini P. Outcomes of surgeries with biological tracheal scaffolds 2008-2011. Material inlämnat till utredningen.
16. Hung SH, Su CH, Lin SE, Tseng H. Preliminary experiences in trachea scaffold tissue engineering with segmental organ decellularization. Laryngoscope 2016 doi: 10.1002/lary.25932. [Epub ahead of print].
17. Wurtz A, Hysi I, Kipnis E, Copin MC. Recent Advances in Circumferential Tracheal Replacement and Transplantation. Am J Transplant 2016;16:1334-5.
18. Gonfiotti A, Jaus MO, Barale D, Baiguera S, Comin C, Lavorini F, et al. The first tissue-engineered airway transplantation: 5-year follow-up results. Lancet 2014;383:238 44.
19. Hamilton NJ, Kanani M, Roebuck DJ, Hewitt RJ, Cetto R, Culme-Seymour EJ, et al. Tissue- Engineered Tracheal Replacement in a Child: A 4-Year Follow-Up Study. Am J Transplant 2015;15:2750-7.
20. Delaere P, Van Raemdonck D. Tracheal replacement. J Thorac Dis 2016;8:S186-96.
21. Delaere PR, Vranckx JJ, Den Hondt M, Leuven Tracheal Transplant G. Tracheal allograft after withdrawal of immunosuppressive therapy. N Engl J Med 2014;370:1568-70.
22. Delaere PR, Vranckx JJ, Meulemans J, Vander Poorten V, Segers K, Van Raemdonck D, et al. Learning curve in tracheal allotransplantation. Am J Transplant

2012;12:2538 45.
23. Mejl från professor Pierre Delaere till utredningen 2016-06-14.
24. Chopra DP, Kern RC, Mathieu PA, Jacobs JR. Successful in vitro growth of human respiratory epithelium on a tracheal prosthesis. Laryngoscope 1992;102:528-31.
25. Nakamura T, Sato T, Araki M, Ichihara S, Nakada A, Yoshitani M, et al. In situ tissue engineering for tracheal reconstruction using a luminar remodeling type of artificial trachea. J Thorac Cardiovasc Surg 2009;138:811-9.
26. Nomoto Y, Suzuki T, Tada Y, Kobayashi K, Miyake M, Hazama A, et al. Tissue engineering for regeneration of the tracheal epithelium. Ann Otol Rhinol Laryngol 2006;115:501-6.
27. Yamashita M, Kanemaru S, Hirano S, Magrufov A, Tamaki H, Tamura Y, et al. Tracheal regeneration after partial resection: a tissue engineering approach. Laryngoscope 2007;117:497-502.
28. Grimmer JF, Gunnlaugsson CB, Alsberg E, Murphy HS, Kong HJ, Mooney DJ, et al. Tracheal reconstruction using tissue-engineered cartilage. Arch Otolaryngol Head Neck Surg 2004;130:1191-6.

29. Kojima K, Bonassar LJ, Roy AK, Vacanti CA, Cortiella J. Autologous tissue-engineered trachea with sheep nasal chondrocytes. J Thorac Cardiovasc Surg 2002;123:1177-84.
30. Sekine T, Nakamura T, Ueda H, Matsumoto K, Yamamoto Y, Takimoto Y, et al. Replacement of the tracheobronchial bifurcation by a newly developed Y-shaped artificial trachea. ASAIO J 1999;45:131-4.
31. Kannan RY, Salacinski HJ, Ghanavi JE, Narula A, Odlyha M, Peirovi H, et al. Silsesquioxane nanocomposites as tissue implants. Plast Reconstr Surg 2007;119:1653-62.
32. Seifalian AM, Salacinski HJ, Tiwari A, Edwards A, Bowald S, Hamilton G. In vivo biostability of a poly(carbonate-urea)urethane graft. Biomaterials 2003;24:2549-57.
33. Kannan RY, Salacinski HJ, Butler PE, Seifalian AM. Polyhedral oligomeric silsesquioxane nanocomposites: the next generation material for biomedical applications. Acc Chem Res 2005;38:879-84.
34. Gustafsson Y, Haag J, Jungebluth P, Lundin V, Lim ML, Baiguera S, et al. Viability and proliferation of rat MSCs on adhesion protein-modified PET and PU scaffolds. Biomaterials 2012;33:8094-103.
35. Jungebluth P, Haag JC, Lim ML, Lemon G, Sjoqvist S, Gustafsson Y, et al. Verification of cell viability in bioengineered tissues and organs before clinical transplantation. Biomaterials 2013;34:4057-67.
36. SVT Nyheter. Macchiarini fortsätter hävda sin oskuld. 2016-05-04. http://www.svt.se/nyheter/inrikes/macchiarini-fortsatter-havda-sin-oskuld .
37. PM Referenser och kommentarer till “Transcription of the Interview with Paolo Macchiarini (unbold text) in the Swedish News Program Aktuellt (bold text) on May 4, 2016.”.
38. Ajalloueian F, Lim ML, Lemon G, Haag JC, Gustafsson Y, Sjoqvist S, et al. Biomechanical and biocompatibility characteristics of electrospun polymeric tracheal scaffolds. Biomaterials 2014;35:5307-15.
39. Jungebluth P, Haag JC, Sjoqvist S, Gustafsson Y, Beltran Rodriguez A, Del Gaudio C, et al. Tracheal tissue engineering in rats. Nat Protoc 2014;9:2164-79.
40. Delaere PR, Van Raemdonck D. The trachea: the first tissue-engineered organ? J Thorac Cardiovasc Surg 2014;147:1128-32.
41. Cyranoski D. Investigations launched into artificial tracheas. Nature 2014;516:16-7.
42. Mejlsvar från Macchiarini till utredningen 2016-08-01.
43. Mejl från Macchiarini till verksamhetschefen på thoraxkliniken, Karolinska

Universitetssjukhuset. 2013-03-17.
44. European Commission CORDIS. TETRA. Autologous Stem Cell Seeded Tissue Engineered Trachea. http://cordis.europa.eu/project/rcn/198788_en.html .
45. Mejl från Monica Bergius, Roche, 2014-09-19 till anonym mottagare, Karolinska Institutet.
46. FASS. NeoRecormon.
http://www.fass.se/LIF/product?9&userType=0&nplId=19980402000045&docType=6
47. Bennett CL, Silver SM, Djulbegovic B, Samaras AT, Blau CA, Gleason KJ, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. JAMA 2008;299:914-24.
48. Bohlius J, Wilson J, Seidenfeld J, Piper M, Schwarzer G, Sandercock J, et al. Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. J Natl Cancer Inst 2006;98:708-14.
49. FASS. Neupogen.
http://www.fass.se/LIF/product?13&userType=0&nplId=19910315000023&docType=6
50. Mejl från Ali Ashraf 2014-09-10 och Gaston Friedmann 2014-09-25 (båda vid Bio-Techne) till anonym mottagare, Karolinska Institutet.

3. The recruitment of Macchiarini and his operations at the hospital

3.1 Strategic considerations

Of the written material we had available and of our interviews shows that the employment of Macchiarini at Karolinska Institutet and at the hospital in 2010 corresponded more need of a strategic nature.

Translational and clinical research. KI already had strong pre-clinical research in the field regenerative medicine. The bridge over the clinical applications was fragile and needed to be strengthened.

National Medical Care. National Medical Care Committee decides which sites should be the National Medical Care. Such care may take the maximum of two hospitals in the country. [1] In 2005, Karolinska University Hospital submitted an application to perform heart transplants National Medical Care, but the Board had decided to give the mandate to the University Hospital in Lund (later Skåne University) and Sahlgrenska University Hospital. Karolinska University Hospital received in February 2010, no to reapply for heart transplants. National Medical Care Board demanded among other things that one could do combined heart and lung transplant; lung surgery was not sufficiently developed at the hospital. Hospital was ordered by the National Board of Health to phase out its heart transplantation [2,3].

Many of KI and the council perceived to National Medical Care Board's decision was contrary to ambitions that the hospital would be leading the country in highly specialized care. Hälsooch Medical Care at the Stockholm County Council deposed because 60

million to support efforts to get more National Medical Care is located at Karolinska University Hospital. Within Stockholm County Council was formed in 2011, a steering committee for the National Medical Care. [4] An investment in advanced airway surgery would be well in line with these efforts.

High-profile operations in ENT. KI Department CLINTEC (Department of Clinical Science, Intervention and Technology) encompasses a range of clinical entities, including ear, nose and neck sick diseases (ENT). ENT unit at KI, as well as management of the ENT clinic at the hospital, strove to create a more high-profile business by establishing a clinical and translational center for luftstrupssjukdomar with strong international position.

Research policy trends. When Macchiarini recruited (and later) were strong research policy signals to recruit internationally prominent - "excellent" - researchers [5]. Moreover, there was the 2008 research bill five billion earmarked for investment in strategic research areas. Within the framework of this venture was awarded the KI 30 million per year for five years (2010-2014) for stem cell research, some of which was used to recruit Macchiarini. In it last year's public debate, including Nobel laureate Arvid Carlsson [6] and Professor Agnes Wold [7] highlighted the research policy initiatives as an underlying cause To Macchiarinifallet developed as it did.

3.2 Recruitment of Macchiarini

The initial contacts. The hiring process KI described in detail in Rock Heckschers investigation of KI's management Macchiarinifallet. KI tied the first contacts with Paolo Macchiarini, while the hospital came in slightly later in the hiring process. KI's principal was present at an EU symposium in Gothenburg, where Macchiarini was one of the invited speakers. Macchiarini followed up the contact which was established with an interest request by mail to the rector's scientific secretary. [8]

The first contact with the hospital appears to have been taken in December 2009, when the hospital RD & E director at the initiative of KI's headmaster invited to a meeting on Macchiarinirekryteringen. By e-mail correspondence shows that RD & E director was hesitant. He found that Macchiarini

gave a scattered and roving impressions with activities in many places at the same time. [9] Macchiarini also met in March 2010, operations manager at the Gastro Centre (then a possible clinical placement for Macchiarini). For the virtues Macchiarini was judged to have heard that he had a large international network. During the recruitment process, he launched the idea of a virtual European Airway Institute, led by him and with one of the nodes in Stockholm. This Centre of Excellence described in section 3.4. KI was contacted by a physician at the ENT clinic via email. It posed the question of the there was interest in hiring Macchiarini at the clinic and be referenced to Macchiarini performed the first transplant in the world that used a stem cell-based technology trachea from a deceased person.

Macchiarini understood at this time, generally as a rising international star. The article published in the Lancet in 2008, where he and his colleagues described the first transplant of stem cell prepared trachea from a deceased person, had attracted much attention. His international reputation is illustrated by him (after he was hired in Stockholm) on an American website was listed as one of the world's 20 most innovative living Surgeons [10]. Time Magazine placed 2012 Macchiarinis luftstrupstransplantationer on his top-10 list of current medical breakthrough [11].

Macchiarini is a thoracic surgeon. After a request from an Italian newspaper (Corriere della Sera) made subject representative in thoracic surgery a survey among key people in the hospital and KI. None of them knew Macchiarini. In June 2010, a letter was sent by 14 signatories to KI's recruitment committee. [12] Initiator was the head of CLINTEC. Most of the signatories came from the academic side but among the signatories was also the former operations chief and the incoming operations manager at the ENT clinic. Although Macchiarini was a thoracic surgeon was no thoracic surgeon among the signatories.

The letter motivated to why Macchiarini should be employed at KI and the hospital. The strategic importance of this recruitment was highlighted. Macchiarini was highlighted as a "world leader" and "the absolute leading researcher in regenerative airway transplant." According to the letter was expected to be up and running with a working business for regenerative airway transplants within three months after the Macchiarini employed at the hospital. They also foresaw that the regenerative research could spread to other nearby areas transplant, as a lung transplant. KI's recruitment committee felt it was not needed any peer review before they took the decision to hire Macchiarini part-time.

Of our interviews shows that the enthusiasm for hiring Macchiarini was clearly greater in KI than on the hospital side. The former hospital director said in our interview with him His strategy to develop the hospital did not include solicitations of solitary international "Stars". The hospital's Research & Education Director was thoughtful because of Macchiarinis split operations at many locations [9]. Long before the new operations manager was appointed at the ENT Clinic In September 2010, he was subjected to great pressure to accept Macchiarini could be employed as physician at the clinic. At the same time it should be said that both the outgoing to the incoming operations manager saw great development opportunities for the clinic in Macchiarinis clinical operations. Neither the outgoing or the incoming business manager undertook any job interview, something that Macchiarini verified in conversation with us. Macchiarini himself claims to have been surprised that it did not require a Certificate of Good Standing in Sweden, as he was used to from other countries.

References.

Macchiarini had collaborated with Martin Birchall, professor of ear, nose and throat diseases in Bristol and London, on the development of luftstrupstransplantationer. At a personal visit to Birchall in London 2010, the then operations manager at ENT Clinic and

one of his colleagues at the clinic credentials on Macchiarini; he was not employee in London but had an unpaid honorary position at the University College of London [13]. As Birchall told us he stressed Macchiarini's technical skill

as a surgeon. At the same time, he considered Macchiarini be a difficult person to work with, but it should be possible to handle him.

The head of the ENT clinic traveled in 2010, along with the head of CLINTEC and Head of Unit at KI's ENT unit, to Florence to investigate whether there was a basis for to establish a European Airway Centre as proposed Macchiarini presented. they state that they not reached by any negative signals about Macchiarini.

In 2010 visited Macchiarini Stockholm and established contact with a number of researchers in regenerative medicine and clinical colleagues at the hospital. He performed "guest surgery" at the ENT Clinic and gave the impression to be a technically dazzling surgeon. There was however torque Stockholm surgeons queried the Macchiarini had, for example for surgery orderly until an aortic arch from a deceased person; This preparation was needed, however, never used.

Investigation has been the Manager of the Centre for Allergy Research, professor at KI received a compilation of e-mail correspondence and comments. [14] In August 2010, was contacted he was president of the pulmonary researchers European organization (European Respiratory Society), an Italian. This expressed severe criticism including Macchiarinis research and his clinical review. KI professor gathered since information from three places where Macchiarini earlier worked: Florence, Barcelona (two referents) and Hanover. All agreed that Macchiarini was a technically dazzling surgeon. There was also strongly critical views on major cooperation difficulties, inability to accept common decisions and too wide and risky indication standings before surgery.

Addition, there were negative reviews his personal qualities. From Italian hold stressed that he did not care about ethical state. In Italy, his CV challenged by a review committee of the University of Florence in connection with he sought a chair (which he was not deemed to be qualified). [15] His employment in Italy and Spain had been completed on the employers' initiative.

Negative signals also came from Hannover, where he not been a university employee but operated private patients. There had been completed with the cooperation Macchiarini because of his inability to accept common decisions. This information was conveyed to the Head of Unit at KI's ENT unit that in turn compiled criticism in emails to the outgoing and the incoming head of operations at the hospital ENT clinic [14].

KI professor who collected information about Macchiarini, informed the a personal meeting the head of CLINTEC. He also informed that the National Institute's rector had "all information". We have not been able to find that one of the hospital side took their

own references on clinical Macchiarinis merit until very late in the recruitment process. It was far advanced when the new Clinic manager took the ENT clinic in September 2010. He contacted a clinical colleague Barcelona, who stressed that Macchiarini had an excellent resume and that he was an "outstanding Surgeon. " In other respects, the Spanish colleague's strong critical reviews. Macchiarini were judged to have a difficult personality and cooperation difficulties. He also took an patients other surgeons deemed inoperable, which resulted in high mortality. They were taken to private patients at very high costs for families. Macchiarini had quit as a surgeon in Barcelona.
His colleague concluded his assessment "... can not be recommended to any institution with a high such reputation as yours. "[16].

The Italian media also had other adverse information about Macchiarini appeared. In newspaper articles in August and September 2010 described his difficulty in getting an academic employment at the University Hospital Careggi because of criticism including the operations he conducted. The newspaper Corriere Fiorentino published a major review of his resume and found inaccurate information. Italy's leading newspaper Corriere della Sera, which previously written about Macchiarini, acclaimed in terms amazed that he would now be employed in Stockholm.

By e-mail correspondence shows that from KI side sought advice could balance the negative image Macchiarini that it received from Italy, Spain and Germany. It leaned heavily against the relatively favorable picture received from London, primarily from Martin Birchall, and they were afraid that the good cooperation with the University College of London Great Ormand Street Hospital would be jeopardized if it rejected Macchiarini. There was a notion that Macchiarinis personal shortcomings still could be handled - the

“may be possible to keep this man the bar, as they apparently did in London ". [14] At the same time appeared in email conversation up some hesitancy within KI. The head of the ENT unit said they have doubts about Macchiarini was manageable. In the correspondence referred to that awaited Rector's decision.

Together with representatives of KI took the business manager a supplementary reference President of the Tuscany region [17], in which he spoke of Macchiarini was the victim of contradictions Faculty of Medicine in Florence and a media campaign. Regions president stressed To Macchiarinis integrity, morality, professionalism and success never been questioned [18]. The statement did not address how Macchiarini worked in clinical work and it is unclear in what as far as regional president had knowledge of this.

This whole process took place within KI. In addition to the negative reference to the newly operations manager got in their contact with Barcelona colleague (see above), we have not been able to prove that from the hospital side has been actively involved in discussions on references from Italy, Spain, Germany and the UK.

The final phase of the recruitment.

On 7 September 2010 the hospital director an agreement with CI to create and fill a guest professor of clinical regenerative surgery united with the position as chief physician at the ENT clinic with Paolo Macchiarini holders [19]. The procedure for signing such an agreement is that the operations manager and division manager to have endorsed the proposal before the hospital director sign. We have no information that the hospital director would have been reached by some negative signals about when Macchiarini he signed the agreement with KI (or later in the hiring process). on 5 October signed KI's principal agreement and the appointment decisions for the professorship.

The formal appointment decision at the hospital was signed by the ENT clinic operations manager November 11 [20]. Macchiarinis appointment at both KI as the hospital was from 1 December 2010 and three years. On application by the head of got Macchiarini The National Board of a specific mandate for one year practice medicine in Sweden (the mandate subsequently extended on two occasions and came to apply to the entire period Macchiarini was employed at hospital; see also section 3.3).

Clinical placement.

Macchiarini is a thoracic surgeon. He was employed, however, at the ENT clinic but came to implement the three of the four luftstrupstransplantationerna and most of its other operations at the Department of Thoracic Surgery. As this may affect the responsibilities associated with luftstrupstransplantationerna we have an interest in the decisions regarding his clinical placement.

Of our interviews shows that employment in the thoracic clinic in Solna was not up to date – here KI had probably a big influence even if we have not been able to clarify the motives. The strategy to build a center for regenerative medicine included that the business would be located Huddinge, where much of the experimental operations were conducted, and where there would be opportunities for cooperation with Huddinge reputed transplant operations in other areas. Since Macchiarinis research focused on regenerative surgery respect as well as respiratory tract esophagus, discussed an initial placement of the medical service at either gastrointestinal or ENT clinic, both in Huddinge.

It is in our interviews revealed the perception that there was a "status difference" between Thoracic Surgery Solna and Huddinge ENT clinic. The recruitment of Macchiarini would partly motivated by efforts to strengthen the ENT clinic status and / or developing the surgical skills at the clinic. Previously, Professor Martin Birchall, London, helped by particularly sophisticated operations of the lower airways of the ENT clinic and now saw an opportunity to have this capacity "in-house". Several of those we interviewed felt that the CI was involved in the final decision on location at the ENT clinic.

3.3 Macchiarinis establishment at Karolinska Institutet and Hospital

Research. At the initiative of KI's headmaster met KI Vice Rector Macchiarini to investigate his knowledge of the regulatory framework for clinical research. Vice Rector found that Macchiarini had good understanding and knowledge. During the call, spoke Macchiarini on completed animal testing and he had regular contact with the MPA Director General - he felt that the MPA regulatory seemed sketchy (Director General seems to have referred to Macchiarini its people, our note). Moreover Macchiarini told me about their plans to implement a patient series of transplants with lungs from deceased, prepared with bio-engineering technology.

When Macchiarini came to KI, he took the initiative to create the Advanced Center for Translational Regenerative Medicine (ACTREM). At this center would be in the laboratory investigate the possibilities producing means based on natural and synthetic scaffolds. They worked multiple organs and tissues in the chest: trachea, lungs, esophagus, heart, chest wall and the diaphragm [21]. The intention was to ACTREM would be an umbrella organization for translational activities in regenerative medicine. We have not come across any examples of that ACTREM research reached clinical application in the hospital. If you search on the net is no Information about ACTREM, only the message on the KI website: "ACTREM Group has dissolved ".

From Macchiarinis laboratory came verbal information that assured that his techniques worked in experimental situations - epithelium was established and there were signs of newly formed blood vessels.

Clinical activity. From the ENT clinic site requesting a special appointment from The National Board for Macchiarini to practice as a doctor in Sweden. National Board made a systematic records in the UK and Italy (and got no hit) before announcing a mandate for one year. The mandate was renewed then after application of the ENT clinic, latest period 2013-12-01-2014-11-30 (ie, the year after the Macchiarinis employment at Hospital ceased). In our interview with staff from the National Board of Health said it did not have gotten any signals about problems around Macchiarini.

In connection with Macchiarini in late 2010 began his employment at the ENT Clinic appointed operations manager representative to be specific contact. The intention was to support Macchiarini to get into the Swedish health care but also to arrange practical matters. IN a weekly newsletter to employees announced the newly appointed operations manager of the former operations manager would "have overall responsibility for the establishment of Paolo's clinical activity" [22]. This came to include questions about the condition before luftstrupsoperationerna. The operations manager also gave two experienced consultant tasked to specifically support Macchiarini in the clinical work. In our interview, stressed business manager that he created with these activities a "life buoy" of support on Macchiarini.

Macchiarinis surgical operations came to mainly be located in the thorax clinic although throughout his time at the hospital was employed at the ENT clinic. Macchiarini have in

interview indicated that this had patient safety reasons: the ENT Clinic in Huddinge was not the about the resources (such as ECMO, "artificial lung") required for advanced airway surgery. That his business was split in two clinics meant that there was some discussion of economic compensation to the ENT clinic for his efforts at the Department of Thoracic Surgery. When the patient was transplanted 3 thoracic clinic without the operations manager at the ENT clinic had been informed and without the transplant decision was preceded by a multidisciplinary meeting arose more significant disagreements (see also section 5.3 and 11.2.5).

At the hospital formed a multi-disciplinary advice for airway surgery because they feared advanced luftstrupsoperationer could lead to demands on care organization around these patients. The former operations chief of ENT which was set to have an overall responsibility for the establishment of Macchiarinis clinical operations, were responsible. Gastro Clinic, where they are used to working multidisciplinary, also linked up. It nevertheless seems that if you are not expecting the transplants would become commonplace - it is unusual

Cancer in the windpipe without metastases where transplantation could be a possible treatment.

During Macchiarini's first year at the hospital, he created many research contacts at KI and hospital and he quickly gained a network of many enthusiasts. Of our interviews, however, appeared that there were also clinical colleagues found him to have a remarkably strong self-image relative to their clinical and research-related activities.

When Macchiarini employed was nekrotrakea (trachea from deceased) to primarily imagined - of those we interviewed could recall that synthetic trachea was speaking. Also Macchiarini have indicated to us that the idea of synthetic trachea did not appear until the patient 1 came to the hospital. After the three transplants were thoughts that begin with transplant of prepared nekrotrakea. Professor Birchall, London, was consulted. He felt that it was necessary very large resources for such activities and thoughts were written off.

Luftstrupstransplantationerna as Macchiarini performed at Karolinska University Hospital the focus of this investigation. But Macchiarini also had time to perform other types of intervention during her employment at the hospital. To find out exactly what he's done, the doctors decided boss along with the hospital director in the spring of 2016 that all operations would go through if it conducted treatments of patients where Macchiarini been involved. The analysis of the data as revealed by the inventory is still in progress and we have only received an initial oral statement from the hospital [23]. According to these preliminary data has only been Macchiarini involved in interventions performed on thoracic and ENT clinics. This concerns a total of 29 interventions, the number of patients is less because some patients have undergone multiple procedures. The hospital has an expert, a retired doctor from the Department of Thoracic Surgery at the hospital, to

make a clinical assess and classify patients into categories benefited, had the dubious benefit and no benefit of engagement. The assessor has, at the writing of this report, examined 14 patients, where three the patient 1, 2 and 3. The other eleven patients' outcomes have been categorized as follows:
- Three patients have benefited from the procedure (including a five-year girl)
- Five patients have had the dubious benefits of surgery
- Three patients had no benefit from surgery

All surgical procedures are mainly advanced cancer surgery. The three patients not has had any benefit from the interventions was very sick and special interventions. According to Chief physician, an external reviewer to investigate cases where patients have not had the benefit of treatment.

The remaining procedures have thus been performed in the ENT clinic, but we have the time of writing no more information. One of the operations performed Macchiarini which then came to lex Maria reported (see Section 4.2.1). Macchiarini was also involved to some non-surgical operations (see section 4.2.2)

Economical conditions. During the construction phase of Macchiarinis research and clinical operations, he received powerful support from the county council and the hospital. He received funds ALF-budget, special funds from the R & D budget, as well as part of the Health and Medical Services investment in National Medical Care at the Karolinska University Hospital. Macchiarini was also successful as seeking external funding. We take this brief these, as his clinical activity had repercussions on appropriations. Macchiarini and his group received two grants from the Swedish Research Council for preclinical research, 1.8 million for a project on biotechnological processes, heart and 10 million for farmed natural and artificial esophagus. Although the Swedish Research Council grants related preclinical research, the Council terminated the latter stop prematurely. The main reason for the decision was that it was felt that the transplants Macchiarini conducted moved on clinical research that is not ethical tested [24]. It had then paid out just under 7 million [25]. An EU funding was also completed ahead of schedule (see section 3.4).

Media information about Macchiarini had a grant from the Knut and Alice Wallenberg foundations seem be based on that foundation was thanked in any / some of the scientific articles Macchiarini published. The reason for this was that Macchiarinigruppen had hired a technology platform

supported by the foundation. Macchiarini searched three times a grant from the Wallenberg Foundation, however, without success. [26]

3.4 Establishment of an international network

When Macchiarini employee he had a very extensive international network. He had worked in France, Italy, Spain, Germany, Britain and the United States (sometimes in an unpaid position). According to the then operations manager at the ENT clinic got Macchiarini task to develop the international network; this included that he would operate abroad (He had part-time employment at KI and the hospital). Also from the KI side (CLINTEC-institution Head of Department and ENT unit manager) it was clear that Macchiarini would build an international Network with Stockholm as a node. According to them, it was included in both research and operations abroad in the service [27].

European Airway Institute. Early in the recruitment process launched Macchiarini idea of a Airway virtual European Institute of nodes in Stockholm, Florence and London. This Centre of Excellence would primarily work with the care of patients with difficult to treat respiratory diseases and with teaching and research [28]. Professor Martin Birchall of the University College of London has indicated to us that the initiative came from him but that Macchiarini on its own initiative took over and came to power there from Stockholm.

As part of the formation of the international network visited the operations manager and the former operations manager at the ENT Clinic of Florence along with Macchiarini in February 2011. Cooperation between Stockholm and Florence and the conditions for a European Airway Institute discussed. Since Macchiarini employed at KI and the hospital, he sought to extend the European Airway Institute to include more centers, including Moscow, Krasnodar and Houston. In that Macchiarini 2013 left the Karolinska University Hospital, the concept of a European Airway Institute have gone to the grave.

International videoconferencing.

As part of the construction of an international network Macchiarini took the initiative for international videoconferences. The first such conference was bilaterally with Florence and proceeded technically well. In February 2012, was organized a videoconference with wider participation. Macchiarini During the recent discussion has taken this video as income to you from the hospital and KI been informed of his activities in Russia and its participation in decisions on luftstrupstransplantation of patients in Krasnodar.

The video conference in February 2012, coordinated by Macchiarinis coordinator for laboratory operations at KI. The conference was attended physicians from five centers in four countries: Stockholm, Krasnodar, Moscow, Florence and Houston. We have received various images of the purpose of the video conference. According Macchiarini the purpose of discussing individual patient and decide to continue the procedure. Participants from Stockholm (Apart from Macchiarini) has given a different picture of the videoconference. They emphasize that the purpose the meeting was to examine whether it was possible to develop a platform for international virtual meetings for clinical knowledge exchange and by extension any scientific exchange [29]. They have indicated that they participated in their administrative functions (operations manager and former operations managerat the ENT Clinic and Department Head at the KI side) and that none of them could help as medical experts in the field luftstrupskirurgi. With the exception of

a brief journal entry none of them had been involved in the care of two patients at this time transplanted in Stockholm and none of them had scientific collaboration with Macchiarini.

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Stockholm Participants have stressed that they are not involved in any operational decisions and responsibility the decision is on the operating surgeon and the management of the foreign clinic where the patient surgery [29]. They claim to not have known Macchiarini's surgical operations in Russia at this time.

According to a summary (without author) from the Russian side discussed possible candidates for luftstrupstransplantation. Prior to the conference had material from seven patients compiled. From Karolinska University Hospital presented a patient, which proposed that a limited part the trachea was removed, thus no transplant. For three of the other patients there were suggestions that they would be transplanted with synthetic trachea. Two patients in Krasnodar came also later transplanted.

The three participants from Stockholm (in addition Macchiarini) thought it was obvious that video conference of linguistic, technical and other reasons, was not an optimum forum for knowledge transfer. Plans for regular videoconferences was closed down after this trial [29]. According Macchiarini cooled interest in the international clinical collaboration from ENT clinic's side when his surgical operations increasingly came to be located in the thorax clinic.

Macchiarinis cooperation with Krasnodar.

It has not been part of our task to examine Macchiarinis operations in Russia. We report here anyway the information we have received to take part. There are documents showing that Macchiarini had a connection to Krasnodar probably already in 2011. There is an undated project entitled "Investigating the molecular mechanisms Underlying and pathways of regenerative medicine approached to the tissue engineering and cell therapy of airways and lungs"[30]. The timetable shows that the project was supposed to begin in October 2011. It is in more places "our group" with references to articles where Macchiarini and his nearest man, a German-thoracic surgeon, is co-author. We therefore find it likely that this project was part of the grant application to the Russian government then granted.

There is also a supporting document from the university "The University's Objectives Associated With the establishment of the research laboratory and it's role in the achievement of These Objectives as well as Their compliance with the university's development strategy"[31]. Two people from Krasnodar, a laboratory doctor and a biomedical scientist, spent two weeks in Macchiarini's lab at KI in April 2012. According to reports from the visit so the aim was to learn to decellularizing agencies, to sow the synthetic casings with cells and to use the bioreactor [32,33]. They thus appears completely to have engaged in laboratory work and their reports Stay contains nothing

about the patient-related activities in Stockholm.

A 6-month follow-up of the two transplants performed at the Regional Clinical Hospital in Krasnodar was published as an abstract at the European Conference on General Thoracic Surgery in 2013 [34]. It described the two transplants as a result of a collaboration between Russian, Swedish and American researchers and surgeons and that all authors had funding from the Russian government. Macchiarini and his nearest man, the German thoracic surgeon, says that co-author of KI, together with five writers from the hospital in Krasnodar and a writer from Kuban State Medical University in Krasnodar.

On the Russian official website for the project "Regeneration of airways and lungs" says Macchiarini as "leading scientists" and KI stands as a participant in the project. The website is also video conference in February 2012, described as the first international video conference on regenerative medicine under the guidance of Paolo Macchiarini. The project had funding from the Russian Government (Grant of the Government of the Russian Federation for the state support of scientific researches, Which are Conducted under the guidance of leading scientists in Russian educational Institution of Higher Professional Education (No. 11.G34.31.0065 agreement dated October 19, 2011) [35]. According to our interviews, it was only in early 2012 that it started to become clear to Macchiarini's clinical employees in Stockholm he was also active in Krasnodar.

EU grants.

In 2012 received a European consortium (Biotrachea) with KI as a coordinator major research grants of nearly 4 million from the EU for the project Biomaterials for Tracheal Replacement in the Age-Related Cancer through a Humanly Engineered Airway. Macchiarini was the main applicant. In addition, KI participated 12 academic and commercial partners from Italy, Germany,

France and Britain. The goal was to experimentally develop synthetic trachea with the long term goal to initiate clinical trials. The project period was from 2012 to 2017. According to an EU statement, quoted by the Macchiarinikritiske blogger Leonid Schneider, pulled the EU prematurely withdrew his financial support and demanded a refund, because it was found that the project failed to establish an Ethics Committee to the [36]. It may be worth noting that the EU has recently given a major research grants with the aim of conduct a clinical trial of transplantation of synthetic trachea prepared with stem cells and with a different organizer [37], ie the same line of research as Macchiarini followed. In the years 2012-2015 participated Macchiarini and his research group at KI as one of five partners in an EU-funded research project (5.65 million euros) which aimed to develop a portable artificial lung (AmbuLung) [38]. The project, coordinated from Germany, submitted in 2015 a Final Report.

Referenser

1. Rikssjukvårdsnämnden.

http://www.socialstyrelsen.se/rikssjukvard/omrikssjukvard/rikssjukvardsnamnden
2. Socialstyrelsen. Ett halvårs övergångstid för att avveckla hjärttransplantationer. Nyhetsnotis 2010-07-01.
3. Socialstyrelsen. Rikssjukvårdsnämnden avslår ny ansökan om hjärttransplantationer. Nyhetsnotis 2010-06-08.
4. Karolinska Universitetssjukhuset. Manual för rikssjukvårdsarbete, odaterad PM.
5. Vetenskapsrådet. Grant for internationell recruitment of leading researchers. http://www.vr.se/inenglish/researchfunding/fundinggranted/grantsforinternationalrecruitmentofleadingresearchers.4.7e727b6e141e9ed702b2fda.html
6. Carlsson A, Eriksson E, Hellstrand K. Leijonborgs reformer banade väg för katastrofen. Dagens Nyheter, DN Debatt 2016-02-18 http://www.dn.se/debatt/leijonborgs-reformer-banade-vag-for-katastrofen/
7. Wold A. Förfallet på KI, Focus 2016-02-19, http://www.fokus.se/2016/02/forfallet-pa-ki/
8. Mejl från Paolo Macchiarini till rektors vetenskapliga sekreterare, KI. 2009-09-01.
9. Mejl från FoUU-direktör, Karolinska Universitetssjukhuset, till rektors vetenskapliga sekreterare, KI. 2009-12-09.
10. Simon S. 20 most innovative surgeons alive today. 2013. http://www.healthcare-administration-degree.net/20-most-innovative-surgeons-alive-today/
11. Park A. Top 10 medical breakthroughs. Lab-grown body parts. Time Magazine, 2012. http://healthland.time.com/2012/12/04/top-10-health-lists/slide/lab-grown-body-parts/
12. Förslag att rekrytera Paolo Macchiarini insänt till KI:s rekryteringskommitté. 2010-06-04.
13. Mejl överläkare ÖNH-klinken, Karolinska Universitetssjukhuset till utredningen. 2016-06-28.
14. Rapport om referenser på Macchiarini av föreståndaren för Centrum för allergiforskning, KI. 2016-04-26.
15. di Sergi Romagnani. Macchiarini, a letter by Romagnani. Letter sent to the Director of "Corriere Fiorentino", Paolo Ermini, by Sergio Romagnani, Professor Emeritus of the University of Florence on January 10, 2016.
16. Mejl från Dr Manuel Spretelsen, Barcelona till verksamhetschefen på ÖNH-kliniken, Karolinska Universitetssjukhuset. 2010-09-03.
17. Brev från prefekten för CLINTEC, chefen ÖNH-enheten, KI och verksamhetschef ÖNH-kliniken, Karolinska Universitetssjukhuset till Enrico Rossi, Presidente de Regione, Toscana 2010-09-12.
18. Rossi E. Brev till CLINTEC:s prefekt 2010-09-20.
19. Wallberg-Henriksson H, Jakobsson B. Överenskommelse om inrättande och tillsättning av anställning som gästprofessor i klinisk regenerativ kirurgi förenad med befattning som

överläkare vid Karolinska Universitetssjukhuset inom Stockholms läns landsting. Dnr KI 3234/10-236.
20. Anställningskontrakt för Paolo Macchiarini undertecknat av verksamhetschefen för ÖNH-kliniken, Karolinska Universitetssjukhuset. 2010-11-11.
21. CLINTEC. Jobbannons 2013. https://ki.mynetworkglobal.com/se/what:job/jobID:21152 .
22. Veckobrev från verksamhetschef till ÖNH-klinikens medarbetare. 2010-10-04.
23. Telefonsamtal med chefläkare på Karolinska Universitetssjukhuset ang inventering av Macchiarinis verksamhet. 2016.
24. Vetenskapsrådet. Beslut att avbryta utbetalning av forskningsbidrag; diarienummer 521-2012-5956. 2015.
25. Mejl från Vetenskaprådet ang utbetlaning av anslag 2016-07-06.
26. Knut och Alice Wallenbergs stiftelse. Angående uppgifter i media om Knut och Alice Wallenbergs Stiftelse och Macchiarinifallet, https://www.wallenberg.com/kaw/angaende-uppgifter-i-media-om-knut-och-alice-wallenbergs-stiftelse-och-macchiarini-fallet (odaterat).
27. Mejl från prefekten för CLINTEC och enhetschefen för ÖNH-enheten vid CLINTEC till KI:s rektor 2016-04-09.
28. Macchiarini P, Birchall MA. A proposal to establish a European Airway Institute. Memorandum, draft 1.1 October 2010.
29. Uttalande från verksamhetschef och fd verksamhetschef på ÖNH-kliniken samt enhetschefen på ÖNH-enheten, KI om den internationella videokonferensen i februari 2012. 2016-02-29

30. Projektplan. Investigating the molecular mechanisms and underlying pathways of regenerative medicine approached to the tissue-engineering and cell therapy of airways and lungs.
31. Dokument från Kuban State Medical University i Krasnodar. The university's objectives associated with the establishment of the research laboratory and it's role in the achievement of these objectives as well as their compliance with the university's development strategy. 2011.
32. Rapport från träning på KI 9–23 april 2012. Associate professor från Kuban State Medical University i Krasnodar. 2012.
33. Rapport från träning på KI 9–23 april 2012. Senior laboratory assistant från Kuban State Medical University i Krasnodar. 2012.
34. Polyakov I, Macchiarini P, Jungebluth P, Pashkova I, Gilevitch I, Kononenko V, et al. Artificial tracheo-laryngeal complex transplantation in patients with tracheal diseases: early results (a 6-month follow-up period). The Krasnodar (Russian Federation) experience. Abstract P-213, 21st European Conference on General Thoracic Surgery 2013.
35. Regeneration of airways and lung, The official website of the project "Investigating the molecular mechanisms and underlying pathways of regenerative medicine approaches the tissue-engineering and cell therapy of airways and lungs". Kuban State Medical University; 2016.
36. EU statement on Biotrachea termination, citerat i krönika av Leonid Schneider: Macchiarini, Birchall, Sefalian and EU-funded human experimentation. https://forbetterscience.wordpress.com/2016/03/27/macchiarini-birchall-seifalian-and-eu-funded-human-experimenting/
37. European Commission Horizon 2020 Programme CORDIS. Autologous Stem Cell Seeded Tissue Engineered Trachea. http://cordis.europa.eu/project/rcn/198788_en.html .
38. Ambulatory bio-artificial lung. http://cordis.europa.eu/project/rcn/104053_en.html .

Report Chapter 4

4. The three patients luftstrupstransplanterades Karolinska University Hospital

We begin this chapter with an overview of the clinical activity Paolo Macchiarini conducted at the Karolinska University Hospital. We also describe briefly how it came about when three patients received artificial trachea seeded with bone marrow cells, and economic aspects of transplantations. Other patients Macchiarini has treated have been highlighted in the media and other. The hospital has made an inventory of his work at the hospital and we finish this chapter with two examples of other patient who Macchiarini has been involved in.

4.1 Three patients have undergone luftstrupstransplantationer

We refer to the three patients who received artificial trachea patients 1, 2 and 3, in the order they has come to the hospital. For a brief description of the sequence of events for the three patients see Box 1-3. [**box 1-3 omitted**]

4.1.1 When the idea was born to use a synthetic trachea?

We have tried to understand how and when it began to consider inserting a synthetic trachea. Already in the submission dated 12 May 2011 from patient 1's Icelandic doctor used the word transplantation [1]:
"This patient has Already exhausted every medical treatment and his only hope of survival and Cure ice, affectionate that the tumor is only locally invasive and has no regional or systemic metastasis, The resection of the tumor with a safe reconstruction,

either via standard airway surgery or using a transplant."

In the interview with the Icelandic doctor, it appears that the word transplant added on the advice of Macchiarini. When the patient 1 is entered at the Karolinska University Hospital May 24, 2011 it can be read in the journal: "Pat has now been assessed by Paolo Macchiarini, tangle generating ... ..dent surgeon at the clinic, and he will now during this hospital stay assess the CT images and also PET CT images to be taken over hospitalization for 2-3 days and assess the possibility of radical surgery which is scheduled to evacuation of the tumor and transplant, a graft polymer coated the patient own stem cells. "

In interviews with the ENT doctor who made the admission note as well with Macchiarini clear that they accepted that the transplant was the only way out. One option would have been to insert called a stent in the trachea to keep the airway open but ENT doctor did not want threaten to cause a major bleeding that had occurred when the patient was operated on the Island (see below).

It examined the possibility to obtain a nekroluftstrupe but was told that it would could take up to six months. Macchiarini felt it was too long a wait and the patient could not risk dying in the meantime. According to a memo (not dated but seems to be written in retrospect) authored by Macchiarini he gave two reasons for that nekrotransplantation was excluded. Since he arrived in Sweden recently, he had not had time to put up a lab with the necessary equipment to effectively be able decellularizing (remove all immunogenic cells) a nekroluftstrupe. Such a lab, he had access to in Italy where it would also be easier to get into the trachea, but the Icelandic Social Insurance did not allow the patient treated where [2]. The only option left was to use asynthetic trachea.

Parallel to the patient underwent tests and that it held a multidisciplinary Conference (esophagus / ventrikelkonferens May 27, 2011, see Box 1), so ordered a synthetic trachea by a professor at University College London (UCL).

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Facts 1. Description of the process for patient first

Patient 1 was a 36-year-old man living in Iceland which in 2009 was diagnosed with low-grade mucoepidermoid cancer of the trachea without metastases. He was treated surgically and then radiation therapy. After operation he had also been treated for miliary (disseminated) tuberculosis. In February 2011, the problems reappearedwith cough and shortness of breath on exertion and a CT scan showed a 25-percent stenosis of the trachea. From Iceland contacted to a hospital in the United States for a second opinion - the answer was palliative care (palliative terminal care). The patient was referred then to the Karolinska University Hospital and Paolo Macchiarini for assessment and possible treatment [1]. The patient was only informed that it would be a short-term stay in Stockholm. The admission note from May 2011, however, it noted a planned major surgery evacuation of the tumor and transplant with a polymer coated the patient's own

stem cells.

The patient's general condition was rated as good, but he had some stridor (wheezing, wheezing breathing noise generated by narrowing of the upper airways). Two weeks before the planned transplant took two biopsies from the trachea (but not from the tumor itself because of bleeding risk) that were tumor free. Examination with CT and PET / CT showed a change at the site of the suspected tumor. However, it is not with these methods to safely distinguish a malignant from non-malignant changes, eg after radiotherapy.

On 27 May, to a multidisciplinary esophagus / ventrikelkonferens with doctors from the oncology, gastrointestinal, orthopedics, anesthesia, intensive care, thoracic and ENT present. It was decided that the patient would undergo surgery and that Macchiarini would collect the surgical team. Two days prior to surgery aspirated bone marrow cells from the patient and the cells used to seed the synthetic trachea in a so-called bioreactor. The transplant was performed at the ENT Clinic in Huddinge 9 June 2011. The trachea and parts of the right and left bronchus were removed and replaced with a synthetic trachea (POSS-PCU). Around the graft, the one part of the patient's mesentery in order to protect the graft and bring nutrients and oxygen. During the operation hit the subject a large, life-threatening bleeding.

Immediately prior to transplant sown the synthetic trachea once more with bone marrow cells and growth factors was added. After surgery, the patient received injections of growth factors for two weeks (see 4.1.4) The record is clear, however, that it occurred to you not given G-CSF because of excessively high levels of white blood cells.

Something remarkable figures Macchiarinis closest man in the lab, a German thoracic surgeon, several times in the journal. He was directly involved in the care of the patient, he was contacted to advise on drug treatment, and he stands as an operator 2 at two bronkoskopier. The German thoracic surgeon seems at times to have acted as a link between Macchiarini and patient. Reportedly from the Board, he is a licensed physician since 2016-03-18 and has no special appointment working clinically in Sweden.

Nine days after the transplant, the patient received a thrombus (clot) in the right pulmonary artery. On July 8, returned to the patient 1 Island. The Icelandic thoracic surgeon came to Stockholm to follow with him on the trip. Shortly before the patient returned to Iceland had been at a computer tomography examination detected an air leak in the graft adjacent to the left windpipe. After the transplant patient 1 returned several times to the Karolinska by about three to five months intervals bronkoskopier. The first visit took place in November 2011 in connection with of a planned bronchoscopy and removal of granulation tissue. On other visits were conducted bronkoskopier, granulation tissue was removed and stents were inserted or deleted. It was discovered fistula between the trachea and esophagus and the trachea and mediastinum (the space between the lungs).

Between return visits Karolinska patient was admitted for long periods in hospital in Iceland because of breathing problems and coughing up blood. His Icelandic medical

attention repeatedly that there were major difficulties in communication with Macchiarini and Karolinska University Hospital and the interest of the patient was weak from Stockholm's side.

Patient 1 gradually deteriorated. From October 2013 he was treated for palliative purposes in Gastro Center at Karolinska University Hospital. November 30, there was a clot formation in the right arm. In December 2013 made a minor surgical procedure since it was considered impossible to take esophagus removed without inadvertently release the graft. The esophagus also operated as a support for the graft. In an attempt to restore normal nutritional made to an intestinal surgery.

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CONTINUED on facts Box 1.

Patient 1 died January 30, 2014, 32 months after the transplant, because of refractory (Non-treatable), respiratory failure and clogged windpipe. He then weighed 57 kg. There were initially differing views on the need for an autopsy, but the issue was solved soon in agreement (see section 11.4.4). The autopsy showed that transplantet 90 percent had loosened and a severe inflammation and abscess formation in the chest. Examination of all biopsies taken from the graft showed no signs of airway epithelium is formed. Instead one saw dead tissue, inflammation, fungal and granulation tissue.

Facts 2. Description of the process for the Patient second

Patient 2 was a 30-year old man from the US who were diagnosed with primary low-grade adenoid cystic carcinoma (ACC) in the trachea in June 2009 after 2-3 months of dyspnea and stridor. No metastases diagnosed. They did a balloon angioplasty and placed a Y-stent in the trachea which normalized the patient's breathing. Chemotherapy and radiotherapy (63Gy) led to tumor regression. The patient was referred then to the ENT clinic at Karolinska University Hospital synthetic luftstrupstransplantation. At enrollment, it is in the record that the patient had no stridor and the general condition was good.

On 4 November, to a multidisciplinary conference of representatives of radiology, thoracic surgery, ENT, general surgery and gastroenterology. Macchiarini present. It was decided to perform a transplant in Solna with "graft stem cell supplements" and that Macchiarini with colleagues at Thoracic Surgery would be responsible for the continued planning.

The operation took place on 17 November 2011. Analysis of the removed part of the trachea and surrounding tissues show that the tumor is not removed radically, that is the tumor tissue were left in the patient. Nine days after the transplantation, the patient received pneumonia and the discovery of a suspected fistula in the trachea. After two weeks, the patient received a pulmonary embolism in lower left lobe and the formation of clots in the large veins in the neck, chest and armpit on the left page. After five weeks,

written patient out to the rehabilitation department but came back two weeks later because of cough and phlegm. Eight weeks after transplantation, the patient returned to the USA of oral antibiotic therapy. Examination of the two biopsies taken from the graft five days and eight weeks after transplantation showed no signs of airway epithelium had formed.

In March 2012, 16 weeks after the transplant, the patient died suddenly of unknown causes. There is no information on the cause of death in the Karolinska University Hospital's medical records.

Facts 3. Description of the process for the Patient third

The third patient is a 22 year old woman from Turkey. At a sweat surgery in July 2011 in Turkey damaged her windpipe. They tried unsuccessfully to repair the damage by sewing, resistant, and put a flap of chest muscle. After being assessed for a synthetic luftstrupstransplantation in March 2012, she checked in at the Karolinska University Hospital July 23, 2012. Her condition was assessed as being stable, but she suffered from recurrent cough. She was not assessed at any Journaled multidisciplinary conference. It should be noted that two Turkish professors in Thoracic Surgery has certified that they participated in a multidisciplinary meeting before operations [3]. We do not have been able to identify the exact circumstances of this meeting.

During an operation before transplantation (exploratory thoracotomy) arose an emergency and one is forced to remove the right lung. At a tube (endotracheal tube) was connected the upper airways with lungas left main bronchus. The patient then received ECMO ("artificial lung").

On August 7, 2102 was carried luftstrupstransplantationen during ECMO.

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CONTINUED on facts Box 3.

For patient 3, there does not have any established protocol before surgery in the same manner as for Patient 1 and 2. It is not clear however possible that Patient 3 received the same type of regenerative medicine treatment patient 1 and 2 (see 4.1.4).

ECMO treatment was completed four days after the transplant, but due to pneumonia and cardiac arrest began ECMO again. This treatment was continued for one month. During this period discovered fistula between the trachea and esophagus and the trachea and chest cavity.

In the spring of 2013 began to implant stents to collapse and was admitted along its entire length. From thoracic clinic's side took the initiative to transplantation with nekrotrakea, but Macchiarinigruppen found the nekrotrakea offered (from Gothenburg) inappropriate

and preferred synthetic trachea [4].

It had by then begun with experiments on rats with synthetic trachea and leaned against favorable short-term experiences of these [4]. Macchiarinis designated employee Jungebluth nekrotrakeainitiativet as "nothing else than a farce Initiated by the Thoracic Clinic" [5].

On July 9, 2013 performed to a retransplantation with synthetic trachea, nor before this time a Journaled multidisciplinary conference. Some time before the patient had again been put on ECMO. The seventh postoperative day, the patient developed a clot in the ECMO circuit, complicated of an acute arterial clot hiking to the right leg, which required emergency vascular surgery to save leg. Solid hemolysis (disintegration of red blood cells) leading to acute renal damage and renal failure patients received hemodialysis in seven weeks. The patient had a chronic renal impairment. fistulation between the windpipe and esophagus remained after omtransplantationen and forced it to therefore, removing the esophagus. To improve the chances of healing around the graft was removed second to 7th rib, nor decreased the leakage of air from the trachea.

According to the journal entries left Macchiarini case in September 2013. During the fall and winter 2014-2015 began to search for a transplant center for retransplantation, now with body from a deceased donor. In September 2015 August 3 patients out of the thoracic clinic after over three years of hospital stay and transported to Temple University Hospital, Philadelphia, USA. There, she underwent in May 2016 transplantation of the lung, trachea and esophagus from a deceased donor.

During the three years at the Karolinska University Hospital patient underwent nearly 200 surgical interventions, bronchoscopy every four hours around the clock and ECMO support on three occasions in a total of 72 days. Biopsies of the two transplanted synthetic luftstruparna have not shown any signs on normal epithelial cells.

4.1.2 Informal contacts led to the conclusion that it was not needed some states

Before the first transplant was a series of informal contacts with the authorities and various people. It took most of the contacts was the former operations manager at the ENT Clinic which was designated to have overall responsibility for the establishment of Macchiarinis clinical operations. We have been able to find that there were mainly four contacts, with the MPA, the scientific secretary of the regional board and the chief physician at Hospital who in turn contacted the Chairman of the Research Council's ethics committee. In several of these contacts the stories differ on what has been said.

The former operations manager contacted an official at the MPA by telephone and thought they where getting to the answer to whether it was vital indication as needed no permission. He considered themselves also have been told that the treatment was considered to be a non-medicinal products. after the phone call with the MPA he sent an email to Macchiarini May 12 where he wrote “I have been in contact with the medical product agency [ ] whos opinion in this case is that the sole responsibility lies within the

framework of the medical authorities (lege artis) in a case where the major indication is survival or not. This opinion was shared by [sekreterare regional etikprövningsnämnden, Stockholm] at the local ethical committee. However should research and clinical research be furthered into a proper clinical project applications to the ethical committee."

In our interview with the former operations manager at the ENT clinic, he told me that he had come concluded that it was a medical-ethical (and not research ethical) problems because the patient was outside the normal treatment. He also observed that MPA's role is unclear when in materials. The official at the MPA has a different view of what was said. He has told the investigation that in May 2011 he received a brief phone call from the former operations manager who told us about a planned engagement with an artificial graft and the patient's own stem cells would be used. It was a seriously ill patient and the officer of the MPA perceived that surgery was considered a vital indication and that surgery was imminent. He did not rule on whether it was medical, pharmaceutical, or if it was needed some states but said it must be investigated. He said it must be the hospital's decision on the where care or not, and that the MPA is the regulatory authority for health care. Information was given then specifically to Macchiarini during the period from November 2011 to April 2012 via email. In this correspondence referred to the existing legislation and the requirement for permit from the Medical Products Agency must always be sought for the use of an advanced therapy medicinal products in clinical trials or the so-called hospital exceptional product.

In March 2012, it is a meeting of the MPA where former operations chief and Macchiarinis lab manager described the process of the stem cell-treated synthetic luftstruparna. One month later held a telephone meeting where, among others Macchiarini and several officials at the MPA participated. During the meeting, explained the man from the MPA's clearly what it where applicable - to the artificial trachea was considered to be drugs and evaluation must take place in an orderly manner and with permission.

In the email quoted above refers to the former business manager that he had contact with the scientific secretary of the regional ethical review board in Stockholm. In the interview he told the inquiry that the scientific secretary in a telephone agreed that it was not research, but life-saving treatment in a multidisciplinary environment. When the former operations manager then wanted to get this confirmed in writing, he received the following response [7]:
"The assessment of what comes out of a research ethical perspective is determined by the principal for research ethics review under the law EPL, i.e. in this case of SCC if there is delegated to Hospital Director / COO. EPL also says that advance from the Ethics Committee can not be given. As we discussed the principal may also consider what is in the Health and sjukkvårdslagens §26 where it is clear that health care is responsible for following up their procedures and operations (Quality) and develop methods (research). In it you brought up in your conversation, you mentioned that this operation be referred to the vital indication; which is that it is perhaps more a medical ethical issue than a research ethics issue. I want to emphasize that this response is given by me as a private person, and that in the event that the matter comes up in the EPN I intend to announce the

disqualification".

The scientific secretary talks about how he remembers it all [7]:
"2011, I was called by the VC [] at the ENT at K told me that it would make an operation on an Icelandic patient. He was rather cryptic and it was hard to understand what he wanted. The is not unusual for researchers in touch and want answers on whether to submit an application. The standard response internally we have agreed within the ethics committee is that no advance notice can be given, without the need to apply if you want to know what the committee thinks. This is also how I remember our conversation."

Contact was also one of the then chief doctors for informal discussion. In the discussion came the chief doctor and former operations manager concludes that:
- The surgery was perceived move on compassionate use
- It was not seen as a radical new approach because Macchiarini previously transplanted nekroluftstrupar
- This was not an ethical problem with reference to the Helsinki Declaration's Article 37
- There were questions surrounding the use of stem cells.

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Head doctor contacted the Chairman of the Research Council's ethics committee. Contact was made by phone and emails. Head doctor asked how it would look on treatment when there was no research or proven experience. The Chairman referred to the guidelines developed by the International Society of Stem Cell Research "Guidelines for the Clinical Translation of Stem Cells" and where particular Recommendation 34. This e-mail exchange has, among other things in the media, in retrospect come to be regarded as the Chairman of the Research Council's ethics committee gave the "green light" for treatment. The chairman has written clarification where it reads that he only referred to the regulatory framework and the stem cell guidelines do not mean that to be freed from search Ethics states [8].

Following these contacts, announced the former operations manager May 27 Macchiarini what that emerged [9]:
"Re the ethical question we have now recieved an answer from [the Chairman of the Research Council Ethics Committee] below. Please read and Consider. I think it supports our original position. "

He has forwarded an email from chief physician describes his contact with the Chairman the Research Council's ethics committee and incorporated Recommendation 34 from the stem cell guidelines. The hospital director has in his interview with the investigation said that he thought that it had all conditions in place before the first transplant.

The Ethics Committee at the hospital were not involved before the operation; in the Council minutes are no note that discussed Macchiarinis business. The chief physician was asked was However, Chairman of the Ethics Council and there appears to have been unclear about his informal advice to Macchiarini (via the former operations manager at

the ENT clinic) might have been interpreted as hospital Ethical Council endorsed the transplants, which Macchiarini argued.

Both the former operations chief and Macchiarini has retrospectively described the sequence of events, the former operations manager in a notice dated November 30, 2014 [10] Macchiarini in a letter to the Lancet in January 2016 [11].

4.1.3 Protocol Transplantation

For patient 1 and 2 are treatment protocols established by Macchiarini [12,13]. The protocols contains a description of the synthetic trachea, preoperative investigations, aspiration and the preparation of bone marrow cells, incubation of the synthetic trachea with bone marrow cells in a bioreactor, transplant and post-operative treatment and monitoring. both protocols also includes an informed consent signed by patient 1 but not of Patient 2. The minutes should have been presented at multidisciplinary conferences decisions but we have not found them in the patient records.

4.1.4 Drug

The protocols for patient 1 and 2 are information about which drugs would be used timulating the regenerative process. The purpose was to stimulate the regeneration of the airway epithelium the synthetic trachea. The active substances of medicaments, colony stimulating factor (G-CSF product names Neupogen Novum) and erythropoietin (EPO; product names NeoRecormin).

According to the protocols, the treatment begins one (patient 1) and two (for Patient 2) days prior to the transplant but according to the records began drug treatment Patient 2 on the day of surgery. The treatment would then continue every other day two weeks after the operation. According to the records got one patient these drugs every day for a fortnight and two patient every other day for twelve days after surgery. Patient 1 also received an additional injection of both drugs on the afternoon of the fourteenth day. The doses of G-CSF is also not consistent between protocols and journal. according to the Protocol be 10 mcg / kg administered as the patient 1 would correspond to approximately 0.8 mg (patients weighing 178 kg the day before surgery), but in the Journal shows that he has received 0.3 mg equivalent just below 4 mg / kg). EPO dose is 40 000 IU in both protocol and medical records.

We have not been able to find any protocols for patient 3. It does not appear from somewhere in

her records that she received a similar drug treatment. However, we have received documents directly from Macchiarini, including a treatment regimen similar to that of patients 1 and 2. For dates judge may refer omtransplantationen patient 3, but it is not

specified anywhere in the document, nor who prescribed the drugs. [14]

4.1.5 Three different materials in luftstruparna
Manufacturers and materials in the synthetic luftstruparna have varied. The first trachea produced at University College London by a graduate student in Martin Birchall's group (Martin Birchall's research is described in Chapter 2). Birchall and Macchiarini, who previously collaborated, was at this time is no longer on good terms with each other. In our interview with Birchall made his doctoral trachea and sent it to Macchiarini without Birchall knew about the. The material was POSS-PCU (polyhedral oligomeric silsesquioxane [POSS] covalently bound to polycarbonate urethane urea [PCU]). The material had previously been used for artificial arteries.

It must also have been pre-clinical evaluation of the material, including biokompabilitetsstudier and toxicological studies. In our interview with Macchiarini he went to London to oversee production. The first copies were produced that were too soft. It took up at least three copies before the final which was then used for transplantation. during the operation, Patient 1, Macchiarini according to one of medoperatörerna have found that the material was too rigid.

Patient 2 received a trachea which was made by an American company, NanoFiber Solutions ™ in Ohio in the United States. The material was PET / PU (polyethylene terephthalate [PET] and polyurethane [PU]).

Patient 3 underwent two transplants since the first synthetic trachea collapsed. The material and the manufacturer of the first trachea was the same as for patient 2. In a memo described the first transplanted trachea completely lost their mechanical properties but the anchorage surrounding structures and stents not made windpipe still held open [5]. During the time between the first and second transplantation was concluded it would be best to develop a trachea consisting of 100 percent PET and such was developed Harvard Apparatus Regenerative Technology, Holliston, Massachusetts, USA.

According Macchiarini, all materials used in the synthetic luftstruparna approved by the Food and Drug Administration (FDA).

4.1.6 The bioreactor and connections to the HART

The protocols for patient 1 and 2 and in scientific articles describes how the synthetic trachea incubated with bone marrow cells and growth factors in a so-called bioreactor [12,13,15,16]. Product name of the bioreactor is InBreath 3D Organ Bioreactor. Biorektorn was originally developed for the incubation of nekroluftstrupar [16]. It is designed so that it can fit in a cell incubator and consists of a chamber, a motor and a remote control.

The idea is that the trachea to be clothed with the respiratory epithelium externally and internally by slow rotation sterile environment and physiological conditions for 48 hours

or longer (time varies the different protocols).

The manufacturer of the bioreactor is Harvard Apparatus Regenerative Technology (HART), Holliston, Massachusetts, USA (the company is now called Bio Tage). The company used the transplants Patient 1 and 2 in their marketing. In a press release one month after transplant Patient 1 wrote to [17]:
"For first time in history, a patient has been given a new trachea made from a synthetic scaffold seeded with his own stem cells in Harvard Bioscience's bioreactor. The patient, a 36-year old man who had been suffering from late stage tracheal cancer, that before this surgery would have been inoperable, is well on the way to a full recovery and will be discharged from the hospital tomorrow. The operation was performed on June 9, 2011 at the Karolinska University Hospital in Huddinge, Stockholm, by Professor Paolo Macchiarini of Karolinska University Hospital and Karolinska

Institutet, and colleagues.

[…]D avid Green, President of Harvard Bioscience, commented, ”We congratulate Professor Macchiarini and the entire scientific and surgical team on achieving this landmark in the history of regenerative medicine. This new type of surgery is likely to greatly expand the patient population that is treatable with organs grown in Harvard Bioscience’s bioreactor. Previously, our bioreactor had been used to seed a patient’s stem cells onto a donor trachea, so treatment was limited by the supply of donor organs. Now that our bioreactor has proven it can be used to seed a patient’s cells onto a synthetic (i.e., manmade) scaffold, patients will not need to wait for a suitable donor trachea to become available.”

It has attracted attention in the media that people from the company participated in the operations. The then CEO of HART says in an interview that staff from the HART attended all operations and it is filmed, for example, that he himself participated in the transplant patient 2 [18,19]. We have not been able to find any permission for this from any of the patients, something normally required when a third party is present at a surgery.

Something else that attracted attention is the possible linkages Paolo Macchiarini has company. He has been involved in a patent but by his own admission has sold its stake and donated money to charity. 2013 HART started a subsidiary in Sweden with headquarters in Stockholm county. According to business description should now including conducting research and development and clinical and regulatory and activities related to the development and commercialization of regenerative medicine. There are also reports that the Swedish subsidiary to have paid wages for staff working in Macchiarinis lab at Karolinska Institutet. No agreement with KI or the hospital has not been detected [20].

4.1.7 Analysis of tissue samples

All tissue samples from the three patients undergo an independent quality assurance calculated to be completed in autumn, 2016.

Patient 1. Prior to the transplant, samples were taken from the trachea above the visible tumor; the was no evidence of cancer spread upward in luftstrupsväggen. The referral to the pathologist in connection with transplantation tumor size was stated to be 2,5x1,1x0,9 cm and curving into the trachea. The microscopic study conducted in surgery showed no evidence of tumor growth outside the trachea removed. At the recent supplementary microscopic examination could not guarantee that there was no tumor spread.

The tumor was judged by Brandwein class II, an intermediate stage between lågaggressiv (Grade I) and högaggressiv (grade II) cancer. Two months after the transplant sent one of Macchiarinis medoperatörer three preparations to analysis. They represented different parts of the synthetic windpipe grown with the body's own cells (According to the referral stem cells, probably taken from patient 1) without being transplanted. You saw no sign of well-developed cell layer.

Samples taken from the inside of the graft at skopiundersökning two months after the transplant showed mainly necrotic (dead) tissue and the growth of fungi and bacteria. There was Also granulation tissue (newly formed scar tissue) with the ingrowth of capillaries. None of the samples taken at later follow-up skopiundersökningar showed convincingly signs of growth of airway epithelium in samples taken from the graft. By contrast, the inflamed granulation tissue in the adjoining areas of the bronchi, sometimes with ulceration. The was no evidence of remaining cancer.

When the autopsy was the synthetic windpipe almost completely loose in the chest; upwards towards the larynx had come loose connection to 90 percent and down to bronchi were no connections at all. The graft was surrounded by purulent fluid and dead tissue. There were pronounced connective tissue transformations in the right lung and the thoracic wall and a fistula between the esophagus and one of
bronchi.

Patient 2. During the operation was microscopic examination of the removed trachea, which showed that not all the cancer tissue in the two main bronchi (airways) could be removed. More detailed examination confirmed the earlier diagnosis adenocystisk cancer. It was judged that the patient has undergone radiation treatment in the home country had reduced tumor size by 90 percent. There was no sign of spread of the cancer to the lymph nodes. In the samples taken from the inside of the graft skopiundersökningar during the first two months after the transplant was seen on at least one occasion squamous epithelium (which is not normal airway epithelium). A sample taken from the boundary zone between the transplant and the patient's own windpipe showed "occasional bronchial

epithelial cells of ordinary appearance".

Patient 3. At transplants exploratory surgery in patient 3 was removed right lung. When the removed lung was examined for signs of inflammation in the airways and a Some connective tissue formations but no widespread lung disease. At follow-up skopiundersökningar after transplantation tissue samples were taken partly from the inside of the synthetic trachea and from the surrounding parts of the airways. When the referral specified to tissue pieces were taken from the graft was found mostly granulation (Newly formed scar tissue), which was sometimes inflamed. In the granulation tissue was seen ingrowth capillaries.

Moreover, there was necrotic (dead) tissue. Early after the second transplant (July 2013) was seen at one point "fragments of respirationsepitel". Overall microscopic examinations confirmed cancer diagnoses among the two first patients. There was no consistent evidence-growth of normal airway epithelial cells in the inside of the grafts (subject to it in the research labs were more advanced surveys). In the areas where the grafts are joined to the patient's own respiratory system there were plenty of vessels powered granulation tissue, often inflamed.

4.1.8 Economy

Stockholm Care AB is a public limited company county council providing care for foreign patients. The company has handled the economic of the three patients transplanted at the Karolinska University Hospital. For the care of one patient, the hospital billed Stockholm Care approximately 1.4 million and Stockholm Care, in turn, invoiced Islands Health Insurance (Sjukratryggingar Islands) just under 1.6 million crowns [21]. The Icelandic health insurance have a specialist team to handle all requests for essential care abroad. Group will consider if the following requirements are met; if treatment is necessary, there are treatment option in the country (Iceland), if the treatment is evidence-based, and if given the a recognized institution (it prefers teaching hospitals). Another requirement is that the treatment must be approved by the Icelandic health insurance before treatment begins.

Iceland Health Insurance approved the Patient 1 had to go to the Karolinska University Hospital investigation, palliative or curative laser removal of the tumor. Then it was discovered that it planned a transplant, contacted Iceland's health insurance Stockholm Care and former hospital director (who is from Iceland). An agreement was established between Iceland Health Insurance and hospital director who said that Iceland would only pay for the portion of the treatment which was based on evidence that the hospital among other things, would account for costs associated with possible side effects.

In our interview with a representative of the Icelandic insurance, it appears that it has been difficult to
draw a clear line between the evidence-based and the non-evidence-based care of patients first Most likely it has paid more than the contract specified.

The total cost for patient 2 amounted to just over 1.2 million. Stockholm Care invoiced approximately 1.4 million but over half a million are still not paid. In this case, it was a private person who would bear the costs of health care. Since Stockholm Care was a faxed check when asked for a payment guarantee, they turned to the hospital then development and innovation director, who also had responsibility for overseas care. After this goes stories apart in the interviews we have done with the former Development and Innovation Director

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in the hospital, Director and Head of CLINTEC, KI and principal at KI. But it actually happened was that the unit manager and department head at KI issued a payment guarantee based on funds a KI / SCC grants. After two years of trying to collect a bill of over half a million crowns Stockholm Care chose instead to adjust the invoice to the CI with reference to the issued payment guarantee from CLINTEC. The invoice is disputed by CLINTEC that claim to payment guarantee not valid for the type of complications that cost concerns [21].

Patient 3 spent 30 months in hospital and the costs amounted in March 2016 to almost SEK 85 million [21]. The Turkish government has been responsible for all costs.

4.2 Other patients

An inventory at the Karolinska shows that Macchiarini been involved in a total of 29 interventions in the hospital (See section 3.3). In our interview with Macchiarini he says: "Everyone talks about the pat 1, 2 and 3. But we did a lot of other things too, and saved a lot of lives that includes stem cells. "Exactly what He says we have not managed to get out. Two patient, in addition to the patient 1, 2 and 3, have received special attention and we have therefore chosen to briefly outline them here.

4.2.1 Lex Maria case

One of the patients who have been treated Macchiarini at Karolinska University Hospital made a lex Maria notification. The patient was in 2010 enrolled at the ENT Clinic in Huddinge severe sleep apnea with slemhinneöverskott. He was operated on several times in order to remove slemhinneöverskottet. At one intervention, he received a tracheal cannula inserted that he wanted get rid of. The patient also had a benpåbyggnad in the cervical spine and a narrowing of the lower part of the trachea. 2011 had a larynxkonferens and concluded that in an intervention could solve all problems and that Macchiarini was the one who could do this. The procedure was at the ENT Clinic in Huddinge in April 2011. Since it had operations in Huddinge weekends so transported the patient to Solna over the weekend. It turned out that there is any surgery story. According to the interviews we have done with two ENT doctors at the hospital as requested by the Macchiarini but could not reach, and there was great uncertainty about how to would handle the patient. When the patient was back in Huddinge, he received a breathing stop on ward. He went into cardiac arrest with anoxic brain damage as a result. They had great

trouble intubate because you did not recognize the anatomy. Operation report must then still do not have existed.

Lex Maria notification of the patient and a close June 20 and July 4, 2011 against Macchiarini and an ENT doctor. National Board (which was the regulator 2012) decision is dated 30 June 2012. The caregiver had the opportunity to comment and stated four identified causes to the event:
- There was no written information to patients. There were no procedures to check or documenting what information patients and families receive, and if they understood given information.
- Deficiencies in documentation procedures have been identified and the absence of specific procedures for non-Swedish speaking doctors to document in the patient record.
- Lack of procedures for the establishment of an emergency plan to breathing difficulties in patients completed advanced upper airway surgery.
- Lack of communication between the Karolinska University Hospital in Huddinge and Solna operating respiratory patients.

As implemented measures specified by the care provider may be mentioned that an individual emergency plan should patients being completed advanced airway surgery, the patients should obtain the written and specific information and it must be clearly stated in the records that the patient received and that the patient understood the information given and that for foreign doctors recruited on a consultancy like conditions should be a clear procedure for how the documentation should be in the patient record.

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The National Board assessment they lifted up the information to the patient is not documented in the journal, but it's a deficiency that does not cause criticism. They also raised it in direct connection to a journal entry in English (surgery was the story in English in this case) will be one of Swedish. National Board found no reason to criticize Macchiarini or ENT physician [22].

4.2.3 Notification of research misconduct on ECMO-treated patient

In discussions on Macchiarinis operations at the hospital have also been questions about non-surgical efforts come up. We therefore take this up a notification of research misconduct concerning the right one Non-surgical intervention and which has some parallels to the transplantation business.

In May 2016 submitted to the National Institute's rector notification (with the anonymous sender) on research misconduct. There was an article published in 2015 in the international journal Respiration [23]. The article had 26 writers and started from 13 departments and clinics, most of them at the Karolinska Institutet and Karolinska University Hospital. First Author were employees Macchiarini’s Jungebluth and last authors Macchiarini.

The article was a case report of a patient treated with ECMO (artificial lung) because of the severe acute respiratory difficulties. Via trachea was supplied enriched mononuclear cells (probably with a high content of stem cells), and the growth-enhancing drug erythropoietin, a treatment that has not previously been tested for this condition. The authors reported improved lung function and improved laboratory variables but the patient died after more than five weeks due to multiple organ failure.

The request was for both academic and clinical issues. For the clinical belonged among other inaccuracies when informed consent was collected, improper use of erythropoietin, doubts regarding the medical safety of the mononuclear cells used, the absence of notification of death to authorities and companies.

The notifier also asked if other patients in the hospital similarly treated. Of record of the case shows that at least one, possibly two, additional patients treated using the same experimental method [24,25].

Seven of the co-authors have signed a letter of reply to the KI principal [26]. They stressed the the answer that it was an appropriate description of the conditions in that case. they relied Helsinki Declaration's Article 37 on the use of untested methods of care, they presented the scientific basis that they had reason to believe that the method would work and they rejected the accusation that they had interpreted their results.

In its application to the Rector wished the notifier that the Central Ethical Review Board (CEPN) would review the case. At the end of July 2016 had not received notification CEPN.

References

1. Remiss patient 1 från isländsk thoraxkirurg, Landspítali, Reykjavik till Paolo Macchiarini, Karolinska Universitetssjukhuset. 2011-05-12.
2. Anteckning om patient 1 från Macchiarini. Odaterad.
3. Intyg från professor Cengiz Gebitekin, Bursa och professor Adnan Sayar, Istanbul till professor Niels Lynöe, ordförande i KI:s etiska råd 2015-01-27.
4. PM från Macchiarinigruppen (författare inte angiven) med beteckningen ”cy-clinical decision”.
5. Minnesanteckning från Philipp Jungebluth angående patient 3. Odaterad.
6. Mejl från fd verksamhetschefen på ÖNH-kliniken, Karolinska Universitetssjukhuset till Macchiarini. 2011-05-12.
7. Mejlväxling mellan fd verksamhetschefen på ÖNH-kliniken, Karolinska Universitetssjukhuset
och vetenskaplig sekreterare etikprövningsnämnden Stockholm. 2011-05-26.
8. Klargörande fd ordföranden Vetenskapsrådets etikkommitté. Odaterad.
9. Mejl från fd verksamhetschefen ÖNH-kliniken, Karolinska Universitetssjukhuset till Macchiarini. 2011-05-27.

10. Tjänsteanteckning av förre verksamhetschefen ÖNH-kliniken, Karolinska Universitetssjukhuset, angående tillstånd före första transplantationen. 2014-11-30.
11. Macchiarini P. Tracheobronchial transplantation. Lancet;387:339. 2016.

12. Transplantationsprotokoll patient 1. Macchiarinigruppen. Odaterad.
13. Transplantationsprotokoll patient 2. Macchiarinigruppen. Odaterad.
14. Patient 3 blood sample. Dokument från Macchiarinigrupen. 2013.
15. Jungebluth P, Alici E, Baiguera S, Le Blanc K, Blomberg P, Bozoky B, et al. Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study. Lancet 2011;378:1997-2004.
16. Macchiarini P, Jungebluth P, Go T, Asnaghi MA, Rees LE, Cogan TA, et al. Clinical transplantation of a tissue-engineered airway. Lancet 2008;372:2023-30.
17. Pressmeddelande från Harvard Bioscience i samband med transplantationen av patient 1.
2011.
18. Film från transplantation av patient 2. https://vimeo.com/32527358 (nedladdad 2016-07-09, password stockhom 11). 2011.
19. Intervju med David Green. https://www.youtube.com/watch?v=EzCdH-zUh7c (nedladdad 2016-07-09). 2013.
20. Mejlväxling med registrator Karolinska Universitetssjukhuset och KI ang avtal med HART. 2016-07-04.
21. Sammanställning av kostnader för patient 1, 2 och 3 från Stockholm Care AB. 2016.
22. Beslut från Socialstyrelsen i ärende anmält enligt lex Maria. 2012-06-30. Dnr 9.2-22158/2011-18. Socialstyrelsen.
23. Jungebluth P, et al. Autologous peripheral blood mononuclear cells as treatment in refractory acute respiratory distress syndrome. Respirarion 2015;80:481-92.
24. Haag J, Baiguera S, Jungebluth P, Barale D, Del Gaudio C, Castiglione F, et al. Biomechanical and angiogenic properties of tissue-engineered rat trachea using genipin cross-linked decellularized tissue. Biomaterials 2012;33:780-9.
25. Future of Organ Development: Alexander Seifalian at TEDMEDLive Imperial College 2013. YouTube-presentation.
https://www.youtube.com/watch?v=DR4D24bDPaQ .
26. Haag J, Heldring N, Hermanson, Holzgraefe B, Jungebluth P, Kalzén H, et al. Answers to case KI 2-1764/2016; Investigation of potential scientific misconduct.

Report Chapter 5

5. The closure of Macchiarinis clinical operations

The settlement of Macchiarinis activity was a gradual process mainly in 2013 with many involved. There were formal and informal decision on ENT and thoracic clinics and in hospital management that he could no longer perform transplants, that he could not take care of the patients he had operated and finally that he could not operate at all. The whole is led to the His appointment as chief was not renewed when it expired in November-December 2013. In this section, we explain what happened on the way to the appointment expired.

5.1 Early signals

During the entire period of employment at the Karolinska University Hospital had Macchiarini support from ENT clinic, but also far from the thoracic clinic. This is illustrated for example in an email to Macchiarini by the head of 30 September 2012.

Macchiarini was under house arrest in Italy and operations manager wanted to show their support [1]:
"Dear Paolo!
Should you need any testimony of you always being on the side of the patient consistently fighting to reduce costs, and of you never trying to get staff any favors out of extremly hard work and dedication, do not hesitate to contact me.
Hang in there!
Hope to see you soon in Stockholm.
[Director of Thoracic Surgery] "

A signal that all was not right came in the summer of 2011. In connection with a course professor of gastroenterology at KI arranged in Florence for the United European Gastroenterology Federation (UEGF) asked his colleagues from Florence on Macchiarini. Dean Medical Faculty in Florence and two other colleagues gave independently a particularly negative image of Macchiarinis personality, where his inability to distinguish between true and false and his difficulty to adhere to regulations highlighted. According to the Italian colleagues were it also suspicions of misconduct in research and suspicion of financial irregularities.

These negative signals conveyed to CLINTEC-head of department but they seem not to have reached responsible for hospitals. The head of the ENT clinic had at one time request from a US clinic where Macchiarini possibly would start, but operations manager clinic discouraged from hiring him because of cooperation problems. Since he left as Director in April 2012 so it is considered as an early signal that he already noticed that it did not work as it should.

Late in 2012 or early in 2013 had the former hospital director and Guidance and Innovation Director a meeting with the hospital director in Barcelona. The meeting addressed another but also came in on the topic Macchiarini. "We hired him not" to be the Spanish Directors have said.

5.2 Operation Prohibition on the thorax clinic in the spring of 2013

We have in our interviews received information from several people that the Department of Thoracic Surgery was issued an operating ban in the spring of 2013. Operations manager himself states that he in spring 2013 Macchiarini decided to not do any more operations on the chest, but he was allowed to continue to care for the patient 3. Then the situation with poor continuity of care become unsustainable sometime during the summer or fall, and then decided to head operations

Macchiarini could not take care of the patient further. We have not been able to find that some of these decisions are documented. However, there are references to operating ban on the thorax in an email as operations manager at the ENT Clinic sent to the hospital director April 11, 2013 [2]:

"I was at our discussion on Monday about the PM's [Paolo Macchiarini's] operating on Karolinska little unprepared for the question and I would like to see the picture mother was out an ENT perspective. We have full respect for the position taken in Thorax. The transplants has been very complicated business, and we can agree to put a moratorium the more reasons clearly by the [operations manager at the Department of Thoracic Surgery]. "
[...]

In view of the above, we think that the "prohibition to operate" to be moderated to a "Prohibition to operate without any interference reached in the multi-disciplinary group". Two days before the mail was sent to the hospital director was an email exchange that included operations manager, department head at CLINTEC and Head of Unit at KI's ENT unit and the former operations manager at the ENT clinic. [3] The former operations manager wrote to sitting of operations:
"I think you should inform div ch [division manager] about how we reason on PM [Paolo Macchiarini]. He goes because he can not operate on K, we lose a clinical skills, a lab, two services (ST research o Postdoctoral Research), an adjunct professor, and the opportunity to be with the cell therapy field. "

Head of Unit pointed out in his email to the operations manager in and said that not Thoracic Surgery had stood by the agreed regarding multidisciplinary conferences and surgery Patient 3. He wrote:
"I think you should immediately contact both [division manager] and [hospital director] again and explain how the country is and why Thoracic ended up in the situation where they are. "

About a month later, on May 6, 2013 sent Macchiarinis Unit at Karolinska an email to operations manager of ENT in the same case [4]:
"On Wednesday, PM will meet with the Rector to discuss the forth time at KI. It looks bright, but they storm clouds we've seen in KS sky looks to be. No meeting with [hospital director] have not nor come to pass, and there seem to be many who act in question while we are standing on the sideline. My suggestion is that we put a little pressure on the [hospital director] with a letter while we correct out some questions and make an effort to correct the incorrect part of history which is becoming hardening in the line KS. Attached is a draft that letter I hope you can subscribe to!"

In the attached letter said among other things that the rumor spread around the patient 3 began to be troublesome for ENT Clinic and the multidisciplinary system that had been created had completely ignored in the decisions made about patient 3. The letter was signed, with operations manager name and concluded:
"When we from the ENT clinic has a desire to cooperate with KI continue the development of regenerative airway surgery, I would like to have a meeting with you regarding how this may occur in the future. I also believe it would be of great value in connection with a Such meetings have representatives of KI present. "

Head of Unit then reported to the prefect May 8, 2013 the business manager had talked the hospital director and Macchiarini talked to the principal [5].

We do not know if the letter is then sent by the operations manager at the ENT clinic. It has for many of our interviews, talk of a KI pressures of Macchiarini and his work at the hospital. These e-mail changes may be part of that pressure.

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5.3 Accident Investigation proposed

Several people have claimed that they called an accident investigation. For example Macchiarinis immediate supervisor at KI, head of the ENT unit at CLINTEC. He told me at our interview with him, they called for information on how it had gone for the patients who had surgery and that they were hoping for an accident investigation. The prefect of the department where Macchiarini was active at KI, CLINTEC, has told me that she had written to the operations manager at the ENT Clinic and proposed an accident investigation.

The email is sent April 9, 2013 [6]:
"NGN form of" accident investigation "of långliggarfallet would be necessary. What decisions were taken in enabled transport here and the treatment of such a critically ill patient without previous conference? This case has received some negative attention outside K and will need to be managed. "

The operations manager at the ENT clinic called for an accident investigation regarding patient 3 shown in the above-mentioned e-mail to the hospital director from April 11, 2013, where both the Head of Unit and the department head is in the copy [2]:
"The patient Thoracic currently dealing with has not been discussed at any multidisciplinary Conference what we know ENT. ENT has in general never informed of PMs efforts in Thorax for other patients. Now they have chosen to operate the Turkish patient without to first seek the advice and support of the multidisciplinary conference. What decisions were taken on enabled transporting hither and treatment of such a critically ill patient without previous conference? The This case has received some negative attention outside K and will need to be managed. Some form of "accident investigation" of the case might be out of place? "

Judging by the written documentation we had access to was the ENT clinic proposed Accident investigation only thoracic clinic taking care of patients 3rd

5.4 Other concerns

We have several interviews received information that there have been concerns regarding Macchiarini's activities that we do not have time to decide. Among other things, the then Guidance and Innovation Director said that he contacted the patient 1's Icelandic doctor who said it there were signs that something was not as it was when it came Macchiarini.

the Icelandic the doctor himself has told the inquiry how little information he had about the patient 1 before transplant and during the other periods the patient was staying at Karolinska. He has also told how odd he thought it was that nothing was prepared when he came to Stockholm to travel back to Iceland with one patient after the transplant.

Even the then hospital director, who had been unusually very involved in the care of Patient 1 (see section 4.1.8), had feelers out in the field and noticed that skepticism grew.

5.5 Several decisions taken during autumn 2013

5.5.1 Meeting between ENT and thoracic clinics

On September 13, 2013, representatives of ENT and thoracic clinics, including business managers, and jointly decided that no more luftstrupstransplantationer "until Furthermore, "would be done in the hospital. [7]

5.5.2 Macchiarini report their experiences with luftstrupstransplantationerna

The head of thoracic clinic took the initiative to a meeting where he invited Macchiarini and several of the people in the thoracic, ENT and gastro clinicians involved in the care of patients 1, 2 and 3. The meeting was held on 2 October 2013. The head described the purpose of meeting in its invitation to Macchiarini [8]:
"Could you have a presentation of the thracheal stem cell transplant experience from Karolinska and worldwide the 2 October 1600 to 1700 and then an hour for discission.

My plan is to invite people clinically Involved "

According to operations manager at the Department of Thoracic Surgery Macchiarini had a poorly composed accounting about their experiences with luftstrupstransplantationer from Karolinska University Hospital and other hospitals. After the meeting decided operations manager to give Macchiarini operating ban on the chest clinic. Macchiarini announced via email and through a personal meeting. The e-mail was motivated decision to the following reasons (reproduced in Läkartidningen, [9]):
- Anastomosis between the artificial trachea and the patient's own tissue releases with time.
- Fistulering to adjacent tissues and organs occurs with time.
- Obstructing granulation in the neighboring bronchi occurs with time.
- It is unclear whether there is any lasting cell growth of the synthetic material.

The conclusion from the thoracic clinic side was that the method must be tested in trials in larger animals before it was ethical to further surgery patients, and therefore stopped all further operations with synthetic trachea. The head also announced the then headmaster of KI of his decision because he had heard that Macchiarini would get a

permanent professorship.

5.5.3 Audit with invited expert from England

On October 15, 2013 a meeting was held with an invited expert in the field luftstrupstransplantationer, Martin Birchall of the University College of London. According to operations manager at the Department of Thoracic Surgery was the reason for the meeting to hold an audit (systematic and independent review) on stem cell modified airway reconstruction where academia and the clinic would be an informal discussion without Macchiarinis participation. The former operations chief at ENT clinic which would have overall responsibility for Macchiarinis clinical activity called the meeting [10].

In an e-mail inquiry has been informed of it turns out that the former operations manager at ENT clinic sent a request to Birchall already August 23, 2013 [11]:
"The email you Because I would like to ask you for a substancial favor. Basically the situation ice to follows. Our mutual friend PM [Paolo Macchiarini] is soon due for a permanent position at the Karolinska Institute (KI) and the Hospital. However, due to circumstances all too well known those to aquinted with PM, additional information is necessary before a final descision can be made. The Chairman (Rector) at KI has thus required an audit or seminar where the current experience regarding tracheal transplants as well as the survey of the scientific status related to stem cell mediated airway reconstruction could be presented and evaluated. It is obvious to me that there is a slight hesitation involved here and that clearifying information is requested The particullarly as to the feasibility to his project quite beside factors that has to do with his personality. "

According to this e-mail, it is thus the principal who should have taken the original initiative to an independent review, an audit of Macchiarinis research.

The head of thoracic clinic explained how he perceived the meeting in our interview with him; Head of Unit and the Head of KI were positive Macchiarini, the then Rector and former Dean of Research at Karolinska Institutet and development and innovation director at the hospital was more listening, and he and a thoracic surgeon who has been involved in several operations was against Macchiarini would continue their activities. In our interview with the business manager for ENT, he told me that it was a good review but it turned out that Birchall nor knew of the Russian business. his view was that the decision was taken after the meeting not to proceed with the method because it was associated with too much complications with complicated after process. The method did not work any else either.

We have received notes from the meeting, the head of the ENT which shows who participated as well as its decision to extend the mandate of the ENT clinic with the condition multidisciplinary control and no operations on the thorax at all. [12]

5.6 Final assessments

The head of the ENT acted after the decision at the meeting on 15 October and took out documents for an extension of Macchiarinis appointment. But when he was November 5 went to division manager she did not sign the document. The head turned to Development and Innovation Director replied that it could be because the hospital director put in [13]. This is confirmed by e-mail to the rector of the Prefect of KI, where the commitment letter is attached with the signature of business manager but not the division manager. [14] according to the then hospital director, he wanted to support the operations manager in keeping the pressure of KI and sent Therefore mail to Division Manager and Head of the thorax with the message that it was not current to extend Macchiarinis employment. The hospital director also had a meeting with KI Rector to tell me that the hospital was not going to extend the mandate. There were two reasons to hospital director did not want to prolong: Macchiarinis behavior (for example, he was unreachable long periods), and that the method was not ripe to use in humans. Macchiarini was not a member of the Medical Association. That he did not extend the appointments were Therefore, never a thing of the tray. Paolo Macchiarinis appointment as chief physician at the hospital was not renewed when it expired November 30, 2013 [15].

References

1. Mejl från verksamhetschef thoraxkliniken, Karolinska Universitetssjukhuset till Macchiarini. 2012-09-30.
2. Mejl från verksamhetschef ÖNH-kliniken till sjukhusdirektör, Karolinska Universitetssjukhuset. 2013-04-11.
3. Mejlväxling mellan fd och sittande verksamhetschef ÖNH-klinken, Karolinska Universitetssjukhuset och enhetschef och prefekt KI. 2013-04-09.
4. Mejl med bilaga från enhetschef KI till verksamhetschef ÖNH-klinken, Karolinska Universitetssjukhuset. 2013-05-06.
5. Mejl från enhetschef till prefekt. KI. 2013-05-08.
6. Mejl från prefekt KI till verksamhetschef ÖNH-kliniken, Karolinska Universitetssjukhuset. 2013-04-09.
7. Minnesanteckning möte ÖNH- och thorax-klinikerna, Karolinska Universitetssjukhuset. 2013-09-13.
8. Mejl från verksamhetschef thorax-kliniken Karolinska Universitetssjukhuset till Macchiarini. 2013-09-16.
9. Lövtrup M. Klinik såg att metoden inte fungerade – stoppade operationerna i det tysta. Läkartidningen 2015;112:DI7A.
http://www.lakartidningen.se/Aktuellt/Nyheter/2015/06/Klinik-sag-att-metoden-inte-fungerade--stoppade-operationerna-i-det-tysta/
10. Mejlkonversation som innehåller inbjudan audit från fd verksamhetschef ÖNH-kliniken, Karolinska Universitetssjukhuset. 2013-10-03.
11. Mejl fd verksamhetschef ÖNH-kliniken, Karolinska Universitetssjukhuset till Martin Birchall. 2013-08-22.
12. Minnesanteckning, audit luftvägsrekonstruktion. Karolinska Universitetssjukhuset och Karolinska Institutet. 2013-10-15
13. Mejlväxling mellan verksamhetschef ÖNH-kliniken och utvecklings- och innovationsdirektör, Karolinska Universitetssjukhuset. 2013-11-05.
14. Mejl från prefekt till rektor, KI. 2013-11-20.
15. Entledigande Paolo Macchiarini. 2013-12-04.

Chapter 6 Reports and other criticism of Macchiarinis clinical operations

In this section we have gathered notifications, warnings and other type of criticism put forward because of Macchiarinis operations at the Karolinska University Hospital. Some entries and warnings have a well founded documentation, others have come to the JIT knowledge through interviews. We have chosen to focus on what has come to the hospital know and have clinical relevance. We describe only briefly the notification concerning Macchiarinis experimental work at KI.

6.1 Early signals and warnings

Section 3.2 The recruitment of Macchiarini we present the references that were taken before the employment as well as the early warning signs that existed before and during employment. In brief, the three strongly negative signals:
- In August 2010 became a professor at KI approached by an acquaintance who is also a professor of pulmonary medicine Modena, Italy, which discourage recruitment Macchiarini. This information reaches the hospital.
- In early September 2010, the operations manager at the ENT Clinic warned of hiring Macchiarini of a senior physician in Barcelona.
- Negative signals from references taken at KI side from Barcelona, Florence and Hanover.

6.2 Delaere

Pierre Delaere is a specialist in respiratory surgery and professor at the University KU Leuven in Belgium.
His area of research is donated trachea from a deceased patient must carry in his forearm several months before surgery to prevent rejection (see section 2.2.1 and, for example, [1]). He has been in the international debate has been highly critical of the use of synthetic trachea. In September 2011 he wrote to CI's Vice Chancellor and raised a suspicion of research misconduct. Rector responded Delaere to the publication that he intended published when Macchiarini was employee of the University of Barcelona and directed him there. [2] The publication it was about was an article in the Lancet of a woman in Barcelona received a nekroluftstrupe [3].

In the summer of 2013 approached Delaere principal back where he once again expressed suspicion research fraud and added more information [4]. He sent three emails, the third in in June 2014, where he says it is "a matter requiring urgent attention" and he suggests that he can come to Stockholm to discuss the whole [5-7]. He also told me that he collaborated with three of the four notifying Swedish doctors (see 6.3 Whistle-blowers). On June 30, In 2014 he received the reply that an investigation had been launched [8]. Delaere then heard of a plurality times and wondered how it happened (eg [9]). Rector gave the KI Ethics Council the task of investigating the issue and their statement was translated into English and sent to Delaere April 12, 2015 [10].

Ethics Council said in its statement that there were no grounds for suspicion Delaeres research misconduct.

6.3 Whistle-blowers

Those in the media have come to be known as whistle-blowers are three thoracic surgeons and an anesthetist, who is or has been employed at the Department of Thoracic Surgery at Karolinska University Hospital. At the time for the first notification, all four employees of the hospital. The three thoracic surgeons are also affiliated to Karolinska Institutet. They have filed a complaint suspected research fraud to KI Rector August 18, 2014 that they have completed twice, March 2 May and 9 May, 2016. According to several interviews, the three thoracic surgeons are very enthusiastic and positive attitude to Macchiarini and his activities when he came to the hospital. One of the surgeons attended to example in the operation of patient 1 and another was involved in the care of the patient 2. These two

also worked to get Macchiarini's nearest man, who was German thoracic surgeon, and Assistant Professor KI, employed at the Department of Thoracic Surgery at the hospital. [11] Among those we interviewed, including the four whistle-blowers, has revealed several versions of the background to the four chose to make a complaint. There is reason to believe that there been various driving forces of each of them.

The anaesthesiologist took a major responsibility for the care of the patient 3. In late 2013, he began, according own admission, look in the scientific literature for a solution and discovered that Macchiarinis articles did not correspond with reality. At the same time there during the fall 2013 started cutting between a thoracic surgeons and Macchiarini's German professor. Thoracic surgeon sought and received funding from the Swedish Research Council

For one, according the research assistant, common idea, and thoracic surgeon reported research plagiarism (No. 2-1309 / 2014). The notification was made April 11, 2014, ie after Macchiarini stopped at hospital. Rector found in its decision that thorax surgeon has been negligent but that it was not of misconduct. [12] In May 2016 requested the thoracic surgeon to CEPN's expert group on misconduct the research could be heard in the case and in July 2016 also requested the National Institute's Acting Vice-Chancellor Expert Group would give its opinion [13].

By June 2014, reported three of the whistle-blowers, including the thoracic surgeon who earlier that year been reported for research plagiarism, the principal work in Nature Communications where Macchiarini
and his postdoctoral fellow co-authored [14,15]. A month earlier they had also sent a notification to the editor of the magazine. [16] In the early 2016 sent the three whistle blowers notification to CEPN (see 6.6).

According to whistle-blowers went early with their suspicions to the National Institute's rector. Their Operations will also have had full knowledge that they were to gather material for the notification. This confirmed by the application with the project title: "Compilation of 3 patients who underwent transplantation of synthetic trakeagraft at Karolinska University Hospital, Stockholm ", which was submitted to the Regional Ethical Review Board July 14, 2014 [17]. It was signed , the head of the Department of Thoracic Surgery and in the application presented the man why took full access to the three patients, all medical records. This therefore means the operations manager, later a commitment date of signing (14 July 2014), should reasonably have known that a notification was going on. Regional ethical review board in Stockholm approved research according to protocol 2014/1: 9 dated 2014-10-15 [18].

In a letter to KI's headmaster August 18, 2014 asked the four doctors that a study of Macchiarini be carried out because of a suspicion of misconduct in research [19]. to the letter enclosed an analysis of six of Macchiarinis publications [20]. The analysis pointed to discrepancies between what is published and what is recorded in the patient records. They also complained of the lack the necessary permits.

On September 12, 2014 left the four doctors a notification to the MPA if they luftstrupstransplantationer performed at Karolinska University Hospital, the issue of the performed in accordance with applicable laws and regulations [21]. This application is then contributing to the MPA made a police report, see section 6.5. On October 13, they turned also an application for review to the Central Ethical Review Board, see section 6.6.

There was silence from KI hold. Notification received international attention, however, first in New York Times, November 24, 2014 - "Leading Surgeon Is Accused of Misconduct in Experimental Transplant Operations". [22] The news was picked up also by several others, such as the scientific journal Nature that described the notification from the four doctors, notification from Delaere (See 6.2) and that the two investigations had been launched [23]. Since ended entire notification including extracts from medical records on the American website Retraction Watch December 12 2014 [24]. It is not clear who or which posted record data on the US Web site, the four doctors denies having done so. An internal investigation at the Karolinska University Hospital demonstrated by the log excerpts who had been included in the records, and when it had occurred. This led to two measures from hospital side: 1. the police on December 22, 2014 disclosure of medical records without the support of the law and the publication on the internet without patients' consent, and 2. the four doctors received a corrective conversation with the business manager, lowest level of disciplinary action [25,26]. The police investigation was closed down because it could not

determine who had provided Retraction Watch with information.

According to the four doctors were accused of the hospital to the notification made incorrectly way. They have also indicated that, before correcting the call, threatened with dismissal but that operations manager managed to negotiate with the hospital's lawyers to mere warnings. The tray coupled in which the layoffs came on the negotiation warning. No threat of dismissal never reached the bay.

After two to three negotiation landed man in the lowest level of disciplinary action where union main argument was that it would not be punished for blowing the whistle. It was agreed the intent was to shed light on what occurred and uncover any anomalies - it was no journal entry of curiosity character. This should also have gained support from the hospital director.

The four notifying the doctors say that they before they submitted their notification been advised of their managers to report a suspicion of research misconduct to KI. KI received the news that the would turn to the Central Ethical Review Board, which they also did, see section 6.6. In the first notification, it appeared that they had been included in the records on 28 and 29 June and 25 July 2014 Patient 1 and 3. It is after you have received permission from family members to go into the records but before it has received the approval of the regional board.

In his reply on April 6 2015 Macchiarini refuted all the allegations. [27] On March 2 and May 9, 2016 completed the four doctors its original notification to CIs new information [28]. One of thoracic surgeons who was co-author on the Lancet article on the first transplant with a synthetic trachea received in March 2016 at his own request removal of his name from Lancet publication [29]. Another three co-authors have withdrawn their co-authorship [29].

Since the four notifiers understood clinic management actions as repression, it can be worth noting an event at the beginning of the same year (2014). Ninety employees at the Department of Thoracic Surgery signed a petition against what they perceived as a repressive culture. A doctor at the clinic who had contact with the media in connection with a report Crash Investigation on patient safety issues (See section 11.7) had to quit his temporary position. According to the signatories and what emerged in our interview with the doctor was the reason right media contact, according to the hospital was economic reasons behind [30].

6.4 Inspectorate for Health Care (IVO)
IVO made a police report June 4, 2015 - IVO judged that responsible / accountable in a research guilty of breaking the law (2003: 460) concerning the ethical review of research involving humans. The matter was subsequently broken by the prosecution. [31] IVO's position was that the three operations have focused on the research, which meant that science and proven experience abandoned. IVO therefore felt for formal reasons prevented to review these operations.

IVO has a current patient case / complaint relating to the care of the patient 3. It is the father to the patient by proxy complaining about the treatment of the nursing staff in the

three years the patient was treated at the ICU at the Karolinska University Hospital before transfer to the USA.

IVO has written to the hospital and asked how to ensure that the hospital's operations be obtained ethical approval when required and received the reply that there are no problems the art. In the current case, according to the hospital matter of vital indication why this question did not arise then.

6.5 MPA

As already mentioned, they sent four doctors in September 2014, a request to the MPA if examination of the luftstrupstransplantationer performed at Karolinska University Hospital and if they are conducted in accordance with applicable laws and regulations [21]. This notification, along with an additional notification, as well as information on KI's website, leading to the MPA made a police report on suspected violation of the Medicines Act in April 2015 [32].

The police report was preceded by a notice to the hospital for treatment of patients with

stem cell modified synthetic trachea (13 February 2015) [33]. The case was subsequently settled by prosecutors as the notification related crimes barred (2015- 08-18). [31]

6.6 Central Ethical Review Board (CEPN)

The four whistle-blowers also sent its first notification to CEPN in October 2014 (see 6.3) as in turn sent the case to the IVO [34]. In early 2016 it received a request to CEPN shall exercise supervision under the Act (2003: 460) on the ethical review of research involving humans On the research conducted by Paolo Macchiarini at the Karolinska University Hospital and the Karolinska Institute. It was about transplants performed in Russia. CEPN dismissed the case without further action by the CI in a statement said that there is any connection to the institution [35].

Otherwise, the following notifications sent to CEPN:
- Three of the whistle-blowers have submitted a notification of suspected research fraud in an article in Nature Communications (see 6.3). According to data from CEPN have a report from the expert received and communicated and the opinion of the expert group can be expected in the autumn In 2016.
- KI's principal received an anonymous report sent on to CEPN. The notification relates misrepresented in an article in the journal Biomaterials where Macchiarini is one of the co-authors [36]. The case is in its final phase.
- Notification by Macchiarinis research assistant to one of the whistle-blowers relating to suspected plagiarism of data in an application to the Swedish Research Council (see 6.3).
- In the summer of 2016 received a notification from the National Institute's rector of suspected research fraud. The refers to the six articles that the four whistle-blowers raised

in the original notification (see 6.3).

6.7 prosecutor

In May 2015 began a preliminary investigation concerning bodily harm, felony, during from 24 July 2012 to 9 July 2013 at the Karolinska University Hospital in Solna. In June 2016 served Macchiarini suspicion of offenses for aggravated manslaughter and aggravated Causing bodily injury for the transplant of artificial trachea and grievous bodily injury in connection with an operation conducted in Huddinge spring 2011.

References

1. Delaere P, Raemdonck DV. Tracheal replacement. Journal of Thoracic Disease 2016:S186-S196.
2. Brevväxling Pierre Delaere och rektor KI 2011-09-12 och 2011-10-20. Dnr 5915/11-608.
3. Macchiarini P, Jungebluth P, Go T, Asnaghi MA, Rees LE, Cogan TA, et al. Clinical transplantation of a tissue-engineered airway. Lancet 2008;372:2023-30.
4. Mejl från Pierre Delaere till rektor KI. 2013-07-16.
5. Mejl från Pierre Delaere till rektor KI. 2013-09-18.
6. Mejl från Pierre Delaere till rektor KI. 2014-01-02.
7. Mejl från Pierre Delaere till rektor KI. 2014-06-25.
8. Mejlväxling Pierre Delaere och rektor KI. 2014-06-25 och 2014-06-30. Dnr 2-2167/2014.
9. Mejl från Pierre Delaere till rektor KI. 2015-03-01. Dnr 2-2167/2014.
10. Utlåtande från Etikrådet, KI. 2015-04-12. Dnr 2-2167/2014. Engelsk översättning.
11. Mejl från thoraxkirurg till Macchiarini. 2012-09-04.
12. Beslut rektor KI i ärende om misstänkt oredlighet i forskning. 2015-04-28. Dnr 2-1309/2014.

13. Läkartidningen. 2016;113:D664. http://www.lakartidningen.se/Aktuellt/Nyheter/2016/07/KI-begar-CEPN-yttrande-om-visselblasare-i-Macchiariniaffaren/
14. Anmälan om misstänkt forskningsfusk till rektor KI 2014-06-24. Dnr 2-2184/2014.
15. Sjöqvist S, Jungebluth P, Ling Lim M, Haag JC, Gustafsson Y, Lemon G, et al. Experimental orthotopic transplantation of a tissue-engineered oesophagus in rats. Nat Commun 2014;5.
16. Anmälan om forskningsfusk till Nature Communications maj 2014.
17. Ansökan om etikprövning till Regionala etikprövningsnämnden i Stockholm: ”Sammanställning av 3 patienter som genomgått transplantation med syntetiska trakeagraft vid Karolinska Universitetssjukhuset, Stockholm”. 2014-07-14.
18. Beslut i Regionala etikprövningsnämnden i Stockholm 2014-10-15. Protokollsutdrag 2014/1:9.
19. Anmälan misstänkt forskningsfusk till rektor KI 2014-08-18.
20. Analysis of Clinical Outcome of Synthetic Tracheal Transplantation Compared to Results Published in 6 Articles by Macchiarini et al. 2014-08-18. Karolinska Institutet Dnr 2-2184/2014.
21. Anmälan från visselblåsarna till Läkemedelsverket om luftstrupstransplantationerna på Karolinska Universitetssjukhuset utförts i enlighet med gällande lagar och föreskrifter. 2014-09 12.
22. Leading Surgeon Is Accused of Misconduct in Experimental Transplant Operations .

New York Times 2014-11-24.
23. Cyranoski D. Investigations launched into artificial tracheas. Nature 2014;516:16-7.
24. De fyra läkarnas anmälan på Retraction Watch. retractionwatch.com; 2014.
25. Polisanmälan 2014-12-22. Karolinska Institutet Dnr 3858-2014.
26. Protokoll från överläggning ang skriftlig varning 2015-01-23 och 2015-02-19. Karolinska Universitetssjukhuset. Dnr 073/2015.
27. Macchiarinis svar på de fyra läkarnas anmälan. 2015-04-06. 2015.
28. Anmälan om forskningsfusk från de fyra läkarna till KI. 2016-03-03. 2016.
29. Department of Error. The Lancet;387:944.
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)30114-3/fulltext
30. Lövtrup M. Kritik mot att läkare fick sluta efter mediekontakt. Läkartidningen 2014;111:CSDH. http://www.lakartidningen.se/Aktuellt/Nyheter/2014/02/Kritik-mot-att-lakare-fick-sluta-efter-medieuttalande/
31. Underrättelse om beslut. 2015-08-19. Åklagarmyndigheten ärende AM-53012-15.
32. Polisanmälan från Läkemedelsverket. 2015-04-14. Polismyndigheten Dnr: 5000-K446303-15.
33. Föreläggande till Karolinska Universitetssjukhuset 2015-02-13. Läkemedelsverket Dnr: 6.3- 2015-013429.
34. Beslut Centrala etikprövningsnämnden 2014-11-17. Dnr: T 4-2014.
35. Beslut centrala etikprövningsnämnden 2016-04-25. Dnr: T 1-2016.
36. Ajalloueian F, Lim ML, Lemon G, Haag JC, Gustafsson Y, Sjoqvist S, et al. Biomechanical and biocompatibility characteristics of electrospun polymeric tracheal scaffolds. Biomaterials 2014;35:5307-15.

Chapter 7 Ethics and Guidelines

In this chapter we discuss general aspects of the ethical issues that become relevant in the context with Macchiarinis operations at the Karolinska University Hospital. We also refers the professional guidelines relevant. There is a wide range of professional and general nature ethical guidelines. But for this discussion, we have restricted ourselves to describe the contents of Two documents are of particular relevance - the Helsinki Declaration and the Guidelines International Society for Stem Cell Research presented. There is also the interpretation of these two documents raised in the public debate on Macchiarinis luftstrupsoperationer.

In this chapter, made no assessment of transplant operations - these are presented in Chapters 11 and 12.

7.1 Benefits, risk and knowledge uncertainty

In all ethical assessments in health care includes possible benefits of an action for the individual patient are weighed against the possible risks. When a new method is introduced in health care is also emerging
question: What scientific evidence is the method? What is known about the possible risks? The weighing of benefits, risks and science during the team's strength is most usually controlled in question of drugs - this is a well-established European and Swedish regulatory framework on which grounds a new drug to be approved. Safety first tested outside the body (in vitro, e.g. in cell culture), then in laboratory animals (in vivo) before

the drug is gradually being tested on more and more people, which records the effects and possible side effects.

For medical equipment usually takes place testing of the material itself and some testing of the product to work properly intended. The equipment must be CE marked. In some cases it may be required that the benefits or risks must be documented in clinical trials before the medical device begins used in clinical practice (see Chapter 8).

To answer the question whether the time was ripe to start applying a new, previously untested method in humans, is not sufficient testing and CE marking of the synthetic material used. Just the fact that animal studies conducted is not enough - the trials must have been risks, both short term and long term, are acceptable in relation to the potential benefit.

When the state of knowledge is very uncertain, there is special reason to be wary of introducing a new method with huge potential risks [1]. The information available for the decision maker can be both quantitative and qualitative lean. Knowledge Uncertainty can do it is difficult, sometimes impossible, to make robust risk assessments.

7.2 Self-determination and informed consent

Central issues in the discussions around the three patients who underwent luftstrupstransplantationer has been: Do they have been fully informed, they have been able to take independent decisions and have the without pressure given their consent? Therefore, we present here the concepts of self-determination and informed consent.

One of the fundamental concepts in medical ethics is autonomy or the right to self-determination. Self-determination is considered to be a value in itself, not just a means to apply other ethical principles. If an individual is an adult and capable of making decisions, then you should not others hinder individual to make independent decisions, at least not as long as the individual does not infringe someone else's rights or hurt someone else.

In the health sector means the autonomy principle that one should be free to decide on examinations and treatments and not pressured. You have the right to know what bet means, how risky it is, the consequences of accepting or refrain from intervention, and what alternative actions are possible. In medical ethics is attached to the requirement of informed consent importance. In clinical research, the informed consent be designed in a special way, and as a rule must both information consent be in writing. [2] In health care outside the clinical research can inform

tion be both written and oral. The laws described in more detail in chapter 8. That patient agree to an action can not deprive medical staff and operations management responsibility that the measure is implemented in accordance with science and proven

experience. For a person to be able to shop and choose independently and take responsibility for their actions he must have access to factual information about the conditions and consequences of various policy options. He will also have understood this information and not have been subjected to coercion or pressure when the hen given his consent.

7.3 New medical assessment (second opinion)

Swedish law provides the opportunity for a new medical assessment of other medical expertise, known as second opinion, for severe disease [3]. This can be considered as a further opportunity for the patient To get comprehensive information as a basis to decide about their care. It is, especially in cancer, not uncommon for a more active curative or symptomatic effort advocated by a second opinion than at the previous assessment - behind second public opinion is often the expectations of the patient on the new treatment. The patient was taking initiative does not absolve the doctor standing for a second opinion the responsibility to provide a balanced and realistic picture of the treatment options and their possible consequences.

7.4 Treatment of vital indication and for humanitarian reasons (Compassionate use)

In discussing the luftstrupstransplantationerna the terms vital indication and compassionate use used. Vital Indication defined in the Medical Dictionary "circumstance in which you have to undertake certain action to save the patient's life "[4]. The definition does not include a time dimension, but there is certain consensus in health care that involves the patient at risk of dying within hours or a few days.

Vital indication can be said to be close to the ethical principle of the "rule of rescue", the notion that there is an ethical imperative to save a fellow human being in mortal danger [5]. In such a situation there rarely space to analyze the costs and long-term effects. Clear examples are cardiac arrest outside the hospital or severe accidents. "The rule of rescue" has been criticized as ethical principles, including other things because it could lead to unlimited resources for emergency life-saving interventions - without taking into account the goal of treatment, or to displacement effects for others patients. The concept of vital indication do not exist in Swedish law.

The term "compassionate use" could be used for a range of diagnostic and therapeutic interventions in health care. In its most regulated form occurs concept in the pharmaceutical area, then more specifically on Article 83 of the EU pharmaceutical regulation (726/2004) [6]. the translation the Swedish EU commonly used is the compassionate use (although other translations also present). Compassionate use is defined in EU regulation treatment for "a group of a chronic or seriously debilitating disease or whose disease considered to be life threatening and can not be treated satisfactorily by an authorizedmedicines "[6]. This group may be subject to certain conditions access to medicines that are already during development, without the drug approved by the Swedish or European Medicines Agency. Compassionate use is rooted in compassion, an ethical principle with deep roots in many cultures. Patients with rare or

particularly difficult to treat diseases would able to receive treatment even when treatment effects are not well documented, unless there are other options to offer.

Mercy principle is not superior to other core ethical principles (so-called euthanasia is banned in Sweden, irrespective of motive). If you invoke compas-

härtighet (treatment for humanitarian reasons), whilst taking into account other ethical principles, For example, weighing the benefits and risks, otherwise the ethical evaluation incomplete. Here we are dealing with situations when you have exhausted other therapeutic options. Not Nor can it plead for mercy to depart from the specific rules that are for health care (for example, the use of stem cells; see Chapter 8).

Treatment that is resorted to as a last straw might also be seen as an expression for mercy. It is usually primarily talk about the "last straw" principle when it comes alternative medical treatments on the patient's request, when the attending physician determined that no curative measures available. A condition is then that the treatment may not hasten death or cause further suffering.

7.5 Use of new untested methods

In discussing the luftstrupstransplantationerna at Karolinska University Hospital has often the question arose whether it moved on clinical research. As developed in Chapter 8, there are clinical research specific legislation and rule needed the approval of the Ethics Board [2,3,7]. The Research Council has instructions on how Clinical research will be carried out, including the permit is also required from the MPA in the case of drugs, including stem cells [3].

In health care, sometimes trying new methods that are not based on whether science or proven experience - they can not be said to meet the requirements of established care. Nor carried out development work as clinical research project. This activity has been called "clinically innovation "," clinical development "or" use of untested methods ". While clinical research aimed at increasing knowledge of the groups of patients, it aims "clinical innovation "mostly to help individual patients. [8] Several of medical progress have such a background. So, for example, parts of transplant surgery has emerged. Often the methods developed and improved gradually, but it has moved on rigorous research.

Helsinki Declaration. World Medical Association (World Läkarorganisationen) has in the Helsinki Declaration developed a series of recommendations for clinical research. Declaration came in the first version in 1964 and last updated in 2013 [9]. The declaration has been of great importance the ethical laws of different countries. Helsinki Declaration imbued with the idea that experiments involving humans should conducted by clinical research and follow a strict, ethically-based framework. Declaration concern still the issue of doctors in some cases can use unproven methods. Over the years luftstrupstransplantationerna performed at Karolinska University Hospital was the 2008

version Declaration of Helsinki [10]. The relevant article number was then 35 (we have chosen the English the original text, as it has been discussed about the Swedish translation is absolutely correct):
"In the treatment of an individual patient, where the samples interventions do not exist or otherknown interventions have been ineffective, the physician, after seeking expert advice, with informedconsent from the patient or a Legally Authorized Representative, May use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviatingsuffering. Where possible, this intervention Should be subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available. "

In Helsinki Declaration latest version (2013), this article has changed the numbering to 37 and "Where possible" has been deleted from the penultimate sentence [9] - it has thus become clearer the requirement to transition to research the use of untested method.

As highlighted in the debate on the Declaration of Helsinki (including by Bengt Gerdin, the KI investigators engaged in fraud case [11]), Article 37 (previously 35) can not be read in isolation from other articles of the Declaration of Helsinki. The document is permeated by the idea of patients' security must be safeguarded in experimental efforts in health care.

Helsinki Declaration concerns a recommendation by an international professional organization. Much of the Ethical Review Act is based on this declaration, but one paragraph that

corresponds to the Helsinki Declaration's Article 37 does not exist in Swedish legislation.

International Society for Stem Cell Research (ISSCR) published in 2008, in cooperation with including Swedish medic inet technicians and researchers, clinical guidelines for stem cell research. [12] Recommendation 34 in this document is of particular relevance to the discussion of transplant synthetic trachea vidmed seeded bone marrow cells at the Karolinska University Hospital
(Box 7.1)

Facts 7.1

Recommendation 34 of the guidelines for clinical stem cell research from ISSCR [12]. Commenting on the detailed contents of Recommendation 34 says ISSCR:
Not following such standards may exploit desperate patients, undermine public trust in stem cell research, and unnecessarily delay better designed clinical trials. Many who provide stem cell-based therapies may claim that they offer innovative medical care not available in other medical institutions because of the conservative nature of medical care. Strict application of the Clinician-scientists may provide unproven stem cell-based

interventions to at most a verysmall number of patients outside the context of a formal clinical trial, provided that:
(a) there is a written plan for the procedure that includes:
i. scientific rationale and justification explaining why the procedure has a reasonable chance of success, including any preclinical evidence of proof-of-principle for efficacy and safety;
ii. explanation of why the proposed stem cell-based intervention should be attempted compared to existing treatments;
iii. full characterization of the types of cells being transplanted and their characteristics as discussed in Section 4, Cell Processing and Manufacture;
iv. description of how the cells will be administered, including adjuvant drugs, agents, and surgical procedures; and
v. plan for clinical follow-up and data collection to assess the effectiveness and adverse effects of the cell therapy;
(b) the written plan is approved through a peer review process by appropriate experts who have no vested interest in the proposed procedure;
(c) the clinical and administrative leadership supports the decision to attempt the medical innovation and the institution is held accountable for the innovative procedure;
(d) all personnel have appropriate qualifications and the institution where the procedure will be carried out has appropriate facilities and processes of peer review and clinical quality control monitoring;
(e) voluntary informed consent is provided by patients who appreciate that the intervention is unproven and who demonstrate their understanding of the risks and benefits of the procedure;
(f) there is an action plan for adverse events that includes timely and adequate medical care and if necessary psychological support services;
(g) insurance coverage or other appropriate financial or medical resources are available to patients to cover any complications arising from the procedure; and
(h) there is a commitment by clinicianscientists to use their experience with individual patients to contribute to generalizable knowledge. This includes:
i. ascertaining outcomes in a systematic and objective manner;
ii. a plan for communicating outcomes, including negative outcomes and adverse events, to the scientific community to enable critical review (for example, as abstracts to professional meetings or publications in peer-reviewed journals); and
iii. moving to a formal clinical trial in a timely manner after experience with at most a few patients.

above criteria to many clinical interventions offered outside of a formal clinical trial will identify
significant shortcomings that should call into question the legitimacy of the purported attempts at medical innovation.

As pointed out by, among others, Bengt Gerdin writes ISSCR- earlier in the document (recommendation 2):
“Regardless of the recommendations encompassed in this document, scientists and clinicians should comply with local policies and adhere to local, national, and international guidelines relevant to research.”

An update of ISSCR guidelines have recently been published [13]. Recommendation 34 of the previous version (3.4.1 in the New) is unchanged in its content, except that it has

added the requirement that the patient can not be included in a clinical stem cell trials. In Chapter 11, we discuss to what extent the Helsinki Declaration's Article 37 (previously 35) and ISSCR's recommendation of 34 can apply to the current transplants with stamcellsinympade synthetic trachea.

Local guidelines. We have in our interviews and our reviews of written material could not be finding that the Karolinska University Hospital is current local policy documents that raises ethical questions about the application of new untested methods in health care. At Karolinska The Institute's Guidelines for Planning, Conducting and documenting clinical and epidemiologicalresearch [14]. This document ten point focuses on procedures and documentation related clinical research and contains no research ethics.

References

1. Wahlström J, Sahlin N-E. Läkaren som riskanalytiker. Läkartidningen 2009;106:3517-19.
2. Lag om etikprövning av forskning som avser människor. Svensk författningssamling 2003:460. https://www.riksdagen.se/sv/Dokument-Lagar/Lagar/Svenskforfattningssamling/Lag-2003460-om-etikprovning_sfs-2003-460/
3. Vetenskapsrådet. CODEX. Regler och riktlinjer för forskning. http://www.codex.vr.se/forskningmedicin.shtml
4. Medicinsk ordbok. http://medicinskordbok.se/
5. McKie J, Richardson J. The rule of rescue. Soc Sci Med 2003;56:2407-19.
6. Europaparlamentets och rådets förordning (EG) nr 726/2004. EUR-Lex http://eur-lex.europa.eu/legal-content/SV/TXT/?uri=CELEX%3A32004R0726
7. Vetenskapsrådet. Juridik och etik. 2016. http://www.registerforskning.se/sv_se/stodtill-digsom-forskar/juridik-och-etik/
8. Lindvall O, Hyun I. Medical innovation versus stem cell tourism. Science 2009;324:1664-5.
9. World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. http://www.wma.net/en/30publications/10policies/b3/17c.pdf . 2013
10. World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. http://www.wma.net/en/30publications/10policies/b3/17c.pdf . 2008
11. Gerdin B. Utlåtande i oredlighetsärende, brev till KI:s rektor 2015-05-13.
12. International Society of Stem Cell Research. Guidelines for the clinical translation of stem cells. 2008. http://www.isscr.org/docs/default-source/clin-transguidelines/isscrglclinicaltrans.pdf
13. International Society for Stem Cell Research. Guidelines for stem cell research and clinical translation. 2016. http://www.isscr.org/docs/default-source/guidelines/isscr-guidelines-for-stem-cell-research-and-clinical-translation.pdf?sfvrsn=2
14. Wallberg-Henriksson H, Carlstedt-Duke J. Guidelines for planning, conducting and documenting clinical and epidemiological research. Karolinska institutet. https://internwebben.ki.se/sites/default/files/null/riktlinjer_exp.pdf

Chapter 8 legal regulations

This chapter is a brief of the main provisions in the form of EU directives, laws, regulations and government regulations involved in the actual air-

strupstransplantationerna. The emphasis is on the regulations that were in force during the years 2011-2013. The description does not claim to be complete.

8.1 Health Care Act

The Health Care Act (SFS 1982: 763), HSL, contains provisions on health care and its organization. In § 1 defined in the Act referred to health care,namely measures for the medical prevention, investigation and treatment of diseases and injuries. HSL is a so-called framework law and contains objectives and requirements of virtually all health health care with emphasis on county and municipal responsibility for such care. Act emphasizes obligations of caregivers but contains no provisions that give patients some legally chargeable rights, a principled stance that pervade the Swedish health care legislation. The level of detail is not so high, but the law is to a large Some of the basic requirements.

The provisions of the healthcare provider obligations inter alia, that health care be conducted so as to satisfy the requirements for good care. This means that it must be of good quality and meet the patient's need for security in care and treatment, be easily accessible, based on respect for the patient's autonomy and integrity, promote good relations between patient and health professionals and meet the patient's need for continuity and safety of healthcare. Furthermore, various efforts are coordinated patient in an appropriate
way.

The caregiver has an obligation to provide the patient or, where appropriate, their family, information as specified in the Patient Act (PL). Through references to PL reproduced in HSL an obligation on the council to give the patient the option to choose treatment options and a new medical assessment ("second opinion").

The management of health care should be organized so that it meets the high level of patient and the quality of care and promotes cost efficiency. The operations manager must ensure that the patient's need for security, continuity, coordination and safety of healthcare are met. If it is necessary to meet those needs, or if a patient requests it, the operations manager appoint a permanent health care contact for the patient (previously called PAL; Patient Responsible physicians). The HSL is also stated that the County Council should participate in financing, planning and implementation of clinical research in the health field.

Before a new diagnostic or treatment that may be relevant to human dignity and integrity of application in health care, the health care provider to ensure that the method has assessed from the individual and social ethical aspects. This refers to an ethical evaluation should made by the caregiver at the transition from clinical research to practical application both from the individual perspectives from a broader societal perspective. It is ethically justifiable for the individual patient may be more doubtful of other persons or groups in society perspective, or on broader societal values (Prop.

2009/10: 83, p. 26).

Finally, the quality of operations systematically and continuously developed and secured.

8.2 Patient Act

Patient Act (SFS 2014: 821), PL, entered into force on 1 January 2015. The purpose of the law is that within healthcare activities strengthen and clarify the patient's status and promoting patient integrity, self-determination and participation. The law should support the patient's ability to participate and be co-creators in their care process. PL contains numerous provisions that could previously found in other laws, primarily HSL and Patient Safety Act (PSL). There are also provisions corresponding

or refers to provisions of other laws. In PL repeated among other requirements that the patient be get expert and diligent care that is of good quality and that is in conformity with science and proven experience.

A particular focus is on the duty to inform the patient and the Act extended and clarified these obligations. Patients should be including information about their health, the methods available for examination, care and treatment, the expected care and treatment process, significant risks of complications and side effects, as well as aftercare. The information must be adapted to individual conditions so that it is understood by the patient. Healthcare must not be given without the patient's consent. The patient may give its consent in writing, orally or by otherwise show that he or she consents to the current operation. The patient may at any time withdraw consent. A permanent health care contact shall also be appointed if the patient requests it.

The PL also regulated the possibility that under certain conditions, to choose treatment options and to get a new medical assessment ("second opinion"). The conditions for getting such new assessment is that the patient has a life-threatening or particularly serious illness or injury. PL contains no express provisions on clinical research.

Patient Data Act

In chapter 3. 6 § Patient Data Act (SFS 2008: 355) states what should be documented in the patient journal. This is one indication of the information provided to the patient, if the positions made in terms of choice of treatment options and the possibility of a new medical assessment. These requirements embodied in the Board's regulations (SOSFS 2008: 14) on information management and record keeping in health care where it is stated that the caregiver
shall ensure that there are procedures for how the patient data should be documented in the patient records. Furthermore, procedures for documentation of patient data to ensure that patient records contains information on the left consents and details of the patient's own wishes in refers to care and treatment. Although measures and observations in

clinical research and drug trial must be documented in the patient's record.

8.4 Patient Safety Act

Patient Safety Act (SFS 2010: 659), PSL, effective from 1 January 2011 and regulates the demands on the health care provider to conduct a systematic patient safety and healthcare professionals obligations of professional misconduct. The PSL also regulates the supervision IVO conducts of health care. Under the law, including all personnel employed in patient care at the hospital healthcare professionals. A special case that also counted the people, as the basis of special regulations, providing services in a profession in health care during a temporary visit to Sweden without a Swedish license for the profession.

The caregiver will plan, direct and control activities in a way that requirement good health is maintained. The caregiver shall take the necessary measures to prevent patients suffer health damage. If such events still occurred have caregiver responsibilities for to investigate these. The caregiver should advance to the IVO report incidents that have resulted in, or had could result in a serious health damage (lex Maria). The notification shall be made as soon as possible after the event has occured. The caregiver shall simultaneously with notification, or as soon thereafter submit their own investigation of the incident to IVO. IVO to ensure that events that have been notified to the Authority has investigated the extent necessary and that the caregiver has taken the necessary measures to achieve high patient. More detailed provisions on notification contained in the Board's regulations and general guidelines (SOSFS 2005: 28) on Reporting Lex Maria.

The caregiver must document how the organizational responsibility for patient safety is distributed within the business. By 1 March each year, the health care provider to establish a patient's story from which it should state how the patient safety work has been carried out during the previous calendar, which measures have been taken to increase patient safety and results achieved.

Healthcare professionals should conduct their work in accordance with science and proven experience. A patient must be given expert and caring healthcare fulfills these requirements. Care should as far as possible be designed and implemented in consultation with patient. The patient should be shown consideration and respect. Health care personnel must contribute to high patient is maintained. Staff should that end report to the caregiver if there is a risk of health damage and the events that have led or could have led, health damage. This applies not only serious medical injuries but also less severe ones.

The requirement for science and proven experience does not apply to processing operations carried out in the framework of a research project. Then apply instead to ethics approval must be in accordance ethical review teams (SFS 2003: 460). In some cases, a

license from the Medical Products Agency have obtained.

Under the Act, a health care provider immediately report to the IVO (up to 1 June 2013, notification,be made to the National Board) if there are reasonable grounds to suspect that a person has identification for a profession in health care and who works or has worked in caregiver, can endanger patient safety. The notification requirement also includes the who has specific mandate to practice medicine. Forms the basis of such notification to the competent deemed inept, there should be investigation to prove this relationship.
For those cases where a council has no authority to hire non-licensed doctors on temporary appointment to the National Board specifically appoint such a doctor to practice medicine in Sweden (SOSFS 2000: 6). It is the county making the application of such a special appointment.

8.4.1 Inspection, care and research

The foundation of Macchiarini case is that patients treated for medical conditions and during these episodes Care treated with untried methods which the investigation found to be research. In the PSL not explicitly issue of clinical research in health care and who oversight responsibility for such activities. IVO under PSL supervision of health care and its staff. With the health care provided for activities covered by HSL.

Drawing the line between healthcare and clinical research is not entirely clear. The legislative history of the law preceded the PSL; Act (1998: 531) on professional activity in the health field, revealed the supervision of health care also includes personnel responsible for injury or risk of damages in connection with clinical research. It also emerged of the former Act provisions on disciplinary responsibility for health care professionals also included clinical research on humans. Although these losses are not reflected in the PSL has hardly legislature intended to any change in the regulatory responsibility would occur. In conjunction with the National Board of customizable lex Maria Regulations PSL (SOSFS 2010: 4) were also kept writing that these regulations also be applied to clinical research on humans. IVO's supervision should in any case cover carers and health professionals adherence to the Ethics Code. IVO has Also Macchiarini case filed a police complaint regarding violation of these provisions.

Supervision could also theoretically could include the patient safety risks that may arise in connection the research and rule violations in general, such as deficiencies in record-keeping, medication and anesthesia in connection with an operation of a research nature. However becomes it is naturally not the case for the IVO to demand that the efforts in the care process who served as clinical research should have been given in accordance with science and proven experience.

It is of course primarily a matter for the IVO to assess how far their oversight responsibility extends when it comes to "research" part of those admissions and the supervision that is assessed relevant and appropriate in the current situation.

8.5 National Board regulations and guidelines (SOSFS 2005: 28) on Lex Maria

The basic rules on the notification requirement stated in the PSL. Regulations and the general advice applies in particular in health care management and in clinical research on humans. The caregiver is responsible for the management system includes the processes and procedures needed to ensure that notification works. The caregiver designate the officers who actually report events to the IVO who have led or could have led to a serious health harm. Such damage if it is permanent and do not call, or have led to the patient is given a significantly increased demand for care or died. An important condition for registration is that the injury could have been avoided if adequate measures. Examples of events that under the Constitution should be reported incorrectly Performed examination, care or treatment, and shortcomings in work practices, health care organization or cooperation between different care units. A care facility or health care provider should inform the other device or caregivers who cared for the patient in the case of an event that may be notifiable occurred in the previous operation. Notification must be received by the IVO within two months from the time the event occurred.

National Board regulations and guidelines (SOSFS, 2015: 12) on the investigation of medical injuries would have entered into force January 1, 2016 but has been withdrawn until further notice (HSLF-FS 2015: 25). purpose is to see how the regulations could be further clarified and improved so that the investigations of health damage can be done in a more appropriate manner.

8.6 Ethical Review Act

The Act (SFS 2003: 460) contains provisions on the ethical review of research involving humans and biological material from humans. Provisions on information and consent such research occupies a large part of the law. The purpose of the law is to protect the individual man and uphold respect for human dignity in research. Such activities may be only be conducted if these values into account. Human rights and fundamental freedoms should be always heeded, while taking into account the interest of new knowledge can be developed through research. Furthermore, human welfare is given priority over society and science. Research is defined as scientific experimental or theoretical work to acquire new knowledge and development on a scientific basis, however, Such work carried out in the context of higher education at a basic or advanced level. The definition is general in nature. In order to assess whether a project is Research must therefore make an overall assessment and several factors may need weighed against each other. The scientific approach of the work, long-term nature and structure and financing is in this context some of the more important components to consider. Also other factors are important, such as whether the work is to be published in scientific journal and the like. There are interfaces with among other activities include performance monitoring, evaluation and quality assurance.

Research may take place only if it has approved by an ethics at one of the regional ethical review boards or by the Central Ethics Committee. Even clean registry studies of

sensitive personal data subject authorization requirement. Further more, the ethical review boards from clinical trials constitute research and therefore should be ethical review and ethical approval is obtained before such trials begin.

Research may be approved only if the risks it may entail for research persons health, safety and privacy are outweighed by its scientific value. Furthermore, research authorized only if it is carried out by, or under the supervision of a researcher who has scientific expertise required. Research, however, may not be authorized if the expected the result can be achieved in a way that involves less risk to people's health research, security and privacy. Another condition for approval is that the applicable provisions for information and consent will be followed. The research subject, in this case the patient, to be informed of the overall plan for the research, the purpose of research, the methods that will be used, the consequences and risks that research can bring, who

the research organization, to participation in research is voluntary, and the research subject's right at any time to cancel their participation.

Research may be carried out only if the research subject has consented to the research involving her or him. An agreement is only valid if the research subject has previously received information if the research. Consent must be voluntary, explicit and specific to certain research. The consent must be documented. If any other statute contains special provisions Information and consent to research, those provisions shall apply instead.

Anyone who intentionally conducts research without consent or breach of a condition of a given approval can be sentenced to a fine or imprisonment not exceeding six months. the central Ethical Review Board (CEPN) supervises compliance with the law, primarily concerning basic medical research conducted by a principal organizer other than health care providers in health care, for example in connection for academic medical institutions. CEPN's supervision does not Such supervision falling within any other authority responsibility. It may e.g. apply the areas IVO, the MPA and the Data Inspectorate has responsibility for.

The regional ethical review boards are independent authorities, based on Ethical Review Act and related regulations, examines applications for ethical approval of research. It is the research organization responsible for such an application is submitted. Ethical Review Act is supplemented by the Ethical Review Ordinance (2003: 615) that are substantially deals with administrative issues surrounding the ethics review process. Among other things, stated that a regional ethical review board must decide within 60 days by the ethical review of other research than a clinical drug trial. In the clinical trial, the board shall decide within 60-180 days. For drugs regarding somatic cell therapy comes to 180 days.

8.7 National Board of Health regulations (SOSFS 2005: 12) on management for quality and patient safety in health care

National Board of Health regulations (SOSFS 2005: 12) on quality management and patient safety in health care was in force until 31 December 2011. The regulations were closer interpretation of the stipulation in the HSL to the quality of operations systematically and continuously be developed and secured. The regulations were expressly also apply to clinical research or Clinical trials of drugs and medical devices for the treatment of a patient health care.

The caregiver was responsible for setting up a management system operations manager would then concrete based on local conditions with the support of health professionals. The management system would ensure that there were procedures for new methods of diagnosis, treatment and treatment could be developed, tested and introduced on a patient safely and how these practices would be followed up and revised. There was also a requirement that the management system contained procedures for the measures to be taken in the application of the methods needed to change or liquidated. Otherwise focused regulations on the procedures necessary skills, cooperation and cooperation, risk management, exception handling, traceability, self-control, monitoring and experience feedback.

8.8 National Board regulations and guidelines (SOSFS 2011: 9) on management systems for systematic quality work

National Board of Health regulations (SOSFS 2011: 9) on the management of systematic quality work effective from 1 January 2012. The Constitution is a supplementary guidebook. these regulations and general advice focuses on the carer's responsibilities and clarify, in relation to previous Constitution, that every caregiver must do a proper survey of all the requirements and goals of the operations according to laws and regulations on health care. The requirements and objectives to be secured under the earlier regulations are also included in the new rules.

The Constitution also contains requirements to submit additional information in the patient's story as established by the health care provider under the PSL and that this should be complemented by a quality story.

8.9 The pharmaceutical legislation

The Medicines Act provides basic rules that clinical trial may performed to investigate a drug's effectiveness. Permission from the MPA required to get carry out such an examination.

The old Medicines Act (1992: 859) applicable at the time of the current procedures. since the January 1, 2016 for the new Medicines Act (2015: 315). The changes in comparison

with the Law, however, is mainly editorial. Act's provisions on information and consent should be applied in clinical drug trials. Ethical Review Act complements this regulation in such trials. The Medicines Act stated that patients should participate in a clinical trial should receive such information the trial that they can decide whether they want to participate in it or not. They must also informed of their right at any time to cancel their participation. Consent to participate in clinical drug testing should always be actively sought and the law regulate how subjects who lack decision-making competence should be treated.

8:10 Drug Administration's regulations and general advice (LVFS 2003: 6) on clinical trials of medicinal products for human use

These regulations, in force until 1 February 2012, would be applied to clinical trial of the drug in humans. For each prospective (forward) study of subjects or patients of a chemical or biological substance in order to clarify its properties as drugs required that a permit application was submitted to the MPA. It was also
trial of a drug in the approved indication, with the approved dosage and approved of administration when the purpose was to further elucidate the efficacy and / or safety. Clinical trials of drugs would be planned, performed, recorded and reported in accordance with international demands on ethical and scientific standards. This is to ensure rights, safety and well being of those participating in a drug trial to trial or patients and to ensure the reliability of results. principles of GCP (Good Clinical Practice, GCP according to ICH, the International Conference on Harmonisation and then in 2015 the International Council for Harmonisation) and the Declaration of Helsinki would be applied. The prerequisite for conducting a clinical trial was to state was released by the FDA and that the approval was given by the ethics board. If in doubt for authorization of a clinical trial was needed, stated that the MPA should be consulted.

The regulations also pointed out that when a patient is taken care of in the context of a clinical drug trial should the rules that apply for medical application.

8:11 Drug Administration regulations (LVFS 2011: 19) on the clinical drug trials on humans

The regulations came into force on 1 February 2012 and supplemented by a guide. The Constitutiondefines clinical trial as "any investigation in humans to determine or verify the clinical, pharmacological or pharmacodynamic effects of one or more investigational medicinal products, to identify the side effects of one or more investigational medicinal or to study absorption, distribution, metabolism and excretion of one or more IMPs, in order to ensure the drug safety or efficacy. "

In clinical drug trials, the principles of good clinical practice in accordance with ICH and the latest Declaration of Helsinki on Ethical Principles for Medical Research on Humans applied. One prerequisite for a proposed clinical trial will get implemented, is that the there are conditions that lead to results that can be evaluated, and that there are sufficient and adequate pharmaceutical, non-clinical and clinical data on the investigational

medicinal product. In addition to permission from the Medical Products Agency also requires ethics approval from the regional ethical review board to get start a clinical trial.

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8:12 Drug Administration regulations (LVFS 2011: 3) on medicines covered by the exemption hospital

The provisions on hospital exemptions are contained in EU Regulation 1394/2007 on medicinal Advanced therapy, which applies as law in the EU since December 30, 2008, and the Medicines Act. The definition of 'hospital exemption and the provisions on state etc. was the Medicines Act Since 1 May 2011, while the regulations, which took effect a month later, contains provisions on the content of the application, labeling, security monitoring, etc. Hospitals exception means in brief that the health service has the ability to use advanced therapy medicinal products, even if the drug has not been tested or approved in the EU. It must then move to custom products prepared in a non routine manner individual patient under a physician exclusive responsibility. For these advanced therapies requiring that the MPA has granted especially the manufacturing authorization for medicinal products covered by the exemption hospitals, where, among other things traceability, safety supervision and motivation for seeking treatment therapy or treatment apparent.

There are no exceptions in the Medicines Act for the "last halmstråets principle" treatment for humanitarian reasons, vital indication or the like. During a transitional period until 31 October 2011, came to therapy products, used since a long time back and the activity in question was known by managers in health care and the authorities could be considered "lawfully on the market" in Sweden.

Systematic evaluation of a medicinal product covered by the provisions on hospital exemptions, ie research aimed at studying the efficacy or safety of humans, however, requires MPA's authorization of a clinical drug trial. The trial then need to be approved of the regional ethical review board.

8:13 Tissues and Cells

Acquis on tissues and cells is based on EU Directive 2004/23 / EC fixing quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. The Directive has been implemented in Swedish law by Act (2008: 286) on the quality and safety standards for handling human tissues and cells. The Act contains provisions mainly on quality and safety in such handling intended for human use. The law aims to protect human health. Act is not applicable for research involving human tissues and cells used for purposes other than use in humans. The directive is also incorporated by the regulations and general advice National Board (SOSFS 2009: 31 and SOSFS 2009: 32) and MPA (LVFS 2008: 12).

By "tissue" means all constituent parts of the human body formed by cells. With "Cells" means individual human cells or a collection of human cells, which are not linked any form of connective tissue. Stem cells are therefore covered by the legislation. In addition, the pharmaceutical legislation observed when cells are essentially manipulated or used for other function than the main body (Regulation (EU) 1394/2007).

The law applicable to the activities of tissue establishments such as biobanks or laboratories in health care. With a tissue establishment referred institution where natural or legal personal conduct operations that include testing, processing, preservation, storage or distribution of human tissues or cells intended for human use or manufacture of medicinal products for human use. The operation may also include procurement, import or export of human tissues or cells.

Anyone who runs a tissue establishment must have a permit. MPA issues permits To run a tissue when handling related to human tissues and cells should be manufacture of pharmaceuticals. IVO is the licensing and regulatory authority when tissues and cells to be used on humans for purposes other than pharmaceutical manufacturing.

There are two exceptions where the law does not apply. The one exception is when the tissues and cells removed from and applied in the same person at the same surgical procedure which is interpreted as the procurement and transplantation takes place without the surgery can be considered closed in between. The second exception is when management intends organs or parts of organs to be

used for the same purpose as the entire organ in the human body, which means that the law does not apply where the intention is that an entire organ is transplanted to a human or when a part of an organ transplanted to use the whole body. The exemptions do not apply when the tissues and cells classified as medicinal products (Regulation (EU) 1394/2007).

Karolinska University Hospital (Vecura and Tissue establishments in Clinical Immunology and transfusion medicine) had reportedly from IVO during years 2011-2013 authorized to conduct tissue establishment of the National Board, from June 1, 2013 from IVO. If stem cells are manipulated material or are intended for a different function than the original, cell therapy is defined as a drug under EU Regulation 1394/2007 on medicinal Advanced therapy.

8:14 acquis on medical devices

The provisions are essentially based on the EU medical device directive (1993/42 / EEC) as implemented in Swedish law by the lagen (1993: 584) concerning medical devices, Regulation same substance and Drug Administration regulations (LVFS 2003: 11) on medical devices. With a medical device referred to in the Act including a product according to the manufacturer task should be used, alone or in combination with others,

to the people detect, prevent, monitor, treat or alleviate a disease or injury, or compensate for an injury or a disability, and further examine, amend or replace the anatomy or a physiological process.

The synthetic trachea thus constituted a medical device. All medical devices which are custom made or intended for clinical trials / performance evaluation, should bear the CE mark when placed on the market. CE marking of a medical device means a declaration by the manufacturer that the product has the performance declared by the manufacturer and the product's clinical benefit is not disproportionate to its side effects when used for the intended purposes and in the prescribed manner. It is the manufacturer who is responsible for a medical device is safe and suitable for use as listed on the product label and in the instructions. The manufacturer shall ensure that the There is clinical data to support the product's alleged performance. Regarding the use of medical devices on the patient's health care must follow the National Board regulations (SOSFS 2008: 1) on the use of medical devices in health care. It states that health care should ensure that only safe and medical technology appropriate products are used. This means that the products will be used in the manner specified by the manufacturer in the information supplied with the product. The manufacturer is only responsible for the intended purpose and use, and can not take responsibility for healthcare choose to use the product for other purposes. That responsibility is incumbent when health care.

The CE mark does not mean that the product is approved by a authority. The basis for the CE marking must include a clinical evaluation. The evaluation shall be based the clinical data obtained from the relevant scientific literature and / or clinical trials. It does not require the approval of medical devices from the MPA or another authority's order for them to be placed on the market. This may occur when manufacturer assured that the product meets the requirements and CE-marked product. Regarding medical devices in higher risk categories, such as synthetic trachea, requires However, the so-called notified body verifies and certifies that products meet the requirements of the EU for the manufacturer to obtain CE-marking products and placing them on the market. these bodies constitute independent organizations in Sweden appointed by the Authority Swedac. Means have a obligation to inform the MPA.

Clinical trials of a medical device should only be carried out when the necessary data of product performance, safety and clinical benefit can not be achieved in any other way than to try the product in humans. At the same time that the clinical trial may be necessary regardless product risk classification. The type of medical device should, in this regulatory framework has undergone clinical testing before it could be approved (Class 3 product, the highest risk category when it was a question of a

implant). It would thus be evaluated for their purpose before it could be used.

In order to conduct a clinical trial requires that the manufacturer has notified the trial to MPA and that the work has not filed a prohibition against trial. The MPA oversees the

manufacturers and products on the market comply with the acquis requirement. To conduct the necessary controls, the MPA has the right to have the information and documents needed and obtain access to areas, premises and other areas where medical devices are available. Detected deficiencies have work great opportunities to intervene.

8.15 Several rules applicable

The synthetic trachea as such was a medical device but as the product must be seeded with bone marrow / stem cells modified to obtain the desired function, it became an advanced therapy medicinal products, in this case a so-called combination product of bone marrow cells / modified stem cells and medical devices. This triggers the requirement of clinical drug trial, where the application also needs to show that the medical device regulatory requirements are fulfilled. The requirement of hospitals except for the care or clinical trial research raised thereby. Whether operations accounted for care or research required in advance permission from the MPA based on the rules that the product is regarded as a drug Advanced therapy. Some permission of the MPA was not.

8:16 Nödrätt the Penal Code

The provisions on nödrätt (24 Ch. 4 § Penal Code) means that anyone who is in distress to avert danger to life, health, property or other important public policy of the protected interest under certain conditions can be free from liability even though the conduct may constitute crimes. The which is relevant in health care is primarily a danger to life and health. The action may not be unjustifiable in view of the nature of the danger, the harm done to another and the circumstances otherwise, meaning that the action must be proportionate to the danger that exists. For a nödhandling must be justifiable basically requires that the act is undertaken in distress should be called for by the interests of much greater importance than that which is sacrificed. Nödrätten should only applied in exceptional cases. At the planned medical interventions that are not immediately life threatening is this rule hardly applies.

Chapter 9 patient Safety

This chapter describes briefly the established methods and tools used or should used for patient safety work to produce results. This forms the background against which the current events should be assessed from a patient safety perspective; partly to understand how the able to take place and to draw lessons to prevent something similar happening again.

9.1 Introduction

Health care is a risky business for safety and health damage are not uncommon. 8.6 percent of all admissions in somatic inpatient care was judged to have caused damage, according to a survey by the National Board published in 2008 [1]. For about 3000

patients was a contributing factor to the death. Chapter 8 outlines the regulations that care has to relate to. The purpose of these laws and regulations is that care is as safe, effective and secure as possible.

To minimize the number of preventable adverse working for more than a decade all hospitals in country - more or less successfully - increasingly to structure patient safety. The work, however, has had limited success both in Sweden and internationally; still the proportion of preventable adverse unchanged high [2,3]. It is likely the best way to achieve a more secure Care is to create a proactive and flexible ("resilient") systems, where the holistic approach goes before individual mistakes and where responsiveness to security issues permeate the entire business.

At the end of each description of methods and tools to strengthen patient safety is a italicized note indicating the relevance to our investigation. Patient safety issues are also taken up in the analysis section of the report (Chapter 11).

9.2 Methods to strengthen patient safety

Organisation. The main strategy of the Karolinska University Hospital in recent years has been to achieve better patient safety, quality, cost and accessibility by focusing on patient flow and care chains. The basis for patient safety should be a clear vision from management that the number of health damage will be minimized. There should be written and the hospital well-known instructions on how the business should be organized so that it meets high patient safety and good quality care. Management's responsibility is to continually work to the system as a whole evolve to become patient-safe, robust and open to change regarding factors that may affect patient safety [4,5].

Karolinska University Hospital has documented how the patient safety work will be organized. It states inter alia that the hospital director to lead and follow up safety support the medical director, nursing director and operations manager. Resources will be allocated for knowledge and methodological and measurement methods for monitoring patient safety [6].

Business managers must have a clear mandate on how the patient safety process to be conducted and followed up, and involve employees in this work. The hospital has a staff of this; Headquarters Quality and patient safety, which is one of seven corporate units with administrative functions. One of the chief doctors are chief of staff and is in hospital management. It is this Staff's task to ensure that the practices in patient safety that are actually used and that adequate monitoring takes place. The hospital's patient safety efforts appear to be adequately organized.

Risk analysis.

The purpose of risk analysis is to evaluate the likelihood of adverse effects and their severity when introducing a new, untested elements in any part of the health care processes. It can for example be on a new approach, a new documentation tool, a new

drug or a new surgical technique. By using this structured model the caregiver can easily evaluate the suitability of a new approach before it is introduced [7].

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HTA - Health Technology assesment, or MTA - Medical Technology Assessment, is a more resource-intensive method that goes through and analyze all the underlying research and documentation. The idea is the same even if the methods differ. These types of assays needed at the hospital in the medical forefront as they have commissioned to develop new methods and contribute to research findings are translated into clinical practice. No formal risk analysis was done before the start of the operation to transplant synthetic trachea.

Deviation.

To open, early and consistent reporting deviations are possible method to prevent health damage repeated. This tool requires employee engagement and willingness to report adverse events. It requires several factors to this should lead to improvements: Openness in the organization with a permissive attitude toward criticism, feedback of deviations submitted and addressed, and that the most dangerous incidents identified.

Karolinska University Hospital has set the goal of a certain number of abnormalities per employee must be reported and this is measured annually. It is doubtful whether this is a measure of the quality in deviation management. There are risks that important, risky incidents drown in the mass of unspecific abnormalities. The recent years of patient research have questioned how effective The divergence is to increase patient safety [8.9]. The important thing is that events are relevant to patient safety be quickly identified, discussed openly and dealt [8.9].

Focus on errors, as well as measures in arrears, are likely to have limited effect on patient safety [9]. A hospital that strives to continuously secure care should instead focus on what goes well and implement proposals that promote secure processes. Such an approach means some extent a paradigm shift and places great demands on responsiveness and willingness to change within organization. This proactive approach is obviously not opposed to the deviations and medical injuries are reported and analyzed. In Macchiarinifallet has been reporting for the deviation not caught up some warning signals.

Lex Maria.

It is clearly regulated what should be reported in accordance with Lex Maria (see Chapter 8). Registration is such is not an end - that is how the caregiver handled the underlying event that is interesting from a security perspective. Inspectorate for Health Care (IVO) focuses most of the caregiver made an adequate investigation and proposed appropriate measures to prevent recurrence. The most important - and where it usually deficiencies -

is that the caregiver really implements its proposed measures, and that the hospital management follow up. If the caregiver (operations manager with the head doctor) does not follow the obligation to sign occurred, or at risk of serious, avoidable medical injuries breached an important part of the preventive security, not only on the current hospital but also in similar healthcare business
nationally.

As stated in Chapter 11, we believe that the lex Maria notification should have been made, at least when it for the third patient who was transplanted with synthetic trachea.

Event Analysis.

All Lex Maria cases will be analyzed by the caregiver - preferably under, the Model Event Analysis SKL designed [7]. Event analysis should also be carried out at needs when other fundamentally important deviations occurred that may affect patient safety. The aim is to understand why the incident occurred and propose measures to prevent similar incidents in the future. Moreover involve patient and family giving another dimension. It is important that the analysis performed soon after the incident and that it carried out an analysis leader who is trained in the methodology. No event analysis has been carried out in connection with transplants partly because lex Maria has not been reported.

Risk individuals.

It is clear from the Patient Safety Act to the caregiver (usually the business manager) must notify the so-called risk individuals to IVO (formerly the National Board) [10]. This notification obligation applies to licensed professionals, but also includes, for example, those that has a mandate to practice medicine. National Board examines foreign doctor's fitness before issuing permission to practice medicine. It is an urgent task because the deficiencies the skills, attitude, interpersonal skills or review can lead to very serious nursing injuries. These unfit people is obviously a potential danger to patients even in other health care providers. IVO must be aware of these individuals to examine their identification and skills. It is not enough redundancy or relocation because damage may occur elsewhere. Experience shows that, from patient safety can often take long time before the unsuitable persons are identified.

When the hospital well Macchiarini identified as risk individual was turned he from the operating business. No notification was not made to the National Board - on the contrary, sought hospital that hisauthorization to act as a doctor in Sweden to be extended. National Board granted the application.

Structured medical record review.

This means that a sample of admissions examined retrospectively in order to identify damage as the basis for development to improve patient safety (For example, the Global Trigger Tool, GGT or cursor-based medical record review (MJG), Karolinska University Hospital, uses). It can often be a effective tool in patient safety. This tool is not relevant in Macchiarinifallet.

Patient Case.

Patients and relatives often hear of a complaint either to the Director, Another director, Patient Board or IVO. These observations should be utilized as part of the improvement work to reduce the risk of health damage, whether it's about attitude or suspected malpractice.

There is a complaint of IVO concerning patient 3 and where the patient's father complained care after surgery [11].

Measurement of patient safety culture.

The single most important factor behind the long-term success patient safety work is that security awareness is always present at the hospital. High patient safety is not just the sum of the work of the various methods and tools as described above. In order that the risk of health damage, reduce management must at all levels actively encourage staff to talk about the risks, to discuss the causes occurred damages, and that the climate in the clinics is tolerant, unpretentious and focused on the patients.

Patient measurements should be performed in all hospitals. They provide a picture of employees' perceptions how patient safety is perceived in the hospital and in their own clinic. By follow the measurements regularly receive hospital management an idea of how the hospital development regarding patient safety. Different areas of improvement can be identified, such as the tendency to report deviations and feedback of the same, the managers' actions concerning patient safety issues, if the culture is permissive or guilt, cooperation issues between clinics, with more [12]. Lack of transparency when it comes to pointing out factual errors or security flaws involves a culture of silence that is harmful to the safety awareness, something that the hospital management in this case, identify.

Questions concerning patient safety culture is central to the operations of transplantation synthetic trachea was handled. Measurements of patient safety culture at the current clinics discussed below, and our estimates are presented in Chapter 11th Patient Dialogs and / or Patient Safety Rounds [13]. In order to evaluate and monitor up every clinic patient work, often carried out at major hospitals, regular meetings

which highlights how the clinic's current security work. This instrument provides hospital management and head doctors to improve and follow up clinics safety. The activities have flaws can get help and those who have a good work can serve as good example. Of

the hospital's Patient Safety 'report shows that there is an ambition to regularly use these models [6].

Other

There are several other areas that are important for patient safety but not have direct relevance to this investigation. These include questions about the place of treatment access, [14] HCAI, nursing quality and availability. Chapter 11 shows our estimates, from a patient perspective, the use of drugs, continuity of care and communication between care providers in connection with transplants [15,16].

9.3 Measurement of patient safety culture

Patient safety culture has been measured on the thorax clinic in 2010 and 2013 and the ENT clinic2011 and 2013 [17-20]. The following 15 sizes and two specific issues have been used in the evaluation:

- Propensity to report the incident
- Cumulative security awareness
- Self-perceived level of patient safety
- Number of reported anomalies
- Immediate superior action on patient safety
- Learning Organization
- Cooperation in the health care unit
- Openness in communication
- Reversal and communication on deviations
- A non-punitive and blaming culture where mistakes are made
- Workload and staffing
- Hospital management support for patient safety
- Collaboration between health care units
- Over Remains and transfers of patients and information between care units and between shifts
- Number of reported risks
- Information and support to patients and families at the negative event
- Information and support to staff at the negative event.

For each dimension is calculated an index value out of 0 to 100. The results shall be interpreted as Index values above 70 indicate that this dimension is functioning well. Index between 51 and 69 states improvement needs and the biggest improvement is the value when the index is 50 or less. We have, through hospital repeated measurements have been able to see change over time. We have compared results for Thoracic Surgery and ENT clinic with the average of national indices 2012-2014 (182 413 postal questionnaires, response rate 64.7 percent) [21].

ENT clinic comes under index number 50 in the following dimensions:

Dimensional Thoracic Surgery
2013 (2010)
ENT clinic
2013 (2011)
Mean nationally
index 2012-2014
Hospital management support to
patient safety
34 (39) 38 (41) 37
Information and support to staff
the negative event
- 64 (46) 62
Propensity to report
events
48 (43) 44 (47) 43
Cooperation between care units 45 (38) - 49
workload and
staffing
27 (43) - 44
Self-perceived level of patient 29 (44) - 53
A non-punitive and
blame culture
54 (49) - 61

In conclusion, is not one of the clinics of Index 70 in any of the dimensions except "Cooperation in the health care units" where the ENT clinic ports 85 in both measurements and Thoracic Surgery 77 (National Index 78). Measurements of the safety culture is not accurate, depending on a variety of possible sources of error. The differences are not statistically processed. The response rate has been remarkably low. This gives uncertain answers and can have several causes; it can, for example, indicate a lack of interest among employees patient safety issues. The measurement itself does not lead to improved patient safety but should be followed by analysis and dialogue. This is done both overall and at the clinical level, one can focus on the clinics and areas where improvement is particularly important position.

References

1. Socialstyrelsen. Vårdskador inom somatisk slutenvård. Stockholm. 2008.
2. Hollnagel E, Braithwaite J, Wears RLE. Resilient health care. Farnham, England, Ashgate Publishing Ltd.; 2015.
3. Vincent C, Aylin P, Franklin BD, Holmes A, Iskander S, Jacklin A, et al. Is health care getting safer? BMJ. 2008;337:a2426.
4. Kohn LT, Corrigan Janet M, Donaldson Molla S (eds). To Err Is Human. Building a Safer Health System. Washington, D.C., National Academy Press; 2000.
5. Lindh M, Sahlqvist L. Säker vård. Natur och kultur. 2012.
6. Patientsäkerhetsberättelse och Kvalitetsbokslut. Karolinska Universitetssjukhuset. 2015.
7. Handbok. Riskanalys och händelseanalys. Tredje reviderade upplagan: Sveriges kommuner och landsting; 2015.

8. Cook R. Sluta rapportera avvikelser. Läkartidningen 2013:13
9. Braithwaite J, Wears RL, Hollnagel E. Resilient health care: turning patient safety on its head. Int J Qual Health Care 2015;27:418-20.
10. Patientsäkerhetslag. SFS 2010:659. http://www.riksdagen.se/sv/dokument-lagar/dokument/svensk-forfattningssamling/patientsakerhetslag-2010659_sfs-2010-659
11. Telefonsamtal med Anders Haag, jurist, Inspektionen för vård och omsorg. 2016-04-01.
12. Att mäta patientsäkerhetskulturen. Handbok för patientsäkerhetsarbete. Sveriges kommuner och landsting. 2013.

13. Frankel A, Graydon-Baker E, Neppl C, Simmonds T, Gustafson M, Gandhi TK. Patient Safety Leadership WalkRounds. Jt Comm J Qual Saf. 2003;29:16-26.
14. Brezika T. Överbeläggningar och rapporterade skador i vården. Sammanställning och analys av rapportering inom slutenvården september 2012 till maj 2013. Patientsäkerhetsenheten, Hälso – och sjukvårdsavdelningen. Regionkansliet Västra Götalandsregionen. 2014.
15. Wallin CJ, Thor J. SBAR – modell för bättre kommunikation mellan vårdpersonal. Läkartidningen 2008:26
16. Woodhall LJ, Vertacnik L, McLaughlin M. Implementation of the SBAR communication technique in a tertiary center. J Emerg Nurs 2008;34:314
17. Patientsäkerhetsmätning 2011. Sammanfattande rapport ÖNH-kliniken. Institutet för kvalitetsindikatorer.
18. Patientsäkerhetsmätning 2013. Sammanfattande rapport ÖNH-kliniken. Institutet för kvalitetsindikatorer.
19. Patientsäkerhetsmätning 2010. Sammanfattande rapport thoraxkliniken. Institutet för kvalitetsindikatorer.
20. Patientsäkerhetsmätning 2013. Sammanfattande rapport thoraxkliniken. Institutet för kvalitetsindikatorer.
21. Nationell satsning för ökad patientsäkerhet. Patientsäkerhetskultur. Sammanställning på nationell nivå av landstingets mätningar 2012–2014. Sveriges kommuner och landsting. 2015.

Chapter 10 The hospital management Macchiarinifallet

10.1 Local regulations at Karolinska University Hospital and Stockholm County Council for the period 2011-2013

Within the framework of the investigation we have tried to get a picture of the local regulations that existed at Karolinska University Hospital and the Stockholm County Council (SCC) for the period 2011- 2013. It's about rules, procedures, guidelines, policy documents and the like that can have a bearing on Macchiarinifallet. For guidance on records management, we take up the document came in 2014 as it relates to the whistle-blower notification (see Chapter 6). At Karolinska Institutet's guidelines from 2006 to plan, execute and document clinical and epidemiological studies, but they contain nothing on patient safety [1].

10.1.1 Employment, delegation and decision-making

During the period 2010-2013 had been at the Karolinska University Hospital, a delegate and decision-making where five decision levels were specified:
1. Hospital Director;
2. Deputy Hospital Director;
3. Division and heads of staff;
4. Business managers;
5. First-line managers [2].

The was specified who had to take decisions, and if you had the right to delegate for categories community / customer (eg contract with SCC), employees (eg employment and approval of sideline) process / development (eg establishment of business plan), the economy (eg construction and renovation local) and regulatory decisions (eg decision not to provide official documents).

In April 2013 they had developed a work and delegation who replaced delegationsoch Decision Procedure by 2010 [3]. This document explicitly states who may decide what and if there is enforcement decision or whether it needs to be reported. You have chosen to share in decision areas in the categories procurement, sourcing decisions and call off the blanket, agreements, internal control and accountability, facilities, employees, government decisions and other.

Decision employment was the division manager in consultation with the HR manager and closest to the boss. This was an enforcement order which did not have to be reported to the hospital director or board.

Beyond these policy documents have annually been produced work and delegation of hospital director and the work plan for the hospital's board of [4-15]. Employment and delegation rules Hospital director about how and what the hen may delegate. Examples mentioned that the hospital director, in addition to being responsible for the ongoing management of the hospital affairs, also will follow the Board's guidelines and instructions. Further examples are that he should be primary executive representative of the hospital and protect its interests at key external contacts in important areas.

The Rules of Procedure of the hospital's Board of Directors stated that it is appointed by the County Council. To establish work and delegation for the hospital director and delegate decision-making powers to the hospital director can be mentioned among the board's duties. The Board has the right to co-opt members and in the years 2010 to 2013 was the then Deputy President of KI adjunct to Board.

Regulatory documents

Employment and delegation rules from 2015 for the hospital are basically structured in the same way Employment and the delegation scheme from 2013 [16]. Work and delegation for the hospital director and the work plan is updated annually. Starting in

January 2014 was appointed CI's Vice Rector as a board member of the county council and then replaced by the Vice Chancellor who was a director until his resignation in February, 2016. No replacement has not been appointed (July 2016).

10.1.2 Ethics policy and mission statement for the Ethical Council at hospital

Ethics and the art of being a human being is the title of the policy that has been at the Karolinska University Hospital since 2005 [17]. It is addressed to all employees at the hospital and

lift reason, conscience, empathy, ethical principles and standards as well as our fellow man as ethical tool to use to deal with ethical problems. At the hospital there is an Ethics Council. In 2006 it established a mission statement that applied until 2012 [18]. It says among other things that the Ethics Council is a hospital-wide group to give support and advice to the Karolinska University Hospital's medical director, management team and all activities. The mission statement of 2012 (still valid) has made some clarifications, For example, it has no decision-making function [19].

Regulatory documents

The Ethical Council in spring 2016 updated its mission statement. It is currently of the hospital's management team for approval and will then apply from in 2016.

10.1.3 Management of foreign patients

At the hospital there was a routine for foreign patients, routine management of elective care request for foreign patients, which was developed in 2007 and revised in 2010 [20]. It states that the Stockholm Care AB's hospital partners and the unit within the county who all elective care, channeled through. Other relevant documents are persons from other countries - Rules and contributions from the healthcare administrator in Stockholm County Council and Guide Caring for people from other countries, from Sweden's municipalities and county councils. [21]

Regulatory documents

People from other countries - Rules and fees from healthcare administrator in Stockholm County Council and the Care of people from other countries, from Sweden's municipalities and county, available in updated versions from 2016 and 2013, respectively [22,23].

10.1.4 Innovation Centre

To make it easier to bring together companies, researchers and clinicians have the Karolinska University Hospital created a special strategic function called Innovation

Centre [24]. Innovationsplatsen provides assistance with the structuring of cooperation, development of cooperation and external evaluation (audit). It is not mandatory for researchers, clinicians, or for companies to channel their cooperation through the Innovation Centre.

Innovation Centre was in operation during the years in transplants with synthetic trachea was performed at the hospital. Neither Macchiarini, the company HART or anyone else who was involved in transplant operations turned to the Innovation Centre in connection with transplantations. However conducted the evaluation meeting held when it was time not to extend Macchiarinis appointment (October 2013) to some extent, according to Innovation Site model of external evaluation. The hospital's Director of Innovation were present at the meeting. At the hospital, no guidelines for the application of new untested methods that are not subject Research.

10.1.5 Guidelines patient safety

2012 was taken at the hospital up guidelines for the deviation [25]. The guidelines included risk analysis, deviation, structured medical record review, event analysis, processing Lex Maria, ethical analysis and measurement of patient safety culture. Roles and responsibilities ready made for each process.

Regulatory documents

We have not been able to find any current overall guidelines. The document is being updated and is expected to be completed in autumn 2016. Guidelines for the management of Lex Maria has been updated [26]. At the hospital intranet Inside there is information on how to go about it when you want to report a deviation:
"In the first place you should turn to their immediate supervisor, another manager, or HR support within

organization. You can also use the system it happens for reporting deviations in health care. Incidentally, should always be used if it is about health abnormalities, environmental deviations or the working deviations. If you feel that you can not be open with their information, make use of the anonymous visselblåsarfunktionen. The service is managed by an external party, Whistleblowing Centre. There are guidelines and instructions for the service [27,28]. Visselblåsartjänsten is meant to be used when an employee suspects that someone, or some acting in a way that affects the hospital's operations. It may involve violations laws, regulations, guidelines at Karolinska or other governing documents.

An employee can For example, reporting on suspected economic crimes, corruption or serious forms of discrimination and harassment. If they move to a specific person may visselblåsartjänsten used only in the event that the person has a key position or is in the

leading position. "

Get notifications have been received via visselblåsartjänsten.

10.1.6 Guideline for accessing patient

What laws and regulations that govern what is permissible and impermissible access to medical record is gathered in a governing document that was produced in April 2014 [29]. Of relevance to whistle blowing DEVICES notification (Chapter 6), the following passage on the disclosure of patient information for research:
"A researcher employed by a health care provider and the assigned permissions to get EMR may access medical records for research purposes, provided that the relevant patients have expressly consented to access medical records for the researcher concerned and for that purpose. The patient's consent must be documented. without patient express consent, an employee's own access to the medical record system for research purposes is not allowed. "

10.1.7 Recruitment Procedures

We have been able to find any documented recruitment procedures for the period of Macchiarini hired. There was a process of recruitment which was revised in March 2011, was likely process is similar even earlier. [30]

Regulatory documents

The process of recruitment was revised again in 2015 and is the current document. [31] Infront of the introduction of the new operating model of the Karolinska University Hospital has also developed principles for recruiting managers [32].

10.2 Measures taken by the Karolinska University Hospital and Stockhoms County Council following the Macchiarinifallet

We have identified several steps the hospital has taken in response to Macchiarinis operations at the hospital.

10.2.1 Visselblåsarfunktion

The hospital director has introduced a web-based visselblåsarfunktion registering anonymously (See 10.1.5). Reports coming in are assessed by the medical director, the hospital lawyer and HR Manager. At the Stockholm County Council proposes, under a new policy and guidelines anti-corruption, an employee or elected in the first place should raise any suspicions if policy violations or these guidelines with their supervisor for further investigation. He will also always be able to contact the SCC Law for consultation and then have the right to remain anonymous.

Special procedures should be an independent inquiry. If there is the suspicion of bribery should the police be made. It appears that the case of a crime only against the new policy and these guidelines, employment law measures to be considered.

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This shall apply pending the new legislation. Decisions on policy and guidelines for anti-corruption to be in the County Council in the fall of 2016 [33].

10.2.2 Group to review the research at the Karolinska University Hospital

In the autumn of 2015 a working group was the hospital director and the acting principal at KI with the mission to establish guidelines for research at the hospital, developing support functions and to clarify responsibilities. The group consists of representatives from the hospital and KI, led by the hospital's medical director who is also the director of quality and patient safety [34].

10.2.3 Preparatory Committee for strategic recruitment

In 2015 was added to a hospital and KI joint review panel for strategic recruitment [35]. The background was that there was no long-term recruitment plan both KI and the hospital, and that there was no generic process leading to long decision times and unclear decisions. Group members are professors appointed in consultation with the principal and Hospital Director and with equal representation of the hospital and KI. With the evaluation panel is also HR representatives from both organizations. The purpose of the panel is that it should be a forum for dialogue between the two organizations regarding recruitment the combination of employees. The group will also work with:
- longterm planning
- Identification and prioritization of strategic recruitment needs
- To develop common recruitment plans based on retirements and the need to strengthen certain disciplines

The evaluation panel began its work on mapping all specialties and all combination services at Karolinska University Hospital.

10.2.4 Inventory of therapy where Paolo Macchiarini been involved

In April 2016 decided the head physician with the Hospital Director to all operations on the hospital would go through if it has been conducted treatments of patients where Paolo Macchiarini been involved. Analysis of the information obtained is still ongoing (see 3.3) but the hospital management have already decided that there should be an external investigation of the cases where it is suspected that patients have not had the benefit of interventions [36].

10.2.5 Informed consent from the patient to be in the media

During the period 2011-2013 were informed consent to be photographed or filmed not regulated to any significant extent. Today there is an indication of consent to photography and other recording with an accompanying consent form. The instructions refer to the Data Protection Act (1998: 204) [37]. 10.3 "marketing" of the operations

10.3.1 The first transplant

Our interviews have shown that Macchiarini was very active in their media contacts before the first transplant (patient 1). The hospital had given exclusive rights to BBC World Service, however, Macchiarini had also contacted other television companies. Chief doctor and hospital Press Officer averted television teams' presence during the operation and let the hospital's own unit Medical photo documenting the transplant. The BBC then got footage.

Four weeks after transplantation published the Karolinska University Hospital and Karolinska respective press release Macchiarinis first luftstrupstransplantation in Sweden. both described the operation as a historical and highlighted it as a last resort for the patient [38,39]. Trans-

plantation attracted much attention in the Swedish media. The Daily News described it as "The world's most advanced example of human spare parts" [40]. Although Macchiarinis previous surgeries around the world described. In the interview in Dagens Nyheter and Aftonbladet Macchiarini told about the benefits of the new technology, he said that the operation gave hope to millions of people in need of transplants. He spoke optimistically about future:
"We did this in a few months. Imagine what we can do in a few years" [39,40].

ENT clinic operations manager interviewed in the media. The hospital director abstained, according to their own reportedly because he generally distrusts care strategies based on a single person. The hospital press officer made a separate interview with Macchiarini. Patients were interviewed, among others, the BBC and the Swedish newspapers [39]:
"I was afraid, very afraid. But now I feel rescued, I am full of gratitude to all who made this possible. "

"The Icelandic doctors, sought hospital with more advanced thoracic surgery. Paolo Macchiarini was the only one who wanted to accept the challenge. "

When the patient eventually returned to Iceland, he became the subject of much attention in the media there. We have not been able to clarify on whose initiative this was done. Even his Icelandic doctors interviewed.

In November 2011, wrote the Karolinska University Hospital and Karolinska a joint press release the outcome of Macchiarinis first transplant in Sweden five months earlier. [39] The operation is described as a success:

"Five months after the transplant patient feel good and live a normal life. his throat has almost entirely been newly formed. [...] ... The body began to produce new stem cells that are in any way find graft and along with the stem cells from the transplant form new cells a new trachea. "

Ny Teknik wrote the same month of the first transplant patient [41]:
"His throat has virtually re-formed. The successful result has given patients throughout the world to seek out the Karolinska. "

We have not sought the source of the information. Karolinska Institutet described in 2012 transplants in very positive terms in a press interview with the Macchiarinis Philipp Jungebluth employee. The patient died 2 was, as Macchiarini said in a press release, to causes unrelated to the transplant to do [39].

Macchiarini was visited in 2012 by a journalist from the New York Times. he interviewed Macchiarini and the first transplant patient, which resulted in an article a very optimistic message about the future of transplants with synthetic organs [42].
The article said patient 15 months after the transplant:
"I was almost dead. There was suffering. A lot of suffering [...] I told him, I prefer to live three years and then die [...] I almost refused. It had only been done in pigs. But he convinced me in a very scientific way [...] Things are good, Life is much better "

NYT article also highlighted that used the patient's own stem cells from bone marrow. Here Macchiarini was more restrained. He said he was now to be convinced that the bone marrow cells died after only 2-3 days. But according to the story he thought that in dying released substances that signaled to other stem cells to seek out the trachea. In this way, the regenerative process started. In addition, he described the good function of the synthetic trachea, it was epitelbeklädd and bled (indicating vascular supply). There were no signs of infection and patient induced cough (a trachea of protection functions). In the article, was also described briefly Macchiarini had transplanted the second patient in Stockholm (which died after 4 months) and two patients in Russia.

10.3.2 The one-year anniversary in Iceland

In 2012, filled the University of Iceland 100 years, and they wanted to then pay attention to the one-year anniversary of

The transplant patient 1 has undergone since he was graduate student at the university. University involved patient 1's Icelandic doctor and KI. With the celebration were among others patient, Macchiarini, Icelandic doctor and a representative of Harvard Biosciences. On December 20, 2012 interviewed patient 1 of Icelandic television.

10.3.3 Other patients

The hospital has not gone out with the press information on patient 2 or 3. But Macchiarini and operations manager at the Department of Thoracic Surgery had agreed to let SVT filming the first transplantation of the patient 3. But because she was in a coma and could not give his permission, stopped filming by a joint decision of the three chief doctors [43]. They emphasized that filming just got done for the journal to document what happened during the operation. Patient 3 has subsequently attracted media attention in mainly negative context and not in the hospital initiative.

In connection with Macchiarini in February 2013, in the United States operated a 3 year old girl born without trachea, lifted the hospital until the first surgery at the Karolinska University Hospital successful and mentioned that one patient was perfectly healthy two years after surgery [44].

10.4 Hospital in media debate

10.4.1 The hospital positions

In connection with the notification to the IVO performed from the hospital side of SVT (January 2015) to transplantations have been done to save the lives of patients and the state is therefore not needed. [39]

In an article in Läkartidningen April 2015, reference was the hospital's attitude on the issue of state from the MPA [45]:
"KS has, however, claimed that it contacted the MPA before the first operation, and that there was a verbal assessment of the basis of the emergency situation, and the fact that conventional alternatives were lacking, it was up to the medical responsibility to assess whether there was scientific support to the patient would be offered an alternative treatment. "

The corresponding statement did Hospital in later statements, for example in connection to the Research Council in June 2015 stopped the disbursement of research funds to Macchiarinigruppen; when people talked about the vital indication [39].

At the press conference in August 2015, when KI's headmaster announced its decision to free Macchiarini from allegations of misconduct in research, also sat the hospital's head doctor on the podium. KI and the hospital felt it was important that both parties appeared united. The both went on line to the operations focused on healthcare and not research. Head doctor repeated the hospital's position [46]:
"Our position has always been that it is a matter of vital indication, it has been in life-saving purposes. There were no other treatment methods, and it was urgent. "

In September 2015, Johan wrote Thyberg, retired professor of cell and molecular biology at KI, a debate article in Dagens Medicin, where he went to hard attacks against the KI management to Macchiarini be exonerated from allegations of misconduct in research [47]. In the same article accused Thyberg hospital:
"As serious as the responsibilities KI is the guilt that rests at the Karolinska University Hospital. It has allowed a previously untried transplant method to get tested without

statutory state and later not even notified the cases in accordance with Lex Maria, in itself a flagrant violation of the law. "

KI's principal and hospital director was entered in Dagens Medicin [48]. They emphasized that patients' prognosis was very poor. Furthermore, they wrote about the need for research ethics review:
"It was not needed because the operations were performed as life-saving medical care, with an experimental technology because no established surgical techniques were possible. Decisions about surgery and

choice of technology was taken at Karolinska University Hospital. The surgeries were made in accordance with § 32 of the then Helsinki Declaration. "

When the Swedish newspaper Svenska Dagbladet in December 2015 raised the issue of transplants moved on research or care maintained one of the chief doctors of the hospital's view [49]:
"Karolinska asked by patients' treating physicians in each country. The operations was carried out on so-called vital indication, that is, in life saving purposes. Other treatment methods was completely exhausted. "

Asked whether they will operate more patients with the same method had been the chief doctor previously responded [46]:
"We will look further at this, together with KI. This is difficult, it is a gray area regarding experimental therapy and what is research and care. I think it's very important that there is transparency and clear checklists so that we all know what to do. "

10.4.2 Statements in connection with the television series experiments and then SVT's documentary

The experiments that were sent during the second half of January 2016 was strongly critical Macchiarini and his activities, both at KI at Karolinska University Hospital [50]. On programs followed a very public debate. Almost invariably posts were highly critical, not least in the media commentator field [51]. Much of the criticism was directed against KI, but also the hospital was severely questioned. The criticisms of the experiments and the subsequent debate followed a number of different tracks; some of the main themes in the criticism of the hospital was [50-52]:
• The transplants were performed without method was ready for use on patients. Among another missing animal.
• The transplants were moving on - or at least had an element of - clinical research. He thus had conducted experimental treatment without ethical review.
• Patients were not as severely ill and had not as bad as forecast Macchiarini and hospital alleged. Therefore it was not a matter of immediate life-saving treatment.
• At Karolinska University Hospital was known Macchiarinis transplant operations Russia and he had participated in (and been responsible for?) decision to transplant

Russian patients.

At least one of them was well worked before surgery and had a fairly benign luftstrupsskada. The transplant was not necessary and it led to her death, said the critics. In a press release commented hospital by one of the head doctors the information arrived in the experiments. The Principal said:
"The programs have brought a number of serious questions about Paolo Macchiarinis business and shown conditions is ethically indefensible. [...] The hospital must of course learn from it that has not worked and we are working on a new and clearer rules for operations with untested methods. We regret, for the three patients' sake, and for all other patients who would having a treatment of this kind, it is not proved effective as we hoped. For the Karolinska University Hospital part, it has not emerged to change our default regarding the three operations carried out with us [...]. They were made to the were no alternative treatments that could save the three patients' lives. "

The hospital also commented on the decision to operate the Icelandic patient and whether he really was sufficiently ill to undergo surgery with Paolo Macchiarinis untried method. IN press release maintained that it was a reasoned decision:
"Our assessment is that it was justified [...]. Surgical decision was preceded by a multidisciplinary conference, with representatives of various specialties, including the referring physician Iceland, and the assessment there were clear: the patient would have died if nothing was done, and there was no established treatment that could cure the patient. "

The media also came up the question why Macchiarini 2013 received his appointment at the hospital extended ("fired"). The hospital press officer commented [39]:

"The hospital had decided not to proceed with the operations, so his appointment was extended not. [...] The hospital decided that the result of them (Operations) was not satisfactory. "

In a press release at the beginning of February 2016 told the hospital that it would appoint a investigation to examine Macchiarinis operations at the hospital. The investigation would be led by Head doctor. Both external and internal experts would be involved. After criticism that the hospital to investigate its own activities announced Monday that it decided to consult an external investigator.

In late February 2016 interviewed the former hospital director of SVT's report on why none of Macchiarinis operations lex Maria was reported [39]. He was self-critical and mean that in hindsight should the third operation have led to a notification. It would, according to themformer hospital director, could lead to a critical external IVO-examination of at least the operation.

The former hospital director also interviewed in Dagens Medicin in March 2016 [53]. The article focused mainly on how it was when Macchiarinis appointment at the hospital not renewed by the end of 2013. The hospital director told me that there was a lot of pressure from KI management to extend Macchiarinis employment. But he had come to the realization that Macchiarini was not a doctor who took the hospital - other doctors were taking care of the complications after his surgery and he did not keep to the hospital's regulations for foreign patients.

The hospital director had perceived transplants care, not research. Since a number of experts were engaged in operational decisions, he had assumed that the method was tested in animal experiments. As in Report interview, he felt that a lex Maria notification should have been made Patient 3.

10.4.3 wider public debate

The public debate surrounding Macchiarini has followed many trails. Several of them have acted on the concrete issues raised in this report, such an acclaimed article Daily News entitled "The bloodied physician societies" [54].

Other contributions to the debate have been global in nature and moved such issues of principle in Clinical Research Vs. medical care [55], that KI's lack of academic culture would be the fundamental problem [56], that ethics education at KI is flawed [57], the requirements of professional medic inet technician should be reviewed [58] and that practical philosophy is miserable [59], especially when the utilitarian orientation [57].

It has been proposed to set up an ethical review system for human studies that do not covered by the Ethical Review Act [60]. An investigation conducted by the Swedish Society of Medicine and Royal Swedish Academy of Sciences has proposed guidelines for the use of unproven therapies of seriously ill patients, and a national committee for the assessment of such methods [61].

There are commentators who have gone so far as to compare Macchiarinis activities experiments during the Nazi era. A leading radio columnist has spoken of "star surgeon with Karolinska Institutet's reputation and blessing in the back had to play doctor Mengele "[62]. DN Chief Editor's thinking along the same lines [63]. Others have objected that such parallels are unreasonable. Partly devalue the Nazi moral crimes and sets the wrong diagnosis of what went wrong at Karolinska University Hospital. It was not a question of evil, and Macchiarinis his collaborators aim still was to save life [64].

The hospital has not participated in the public debate on these broader aspects of Macchiarinifallet.

10.4.4 notifications against Macchiarini

In December 2014 wrote Läkartidningen the notification of misconduct in research previously received during the year to KI against Macchiarini from four doctors at the

hospital [65]. Mention Also the hospital was investigating if the notifying doctors guilty of hacking. The news

received international attention including the New York Times ("Leading Surgeon Is Accused of Misconduct in Experimental Transplant Operations ") and Nature (" Artificial tracheas during scrutiny ") [66,67] (see also section 6.3). In April 2015, the media reported that doctors sagging warning from the hospital despite the fact that from the hospital Page concluded that they lacked qualified support to collect log data items.

In TV series experiments (January 2016) spoke of the notifying physicians [50]:
"We were first informed that we would be reported to the police and then it was changed to that we would get gravest warning can be obtained from the hospital, from our own operations manager. "

Also, the hospital took in its press release in connection with the experiments up to the fact that notifying doctors threatened with a written warning. The hospital said that we had to investigate journal terminals because they involved extensive deviations from the rules. But because the purpose was so clearly plenty refrained hospital from a warning (see section 6.3).

Macchiarinis statements. Macchiarini does not have its own opinion articles, but for TV series The experiments he performed his comments in interviews in the News (SVT) [68] and Läkartidningen [69]. The interviews were based on a written report in which they responded Macchiarini allegations against him. [70]

In interviews and background document Macchiarini told about how the recruitment to KI went through the background to the transplants. According to Medical News article, he stressed that there were "hundreds of articles on large animal studies of transplants with synthetic windpipe."

He stressed that there was sufficient knowledge of the materials used in the first luftstrupstransplantationen concerning biocompatibility, biotoxicity, sterility, adhesion of cells and manufacturing. He also emphasized that the patient was very ill, that time was very scarce and that a multidisciplinary team was behind the decision to operate.

According Macchiarini was more than 30 people from both KI and the hospital involved in the decision to transplant. Even his transplantations in Russia was raised in the interviews. Here referred to Macchiarini pending litigation. But he mentioned that both KI Karolinska University Hospital participated in the decision of the transplants in Krasnodar.

When Läkartidningen journalist asked about the results of the transplants with synthetic trachea (according to journalist was 6 of 8 patients as dead) stressed Macchiarini that not all died of causes related to transplants. He emphasized the need for clinical trials and

mentioned that other researchers initiated studies in the US and the UK with a technique similar the one he used.

In a memo commented on the four physicians in 2014 reported Macchiarini of research misconduct detail Macchiarinis interview in the News [71]. They gave a number of examples to support the transplant operation was experimentally. They also stressed that Macchiarinis statements Animal experimental data were wrong and queried the assertion that the synthetic material had undergone extensive testing. Furthermore, they criticized what Macchiarini said about how seriously ill patients and their prognosis was. They considered that Macchiarini was wrong when he said that there was the required permits and when he pleaded began clinical trials.

10.4.5 Internal information

Internally within the hospital have been reported and commented as registration of misconduct in the research came when KI's principal Macchiarini acquitted of the charges and when SVT sent a critical mission audit program. In connection with the television documentary experiments was broadcast in January 2016 put out a text on the hospital's intranet where the message was: "We consider Still, despite the harrowing scenes from Russia, that what we said about the three operations with us, we defend, it has been life-saving purposes when there have been other options."

References

1. Guidelines for planning, conducting and documenting clinical and epidemiological research. In. Karolinska institutet; 2006.
2. Delegations- och beslutsordning för Karolinska Universitetssjukhuset. Kshd 11/2010. 2010-06-24.
3. Arbets- och delegationsordning för Karolinska Universitetssjukhuset. Kshd 15/2013. 2013-04-30.
4. Instruktion för sjukhusdirektören Karolinska Universitetssjukhuset. 2010-04-27.
5. Instruktion för sjukhusdirektören Karolinska Universitetssjukhuset. 2011-04-20.
6. Arbets- och delegationsordning sjukhusdirektör Karolinska Universitetssjukhuset. 2012-03-22.
7. Arbets- och delegationsordning sjukhusdirektör Karolinska Universitetssjukhuset. 2013-03-21.
8. Arbets- och delegationsordning sjukhusdirektör Karolinska Universitetssjukhuset. 2014-03-27.
9. Arbets- och delegationsordning sjukhusdirektör Karolinska Universitetssjukhuset. 2015-04-24.
10. Arbetsordning styrelsen Karolinska Universitetssjukhuset. 2010-04-27.
11. Arbetsordning styrelsen Karolinska Universitetssjukhuset. 2011-04-20.
12. Arbetsordning styrelsen Karolinska Universitetssjukhuset. 2012-03-22.
13. Arbetsordning styrelsen Karolinska Universitetssjukhuset. 2013-03-21.
14. Arbetsordning styrelsen Karolinska Universitetssjukhuset. 2014-03-27.
15. Arbetsordning styrelsen Karolinska Universitetssjukhuset. 2015-03-18.
16. Arbets- och delegationsordning Karolinska Universitetssjukhuset. K1254-2015. 2015-05-07.
17. Etik och konsten att vara en medmänniska. Etikpolicy. Karolinska Universitetssjukhuset. 2005.
18. Uppdragsbeskrivning för Etikrådet vid Karolinska Universitetssjukhuset. 2006-06-21.
19. Uppdragsbeskrivning för Etikrådet vid Karolinska Universitetssjukhuset. 2012-09-14.
20. Rutin för hantering av elektiv vårdförfrågan för utlandspatienter, Patientavgiftssektionen. Karolinska Universitetssjukhuset; 2010.
21. Vård av personer från andra länder. Femte omarbetade upplagan ed, Sveriges kommuner och landsting; 2010.

22. Vård av personer från andra länder. Sjätte omarbetade upplagan ed, Sveriges kommuner och landsting; 2013.
23. Personer från andra länder - regler och avgifter. Hälso- och sjukvårdsförvaltningen, Stockholms läns landsting; 2016.
24. Karolinska Universitetssjukhuset. Innovationsplatsen. http://www.karolinska.se/innovationsplatsen.
25. Riktlinjer för avvikelshanteringsprocessen. Karolinska Universitetssjukhuset, Kavlitet och patientsäkerhet; 2012.
26. Hantering och ansvarsfördelning vid anmälan av allvarliga vårdavvikelser enligt lex Maria, riktlinje. Karolinska Universitetssjukhuset, Kvalitet och patientsäkerhet; 2016.
27. Riktlinje för visselblåsning. Karolinska Universitetssjukhuset, Kommunikationsavdelningen; 2015.
28. Anvisningar för hantering av ärenden i tjänsten WhistleB. Karolinska Universitetssjukhuset, Kansliavdelningen; 2016.
29. Riktlinje för åtkomst till patientjournal, 2014-04-29, Dokumentnr STAB0952. Kvalitet och patientsäkerhet, Karolinska Universitetssjukhuset; 2014.
30. Process för rekrytering. Karolinska Universitetssjukhuset. 2011-03-11.
31. Process för rekrytering. Karolinska Universitetssjukhuset. Reviderad 2015-02-10.
32. Principer för chefsrekrytering. Karolinska Universitetssjukhuset. 2016-01-20.

33. Mejl till utredningen från Anne Rundquist, chefsjurist Stockholms läns landsting. 2016-05-03.
34. Uppdrag för arbetsgruppen ”Forskning vid Karolinska Universitetssjukhuset”. 2016.
35. Beredningsgrupp för strategiska rekryteringar. Karolinska Institutet och Karolinska Universitetssjukhuset. Bakgrund och funktion. Powerpoint till utredningen från FoU-direktör Karolinska Universtitetssjukhuset. 2016-05-06.
36. Telefonsamtal med chefläkare på Karolinska Universitetssjukhuset ang inventering av Macchiarinis verksamhet. 2016.
37. Anvisning för samtycke till fotografering och/eller annan inspelning. Karolinska Universitetssjukhuset.
38. First Successful Transplantation of a Synthetic Tissue Engineered Windpipe. Pressmeddelande Karolinska Universitetssjukhuset. 2011-07-07.
39. PM Mediesammanställning: Karolinska Universitetssjukhuset och Paolo Macchiarini.
40. Han är först i världen att få en ”odlad” luftstrupe, Dagens Nyheter 2011-07-08. http://www.dn.se/nyheter/han-ar-forst-i-varlden-att-fa-en-odlad-luftstrupe/.
41. Karlsson-Olofsson U. Stamceller och nanofibrer räddar livet på cancersjuk. Ny Teknik 2011-11-24. http://www.nyteknik.se/innovation/stamceller-och-nanofibrer-raddar-livet-pa-cancersjuk-6336126.
42. Fountain H. A first: Organs tailor-made with body’s own cells. New York Times 2012-09-15.
43. Mejlkorrespondens mellan Macchiarini, verksamhetschefen på thoraxkliniken och presschefen
vid Karolinska Universitetssjukhuset 2012-07-31--08-01.
44. Karlsson-Olofsson U. Odlad luftstrupe räddade livet. Ny Teknik 2013-04-30. http://www.nyteknik.se/industri/odlad-luftstrupe-raddade-livet-6336121.
45. Lövtrup M. Klinik såg att metoden inte fungerade – stoppade operationerna i det tysta. Läkartidningen 2015;112:DI7A.
46. Konflikt om KI-kirurg trappas upp: ”Skandal”. Svenska Dagbladet 2015-08-31. http://www.svd.se/konflikt-om-ki-kirurg-trappas-upp.
47. Thyberg J. ”Att KI-kirurgen frias av rektor är en sällan skådad skandal”. Dagens Medicin 2015-09-09, http://www.dagensmedicin.se/artiklar/2015/09/09/att-ki-kirurgen-frias-av-rektor-aren-sallan-skadad-skandal/.
48. Hamsten A, Samsom M. ”Vårt beslut vilar på saklig grund”. Dagens Medicin 2015-09-16. http://www.dagensmedicin.se/artiklar/2015/09/16/vart-beslut-vilar-pa-saklig-grund/.
49. Leijonhufvud: KI-operationer är sannolikt forskning. Svenska Dagbladet 2015-12-16. http://www.svd.se/leijonhufvud-ki-operationer-ar-sannolikt-forskning.
50. SVT Dokument inifrån. Experimenten. http://www.svt.se/dokument-inifran/experimenten-stjarnkirurgen, http://www.svt.se/dokument-inifran/se-program/dokument-inifran-experimenten-

avsnitt-2, http://www.svt.se/dokument-inifran/se-program/dokument-inifran-experimenten-sanningens-labyrint.
51. Lundälv J. Macchiariniaffären och primum non nocere. En mediestudie om reflekterande forskare och läkare i tre medicinska tidskrifter. Svensk Kirurgi 2016;74:124-127.
52. Risberg B. Karolinska är etikens Tjernobyl. Läkartidningen 2016;113:DWWE.
53. Dagens Medicin. Han vägrade att förlänga Macchiarinis anställning. 2016-03-17. http://www.dagensmedicin.se/artiklar/2016/03/17/han-vagrade-att-forlanga-macchiarinis-anstallning/ .
54. Kjöller H. I nedblodade läkares sällskap. Ledare. Dagens Nyheter. 2016-05-31. http://www.dn.se/ledare/signerat/hanne-kjoller-i-nedblodade-lakares-sallskap/ .
55. Broström L. Karolinska blandar bort korten om fuskanklagelse, Dagens Medicin 2015-09-23, http://www.dagensmedicin.se/artiklar/2015/09/23/karolinska-blandar-bort-korten-om-fuskanklagelse/ .

56. Tännsjö T. ”KI har bländats av Nobelpriset och saknar akademisk kultur”, Dagens Nyheter 2016-02-12. http://www.dn.se/debatt/ki-har-blandats-av-nobelpriset-och-saknar-akademisk-kultur/ .
57. Frostegård J. Därför är den medicinska etiken på KI bristfällig. Dagens Nyheter 2016-02-19. http://www.dn.se/kultur-noje/kulturdebatt/darfor-ar-den-medicinska-etiken-pa-ki-bristfallig/ .
58. Ludvigsson J. Fakulteterna bör granska kraven på professionella medicinetiker. Läkartidningen 2016;113:DYPP.
59. Ruin H. Den praktiska filosofins elände. Svenska Dagbladet 2016-02-26. http://www.dn.se/kultur-noje/kulturdebatt/den-praktiska-filosofins-elande/ .
60. Wallerstedt S. Oredlighetsfallet vid KI och behovet av etisk granskning: Forskarsamhället har ett medansvar. Läkartidningen 2016;113:451.
61. Kungliga Vetenskapsakademin, Svenska Läkaresällskapet. Rapport: Kliniska riktlinjer för användning av obeprövade behandlingsmetoder på allvarligt sjuka patienter. http://www.kva.se/globalassets/vetenskap_samhallet/halsa/2016/rapport-etikutredning.pdf .
62. Godmorgon världen! (Sveriges Radio). Göran Rosenbergs krönika om KI-kirurgen som lekte Mengele. 2016-02-11.
63. Wolodarski P. Människan utnyttjad i hennes svagaste tillstånd, Dagens Nyheter 2016-02-13. http://www.dn.se/nyheter/peter-wolodarski-manniskan-utnyttjad-i-hennes-svagaste-tillstand/ .
64. Kraulis P. Nej, Macchiarini är ingen Mengele. Det är värre än så. 2016-02-14. https://kraulis.wordpress.com/2016/02/14/nej-macchiarini-ar-ingen-mengele-det-ar-varre-an-sa .
65. Lövtrup M. Fuskanklagelser efter världsunik operation på Karolinska. Läkartidningen, 2014;111:DAML.
66. Leading Surgeon Is Accused of Misconduct in Experimental Transplant Operations. New York Times 2014-11-24.
67. Cyranoski D. Investigations launched into artificial tracheas. Nature 2014;516:16-7.
68. SVT Nyheter. Macchiarini fortsätter hävda sin oskuld. 2016-05-04. http://www.svt.se/nyheter/inrikes/macchiarini-fortsatter-havda-sin-oskuld .
69. Lövtrup M. Första stora intervjun efter tystnaden. Paolo Macchiarini tror fortfarande på sin metod. Läkartidningen 2016;113:D3TY.
70. Macchiarini P. Memorandum: Background to my recruitment at KI 2016.
71. PM. Referenser och kommentarer till “Transcription of the Interview with Paolo Macchiarini in the Swedish News Program Aktuellt on May 4, 2016.”

Chapter 11. Analysis and summary assessments

11.1 The basis for our analyses

In today's discussions in Macchiarinifallet dominate hindsight. With hindsight, some of what happened seem unreasonable, almost absurd. Also when it comes to our analyzes and assessments there has been a clear risk that they would be characterized by hindsight.

But if we want to learn something from Macchiarinifallet, we need to describe not only what happened, but also try to get an insight into how it could happen.

Therefore, we have, as far as possible, in our analyzes assumed the situation when various decisions were taken - when Macchiarini employee, when you decided to transplant when Macchiarinis employment at the hospital was closed, etc. What considerations were made when you took decision? What was the basis? What was the state of knowledge? How did you feel to the regulatory framework there were at that particular time? How reasoned husband? What was reasonable to expect of health professionals and decision makers at the time?

There, our analysis is based more on what we know today than in the situation when events occurred, we have in the text particularly mentioned it.

11.2 Macchiarinis employment at the hospital

11.2.1 Strategic investments

summary assessment

The appointment of Macchiarini at Karolinska Hospital and was part of a coherent strategy to build a center for advanced airway surgery. Macchiarini was covered by the international media as one of the world's leading surgeons. In his personal and his activities were positively charged concepts such as "translational research", "regenerative medicine "," stem cells, "" Nanotechnology "," international leader "and" star surgeon ". It is easy to comprehend that the overall concept around the recruitment of Macchiarini seemed very attractive and visionary.

At senior management level seems the enthusiasm for Macchiarini have been significantly higher in CI than on the hospital side, but both at the clinic and at KI were high expectations that he would very soon get started with luftstrupstransplantationer. This may have contributed to excessively fast decisions about how Macchiarini and was hired.

Although we in this report finds multiple system failures that may have contributed to Macchiarinifallet developed as it did, it could not be taken to mean that more generally impose direction to Swedish clinical research recruit top international forces.

The appointment of Macchiarini at Karolinska Institutet and Karolinska University Hospital were included in a clear strategy to build a center for advanced airway surgery (Chapter 3). Macchiarinis large international network would ensure that the center received a leading international position. You also assessed that there was clear potential synergies with KI's successful experimental research in regenerative medicine. Macchiarini would become a central figure who bridged over from the successful basic research to clinical applications. Economically made KI and Karolinska University Hospital very large strategic investments in the area regenerative medicine and Macchiarini and his team. He also had large research grants inter alia, the Swedish

Research Council and the EU.

Macchiarini came to KI and the hospital at a time when there were very powerful research policy support to recruit excellent researchers from other countries. In Macchiarini and His activities were the same person and the same concept positively charged

concepts such as "translational research", "regenerative medicine", "stem cells," "Nanotechnology", "international leading "and" star surgeon ". It is easy to comprehend that the overall concept around recruitment of Macchiarini seemed very attractive and visionary. At senior management level seems enthusiasm have been significantly higher in CI than on the hospital side.

Macchiarinis good international reputation illustrated by him (after he was hired in Stockholm) was listed as one of the world's 20 most innovative surgeons are now living on an American website [1]. Time Magazine placed Macchiarinis luftstrupstransplantationer on its top- 10 list of current medical breakthrough [2].

We believe that Macchiarinifallet can not be taken as evidence that more generally condemn direction to recruit top international forces in clinical research. The case shows, however, that the recruitment must be particularly careful, because it is not just about academic excellence, but also about the ability to work as a doctor in a Swedish context. If it thereof These are a key person in a clinical front line area must be extra carefully insure that person is the right one.

The expectations were very high, as shown by the letter in June 2010 to KI's recruitment committee from 14 signatories. It was estimated to be up and running with a working regenerative airway transplant operations within three months after the Macchiarini employed at Hospital [3]. After the first transplant was carried out well, it seemed as if time were running out - there had been more than six months ago Macchiarini hired. It is very likely the high expectations of rapid results from KI and clinic lines and from Macchiarini himself, helped to took fast - too fast, it would appear - a decision on the two first transplants. In this rapid process was patient safety issues in the background.

11.2.2 Recruitment

summary assessment

In recruiting judged Macchiarini be a technically skilled surgeon. We have not encountered any information to the contrary. However, there was before appointment signals a lack of qualities as a surgeon in other respects, especially when it came indication positions, ie which types of operations performed on the patients.

From the hospital side were no own references Macchiarinis clinical merits until a very late stage of the recruitment process. The warning signs came when suppressed. pressures KI and some time pressure seems to have contributed to Macchiarini hired as chief despite strong negative signals from his earlier clinical staff. In the hospital's time-pressed hiring process was patient safety issues in the background.

To Macchiarini employee at a clinic but came to have large parts of their surgical operations at another clinic contributed to unclear responsibilities. The hospital does not seem to have had enough control over Macchiarinis activities abroad.

Reference checking. We take this up only the references concerning Macchiarinis clinical merit. His academic credentials and references have been investigated by Sten Heckscher and employees. In chapter 3 we described how Macchiarini at enrollment was surrounded by an international reputation as an innovative and technologically highly skilled surgeon, an impression that was reinforced at Initial reference deletion. His luftstrupstransplantation in Barcelona in 2008 had been widely attention in the scientific literature and in the media. Before he was hired, he had "Guest surgery" at the ENT Clinic and gave the impression that the surgeon be technically driven. In the early stages of the recruitment process had not revealed any warning. However, we have not been able to find that one of the hospital side took their own references Macchiarinis clinical merits in the earlier stages of recruitment. The recruitment process was far

advanced when a new clinic director took the ENT clinic in September 2010. He contacted a clinical fellow in Barcelona and then received strong critical reviews Macchiarini (Chapter 3).

We find that the reference-taking when it comes Macchiarinis clinical merits, medical judgment and interpersonal skills have not followed the order you usually apply when adding Chief of the Swedish healthcare. Technical skills gained in Macchiarinis cases completely overshadow the shortcomings regarding other clinical qualities that came to light at the reference shooting at a late stage of recruitment process.

Two people had the formal responsibility for Macchiarinis part-time employment at the hospital: the newly appointed operations manager at the ENT clinic (who signed employment) and the hospital director (Which signed an agreement with KI on hiring Macchiarini).

Management of warning signs. At the time of employment was thus Macchiarinis very clear warning signs. They came from former employers and colleagues in Italy, Spain and Germany. At KI side reached the Prefect and Rector (CI's handling of the warning signals investigated by Sten Heckscher and employees). The newly appointed operations manager of ENT clinic took as mentioned above have a reference that was unequivocally negative.

Despite the unfavorable clinical references operations manager got and despite his great doubt he still with that Macchiarini was employed as chief physician at the clinic. This was probably due to the recruitment process has already come a long way when operations manager took and the pressure exerted by the KI side. We have no evidence that the hospital director reached by some negative signals about Macchiarini when he signed 2010-10-07 agreement between KI and hospital employing Macchiarini - this was in accordance with line responsibility where the recruitment of employees normally clinic task.

Together with representatives of KI took the business into a complementary reference from regional president of Tuscany, where he spoke about Macchiarini was the victim of contradictions Faculty of Medicine in Florence and a media campaign. The statement did not address how Macchiarini worked in clinical work. It seems strange that the hospital and KI turned to a region president of the new reference, when it was Macchiarinis clinical operations who had been questioned.

It is obvious that the serious warning signals reached KI at several levels of management and management ENT clinic but that dismissed them when you got at least one more positive reference. This reflects, in our view, a questionable view of the referees - it can not a matter of finding a favorable reference when reached by several negative reviews.

Our the impression is that the KI side was so focused on recruiting Macchiarini that it took too easy on the warning signals and that exerted strong pressure on the hospital to combine a job KI with a medical service of part-time at the hospital. This course not absolve the hospital from the responsibility of Macchiarini hired as a consultant.

Clinical placement. Macchiarini regarded as a prestigious top recruiting when he came KI and Karolinska University Hospital. The strategy to build a center for regenerative Medicine concluded that the operation would be located in Huddinge, where much of the experimental activities conducted and there would be opportunities for cooperation with Huddinge reputed transplant operations in other areas. Although was Macchiarini thoracic surgeon determined that he would have his academic and clinical placement to ENT unit at KI and the ENT clinic at Huddinge (thoracic clinic is located in Solna).

We perceive that the KI management was proactive in this decision - for the reasons we have not been able clarify wanted to avoid that, he was employed at the Department of Thoracic Surgery. It was considered not Macchiarini largely would become effective on another clinic than he was employed at, and that this could lead to complications in terms both the liability issues that follow-up and continuity of care. There were, not unexpectedly, a Some discussions about ENT clinic should be able to receive financial compensation when Thoracic Surgery exploited Macchiarinis surgical services.
Clinic Management at the ENT clinic was aware that Macchiarini had clinical activity abroad parallel with employment at the clinic - in fact this was part of the strategy

to build an international network. We have yet realized that they had only vague notions what activities in the other countries involved and that it had sufficient control over the Operation.

11.2.3 International network

summary assessment

Macchiarini initiated a virtual Europe Airway Institute, coordinated from Stockholm. This might seem far-sighted from an academic standpoint. But from a clinical point of view, it became problematic. As part of the construction of EAI, was organized in 2012 an international video conference that has become disputed.

We note that participants from Stockholm - beyond Macchiarini - had management functions and could hardly contribute to medical experts in the field luftstrupskirurgi. The video conference was one of several examples of how the conferences with many participants came to "Dilute" the responsibility for Macchiarinis transplant operations.

As described in Chapter 3 had Macchiarini already during the recruitment phase, the idea of building up a virtual European Airway Institute coordinated by him from Stockholm. Initially included partners in London and Florence. The idea was that in Stockholm would focus on upper airway surgery [4], in Florence on the lower airway surgery and in London on airway surgery in children. The proposal was lacking information about the planned institute would relate to the EU regulatory framework for cross-border healthcare.

Later were also involved Russian centers (Moscow and Krasnodar). This initiative was supported by the KI and the clinic management of the ENT clinic. In Macchiarinis service included both research and operations in order to build up an international network [5]. This arrangement would seem foresight from an academic standpoint, but from a clinical point of view it was highly problematic (see Section 11.4.2).

As part of the construction of an international network Macchiarini took the initiative in international Video conferences (Chapter 3). The first such conference was bilateral in Florence proceeded technically well [6]. In February, was held a video conference with participants from Sweden, Italy, Russia and the United States. Macchiarini During the recent discussion has taken this video as evidence that the man from the hospital and KI been informed of his activities in Russia and its participation in decisions on luftstrupstransplantation of patients in Krasnodar.

Those who participated from Stockholm emphasized that they had not participated in any surgical decision and that decision was the responsibility of the operating surgeon and the management of the foreign clinic where the patient underwent surgery. In a Russian abstract of the video conference mentioned that the patients discussed but nothing about the clinical decisions taken. In contrast, describes in general terms how the Krasnodar is

preparing "Several transplantations of nanocomposite trachea seeded by autologous mesenchymal cells of the patient ". [7]

Of the material we had available, it appears that Macchiarini at this time worked not only in Stockholm but also in the Krasnodar. Participants from Stockholm says it does not have had realized that Macchiarini was the one that would operate in Krasnodar [8]. But the Russian clinic Macchiarini may have perceived as "their" surgeon at the conference, which may have contributed to that responsibilities were unclear.

Participants in Stockholm perceived technical quality of the conference as substandard, something not encouraged more video conferences [8.9].

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11.2.4 The settlement of Macchiarinis clinical operations

summary assessment

Although he might have acted earlier, we believe that the operations manager at the Department of Thoracic Surgery acted quite adequate when he became fully aware of the unfavorable results of the three transplantations. From April 2013 were Macchiarini no longer operate the clinic. From the ENT clinic struggled to accept, but the hospital director decided to Macchiarinis appointment as chief would not be renewed when it expired in November 2013. The hospital stood against Under pressure from KI to extend the mandate.

Macchiarinis surgical operations. In Chapter 5, we explain how it was when Macchiarinis appointment at the hospital was not extended. When the unfavorable results of transplants became obvious acting hospital director and operations manager at the Department of Thoracic Surgery [10] - Macchiarini received from April 2013 no longer thoracic surgery at the clinic (where he conducted most of its operations). This was also other surgical procedures than transplants. We believe that the business manager's actions were adequate.

From the ENT clinic's questioned to this decision. The head of the ENT clinic suggested in emails to the hospital director an "accident investigation". Our interpretation of the email (and connecting email conversation) is that he primarily wanted to investigate the fact that not ENT lead advance informed that Macchiarini completed the third luftstrupstransplantionen of Thoracic Surgery and that no multi-disciplinary conference preceded the surgery [11,12]. The hospital director was critical to Macchiarinis transplantation [13] but no investigation of decision making for the patient 3's transplant was not initiated.

At a meeting with clinic managements of ENT and thoracic clinics in September 2013 it was confirmed by both sides to the business with luftstrupsoperationer "currently" not would continue, an evaluation was needed and that there was no question to employ

Macchiarini at the Department of Thoracic Surgery [14]. This agreement matures us greatly to have been justified. According Macchiarini missing hospital infrastructure to manage the care of patients with need for prolonged intensive care. He said that the hospital had neither medical or financial ability to cope with this type of care and the lack of logistical know-how for a formal clinical trial [15].

Also from CLINTEC-the institution had one objection: "The clinical system seems presently not ripe" because the hospital / County Council "can not create special resources for this type of experimental surgery" [16]. This would, in our judgment, could possibly have been correct if it were for further transplants. But it was not a lack of resources that decided the outcome of the three patients transplanted [16]. Probably Macchiarini and prefect right in these assessments. Our conclusion is that the hospital should have done more thorough assessment of the resources required before transplant operations began.

It also took the initiative for a meeting in October 2013 where it invited an international authority the area luftstrupstransplantationer (Chapter 5). At the meeting - where decision-makers from both Hospital and KI participated - the decision was taken to Macchiarinis appointment would be renewed but that his surgical operations at the thoracic surgery clinic would be closed. [17] Macchiarinis continued clinical activity would only be delegated by the operations manager at the ENT Clinic [18].

What they intended with the decision sentence "The hospital assumes responsibility for patients who have operated so far. "We have not been able to ascertain. We find that the thorax clinic and hospital management assessment and process at this stage of Macchiarinis activities was correct.

The appointment at the hospital. Macchiarinis appointment as Chief stretched to November-December 2013. The commitment letter concerning the extension of the mandate that ENT clinic operations manager wrote in November 2013 was in line with the decision taken at the Conference in October 2013 (see above). Given how Macchiarini worked in his clinical activities

activities, as was noted at the conference, we have, however, difficult to see an extension of his appointment as chief was justified. Division manager (operations manager's immediate supervisor) did not sign the commitment, since hospital director intervened. The hospital director and his closest collaborators in the Staffwas based on the signals they received (partly from elsewhere than from the hospital) come to the conclusion that Macchiarinis appointment as chief would not be extended. The hospital director took one according our opinion informed decision.

Relations with KI. Our interviews with employees at the hospital have shown that during the closing process, pressed from the KI side to Macchiarinis clinical extension would continue. It referred in particular to Macchiarini had very large research grants (Partly for

its clinical research) and that he had many employees in his research group. This may have been one reason why the operations manager wanted to extend Macchiarinis appointment. As the hospital director in place of the operations manager took the decision not to extend the mandate came from the hospital side to resist the KI pressure.

11.3 Before transplantation

11.3.1 was enough scientific evidence to transplantation of synthetic trachea?

Summary assessment

Transplantation of various types of synthetic trachea had previously been performed in laboratory animals with highly variable success. In contrast, the concepts used in transplants – the specific synthetic materials, exposure of bone marrow cells and very high doses of growth stimulatory drugs - brand new and had not been tested in either animals or humans. We believe that there was insufficient scientific evidence to apply the concept in humans. It was contrary not only to science and proven experience; it was also too early to implement a scientific study in humans.

As stated in Chapter 2 was limited favorable experiences from luftstrupstransplantation biological body reported in the scientific literature. Macchiarini had also conducted several such transplants in Florence [15]. At one of these operations had surgery and anesthetic staff from Karolinska University Hospital were present.
Synthetic trachea other hand, had not previously used in humans. Bone marrow cells had previously been used in any single patient in conjunction with transplantation of a trachea deceased person but the combination with synthetic trachea in humans was new. The use of medicament to stimulate cell growth (and the doses used) must also is designated as an unproven method with regard to synthetic trachea in humans (but had previously described in connection with transplantation of nekrotrakea [19]).

As reported in Chapter 2, many research groups around the world conducted extensive in vitro studies and laboratory experiments when the first luftstrupstransplantationen conducted at the Karolinska University Hospital in 2011. The synthetic materials used had undergone tests of toxicity and biocompatibility, this with favorable results. Would this material be enough to start with transplants of synthetic trachea of person? When going from animal to applications in humans of a new method usually in the ethics review set a number of requirements. As for transplantation at Karolinska University Hospital, there were obvious shortcomings:

• The discrepancies were large and partly unexplained as to the results from animal studies conducted by various research groups.
• There was no long-term studies in laboratory animals with the type of trachea used in transplant patients.
• combination of exposing the synthetic graft of bone marrow cells and to bring large

doses of growth-stimulating drugs to the patients had not previously been tested.
• The operators had not practiced this combined concept of large animals.

Against this background it is not surprising that there have been researchers in the field who made completely different judgments than Macchiarini and his colleagues it was time to start applying transplantation of synthetic trachea of humans. We now know that the risks of luftstrupstransplantationer was too big with the technology were used. Such determination is of course characterized by hindsight. When operations were performed characterized by the state of knowledge instead of great uncertainty. These risks mainly relate that, in contrast to when using synthetic materials of other transplants, created synthetic material in an infection prone environment. Also the use of a growth-stimulating drugs not intended for human use and of another drug in very high doses was to take unjustifiable risks.

As we addressed in Chapter 7, there is particular reason to be wary of introducing a new method with huge potential risks in the knowledge situation is very uncertain or unstable. We can did not find that any such considerations were made before the transplants - at least there they not reported in the preoperative protocols. Nor have we in our interviews found examples on this. At the multidisciplinary conferences do not seem to matter of risk and the uncertain Scientific evidence have been highlighted enough.

As we described in Chapter 2, the whole idea of transplantation of synthetic trachea questioned in the recent public debate. It might then be worth recalling that synthetic materials currently used in fairly large scale in health care, and then you work - in sterile environments. In the non-sterile environments, the problems are far greater, especially with regard to synthetic trachea. The trachea is a body which involves special mechanical and biological challenges. underway nevertheless, several countries preclinical development of synthetic trachea transplant and Clinical trials are planned (or possibly has started). We do not have the skills to assess how realistic such trials could be.

11.3.2 Clinical research or not?

summary assessment

A number of factors suggest that the transplants were moving on clinical research, which according Ethical Review Act also refers to development on a scientific basis. The regulatory framework for research would have been followed.

There may have been a major humanitarian element (compassionate use) when you took the decision to transplant - it often does when it offers patients to participate in scientific studies, especially for difficult diseases. A humanitarian element does not reduce the need for review under the Ethical Review Act.

The hospital and KI has maintained the view that it has not moved on clinical research. This risk the continued slide in the application of regulations governing clinical research. The hospital's firm opinion that the intervention was not research, but health care is

problematic also other viewpoints. According to established terminology it means in this case luftstrupstransplantationerna has not been in accordance with science and proven experience.

In the debate on luftstrupstransplantationerna has been a key issue: it has involved medical / clinical development (which Macchiarini, hospital and KI argued) or clinical research that would have required the approval of the ethics board (as many of the critics argued)?

We first want to clarify our understanding of some basic points:
• Ethical Review Act definition of research (see Chapter 8) is so general that it does not provide any leadership in this specific case. We would point out that the law also refers to research "development on a scientific basis. "
• It is common to use a pragmatic definition of research: it published in a scientific journal is research. However, this is in our opinion too simplistic, among Another reason that most scientific journals contain much material not can be described as research and far from all the research published in the form of articles in scientific magazines.

• Description of individual patients and their treatment (case studies) are common in the scientific literature and may provide important scientific information. Usually knows the attending doctor / medical staff not until afterwards if a case report is justified or not. Therefore, it is seldom necessary to pre seek research ethics approval and Ethical Review Act does not allow subsequent approval. Therefore published most case reports without there permission from the ethics board (or equivalent in other countries).

• Health care for humanitarian reasons or clinical research? We believe that this is an all too easy way To look at the issue around Macchiarinis business. Many seriously ill patients to gain access to new, not yet proven methods, while they want to contribute to increased knowledge about the disease and its treatment. Similarly, researchers / clinicians will help individual patients while engaging them in a research project.

Once this is said, the question still remains: Was it beyond treatment on humanitarian grounds a concurrent research agenda? Alternatively, it was about development of scientific basic? In both cases, the approval of the Ethics Board have been required.

Medicinetikern Linus Bostrom has the debate around Macchiarini pointed out: "If any aspect of operation, the implementation was guided by scientific considerations rather than purely clinical would be operations of these elements to be considered research, although they also intended to be life-saving treatment. "[20]. As seen from the scientific article where the first luftstrupstransplanterade the patient was described [21], conducted a series of analyzes of the scientific reasons rather than clinical.

The Swedish Research Council (VR) discontinued in 2015 the payment of a major grant to KI for project development of farmed natural and bioartificial esophagus with

Macchiarini as project [22]. IN decision included, among other things, an assessment of whether Macchiarinis trakeatransplantationer was to consider as research or not. VR wrote:
The development and transplantation of synthetic trachea is a scientific experimental work to acquire new knowledge in an area where there basically is no knowledge, and any tested experience is definitely not. It therefore argues that the operations is performed without medical care component of the research seems to be in a dilemma. Because science and proven experience missing, the patients in this case received medical treatment differs from patient safety law requirement of compliance with good clinical practice. Seriously ill patients were offered the experimental treatment whose aim has been to systematically create new knowledge. It is the Research Council's firm view that the current transplants is research.

The fact that it concerns a small number of patients play in this context does not matter, what matters is that these are just a methodical search for new knowledge, development and scientific

trying new methods. It is also important to see the big picture, not to focus on individual aspects of research, individual projects or papers. The research group's work constitutes a whole and looked at in this way, they constitute a systematic search for new knowledge, that is say research.

In its decision quoted VR also KI's external investigator Bengt Gerdin [23] and agreed with his assessment:
An issue to be clarified is the limit for research and care goes into the current case. The investigator believes that the measures implemented in the three patients were included in definition of research at the moment any reflected upon and planned to spread and use the information in a scientific way. This includes any kind of description of what has been done and what it led to, as well as all management of research material for analysis, beyond that healthcare requires. Based on this approach, the investigator believes that the scientific Publication of the results of the performed operations means "research refers to people ", and is therefore in Ethical Review Act.

We share the assessments VR and Bengt Gerdin done. We also find other circumstances suggesting that the transplants are considered to be a component of a research:
• When Macchiarini employed at KI and the hospital was with the stated ambition of the three months should be started with a functioning regenerative airway transplantation as part of the planned cooperation between the Institute and the hospital. [3] The management at the KI-institution Macciarini belonged (CLINTEC) made clear in February 2011 that it expected that the activity would be started before the end of the year [4].
• Several of the samples were taken before and after the operations turned mere research purposes, not a direct patient needs and many test results from laboratories outside the hospital were sent directly to Macchiarinis research.

• In connection with the autopsy of patient 1 was part of the samples taken to be considered Research samples. Department (CLINTEC) got the disposition of these samples [24].
• The title of the publication Lancet study was designated as a proof-of-concept study [21]. This type of study is usually regarded as a research stage in the development of a new clinical method.
• Representatives of an academic institution (CLINTEC) issued a financial guarantee the care of the patient 2 at the hospital [25].
• In the Karolinska Institute's annual report 2011 highlighted the first luftstrupstransplantationen as one of the year's most important research news [26]. At an internal conference in October 2013 examined Macchiarinis transplantation (see Chapter 5). Present were, among others Macchiarinis Managers at both hospital and KI side (including KI's headmaster). According to the unofficial memorandum, prepared as a discussion aid [17], they made the following assessment:
"The time is not ripe to proceed to surgical use artificial materials on human then it basically still in a stage of research and you will find that the way is not ethically. "

Our conclusion is that there was a clear research component, above all in the first luftstrupstransplantationen. This applies not least to the extensive sampling (biopsies and blood samples) with advanced analyzes. Macchiarini and his team should have sought approval of the ethics board.

It should be added that clinical trials are in effect research. Therefore, ethics approval is obtained before such trials begin.

There was no time for ethical review? It has been argued that patients' well advanced disorders made that there was not time for an ethical review process. This raises three questions:
• Where medical conditions so advanced that there was no time for respite, including research ethics assessment? This issue we deal with in section 11.3.5.

• Is the ethical review boards processes too cumbersome to handle this type of errands?
• Had there been the opportunity to plan for the kind of "semi-urgent" intervention that Macchiarini and his associates believed existed?

There is a lot in Macchiarinigruppens adoption of decision by the ethics board to approve a project on artificial trachea seeded with bone marrow cells could pull out about time. We believe that the Ethics Committee would have questioned the preclinical documentation, the design of patient information and the idea to insert a synthetic body in an area openly exposed to infectious agents. The Board would have required authorization from the Medical Products Agency for use of the combined product synthetic trachea plus bone marrow cells and for use of the drug in the way that Macchiarini and his colleagues did. Macchiarinis research team conducted a long-term research aimed at respiratory transplants in humans. It can hardly have come as a surprise

to would get requests based on whether the method could be applied to patients. with planning it should have been time for research ethics application, where the planning took into account the possibility that the additions would be required. Even if, contrary to our assessment, would accept that there was no time for assessment the Ethics Board before the operation the patient 1, so the research team should have sought
Research ethical permission if it intended to offer more patients this new untested method. We find it important position to emphasize that, regardless of whether the transplants are considered mainly clinical research or mainly health care, patient safety must be assured. Operational responsibility remains the same (see Chapter 9).

11.3.3 vital indication and compassionate use (treatment on humanitarian grounds)

summary assessment

The hospital has the debate surrounding transplants maintains that it has moved on vital indication and compassionate use (treatment for humanitarian reasons). We believe that this was not of vital indication in the sense that most Swedish clinics adds in the concept. Before the transplant, there have been a large element of compassionate use. But this means not that other ethical values can be set aside. Nor can it be used to justify departure from current regulations, especially as it concerns the protection of research subjects and patient safety.

When the hospital publicly defended luftstrupstransplantationerna the concept of vital indication used. The term has also been used in some of our interviews. It seems then to have intended to patients' condition was life-threatening in the longer term. We note that this use of the concept is different from that which is generally relate to vital indication - that it is about a condition that can lead to death within hours, days or possibly a week. for no of the three patients were luftstrupstransplanterade vital indication in the sense that it there was danger to life within a few days.

As we explained in Chapter 7, the concept of treatment on humanitarian grounds (the Compassionate use) have both a clearly defined legal role in the pharmaceutical sector and the broader ethical application, then as an expression of mercy. When the discussions on transplants relied on compassionate use it in the latter interpretation.

Based on what fairly unanimous emerged in our interviews, there was a large element of compassionate use when the decision was taken that the patients would undergo luftstrupstransplantation. The argument for compassionate use has been used extensively by Macchiarini and the hospital to justify transplants focused on health, not on research. It appears

have used the term compassionate use wide - for immediate life-saving interventions for symptom relief (Closest palliative treatment), and for long-term cure (curative treatment). The illustrates, in our opinion, the problems surrounding the use of non-judicial and

poorly demarcated concepts that vital indication and compassionate use.

We have no reason to doubt that Macchiarini and his associates driven by a strong desire to help severely ill neighbors. However, we believe that
• compassionate use must be weighed against other ethical values,
• Arguments for compassionate use can not be used to justify departure from the prevailing regulations, especially that which concerns the protection of research subjects and patient safety,
• compassionate use may be one of many designs for a medical intervention; the fact that compassionate use invoked does not mean that other motives are irrelevant.

11.3.4 Autonomy and informed consent

summary assessment

The three patients were fully capable of making decisions. The patient 1 had to give written informed consent was unconventional for the Swedish health care but basically a good initiative and in accordance with the guidelines of the international stem cell researchers ISSCR organization.

The information, however, contained texts that left no room for the patient not to understand or forgo surgery. If the information had been presented to an ethics board would not have approved. The oral information seems to have contained pressure. There are question marks about whether patients 2 and 3 gave written informed consent or not.

As we reported in Chapter 4, the patients seem to have been well informed about their illnesses. The was also fully capable of making decisions. Patient 1 was not informed that luftstrupstransplantation was current when have come to Karolinska University Hospital; it was however patient 2 and 3. An account of how the verbal information we went to the Macchiarini, who assured that patients were fully informed. Patient 1 has himself in a filmed interview, reproduced in TV series The experiments told us:
”When I was going from Iceland to Sweden I didn´t know that it would be such a big operation. […] I was very scared, very terrified and the other thing that which made me big scared was that this was happening for the first time. I said no, I said no… He told me straight, you know, we did not try this into human being, we tried this into pigs and animals so… maybe it was working with animal so… He was very confident...enough to…make me… you know, persuading on to make me to believe on this”.

Patient 1 also received written information (Chapter 4). The information contained formulations which must be perceived as strongly pushing, sometimes manipulative, with a view to patient would accept the planned surgery. The information was used very advanced medical terminology, that must have been difficult to evaluate or even understand for a non-medically trained person. There was no information about possible risks in addition to the assurance that the drugs intention to use has no side effects (which was not the proper task). Nor was there Information about this type of intervention has not previously been tested in humans. Our assessment is that, if it had been about a research project with the usual ethics review, it had written notice is not approved by the

Ethics Committee. Now's not regarded Karolinska University Hospital intervention and research, but as healthcare. As we pointed out in Chapter 7 of the guiding ethical principles surrounding the self-

determination and informed consent for medical care for Research. Self-determination principle means that the patient will have to decide on investigations and treatments without pressured. You should know what the operation entails, how risky it is, what the consequences will be if one accepts the respective waiver of the operation and what alternative action are possible.

The written information to the patient 1 ends with a declaration from the patient he received full information to all his questions answered and that he approves the procedure. Together with Macchiarini he signed informed consent. Here we would like to point out that a approval of a patient has no formal status. It does not relieve a physician responsibility to give careful consideration to the balance between potential benefit and possible risk when a procedure.

In a situation where neither the doctor in charge reasonably have sufficient knowledge about the procedure and its consequences was a statement from the patient that he received full information almost absurd.

Patient 2 was written information but consent was not signed by the patient and it is highly uncertain whether he has received the written information before the operation.

Concerning Patient 3, we have not been able to find any written information or written consent. Macchiarini has emphasized that in patients contract with Stockholm Care entered into information that they are aware of the risks. However, we believe that this extremely brief Information can not replace informed consent.

No written information is not required under Swedish law. However, the content of the oral the information described in the patient record. Journal entry about the content of the information lacking in both Patient 2 and Patient 3 (it's at least not in the intended location in the journal).

11.3.5 Clinical assessment before transplantation

summary assessment

In none of the patients there was no immediate threat to life. In the longer term had progressive cancer in two of the patients could lead to death. In the third patient meant complications to luftstrupsskadan, such as severe infections, a certain threat to life.
We believe that there is scientific evidence to firmly say how long survival of the patients would have had if they had not been transplanted. The two external experts we hired has, with reservations for the uncertainties in the estimates, found that the two first

transplant the patients who had both cancer, had an expected survival of at most a few years.

Prior decisions to transplant was performed multidisciplinary conferences for two of the three patients. No conference was conducted before one of the two transplantations of the third patient.

At the conferences were conducted not discussed the critical issues. The conferences came to provide support for transplant operations and led to the responsibilities could be perceived as unclear. The final decision to luftstrupstransplantationerna was carried out remained at the operating surgeon (Macchiarini).

Gastro Clinic in Huddinge had great experience in coordinating major surgery. the clinic was given responsibility for coordination in the operation of the first patient was a well-motivated initiative. To The first transplant was performed without access to the heart-lung machine subjected the patient, however, to unnecessary risk.

When operated patient 2 and, in particular patients 3, overall it is not sufficient information on the progress of patient 1 (or did not take sufficient account of the information they had). Patients were given no opportunity to discuss operational decisions by an independent expert.

The patients' medical conditions prior to transplantation and prognosis. The two first patients had both cancers localized to the trachea, and no signs of metastases. The

had the rare cancers. The summaries are available in the scientific literature therefore includes only a few patients. This makes it very difficult with any degree of probability ruling on a typical progression for patients with each cancer.

According to the investigations of the patient 1 as has been done in Iceland was seen at bronchoscopy (examination of the trachea and bronchi) in February 2011 a "massive displacement" of the trachea [27]. At the microscopic examination of tissue material was seen only granulations (scarring) and no sign of cancer.

When the patient in May 2011 came to Karolinska University Hospital was described in the admissions records he had good general condition but he had stridor, a respiratory sounds one usually hear the narrowing of the airways. The interpretation of the diagnostic imaging and skopiundersökningar performed before the operation varies considerably. Macchiarini and doctors at ENT clinic has interpreted the changes observed as very serious with the threat of death within six months. The conclusion to the multidisciplinary conference before the operation was the same. Among Macchiarinis scientific staff there were those who received the impression that the patient just had two weeks to live. [28]

Critics, especially the four notifying doctors, has had two main objections:
a) The pictures of luftstrupsförträngningen taken before surgery has been interpreted, partly because incorrect image section selected. The tumor that was removed during the operation was not "big ball" as it was said before the transplant; it measured 25 x 11 x 9 mm.
b) Some of the changes seen in different diagnostic examinations may well have been caused by scarring from previous surgery, radiotherapy and / or tuberculosis. Microscopic examination of the trachea removed at surgery showed growth of cancer of the same type when the patient first underwent surgery in Iceland 2009 (section 4.1.7).

Operation The stripes were free of cancer, that is, it seemed like it removed all the cancer. We have hired two experienced external experts, an oncologist and a lung doctor, to assess the forecast on the basis of the information in the patient records, scientific literature and their own experience. Forecast assessment assumes that they would have chosen palliative measures, like what suggested when Iceland consulted an American expert. These measures would, according to the hired experts could be, for example, tumor reduction with laser therapy, local radiation therapy through microscopy and possible stent placement.

Estimates are difficult, not least because cancer is rare and the summaries made based on small case series [29-31]. The fact that it concerned a relapse of cancer after radiotherapy worsening prognosis. The one of the experts we consulted estimated survival for about two years, the other has found that survival can "be from a number of months to year. "

Thus, the scientific evidence is weak and there are several possible interpretations of the surveys conducted before the transplant. We believe that the prognostic assessments made rests on shaky ground. It is not possible to safely determine how long the patient would have survived if he had not been transplanted, but the most likely seems to be that he would have died last a few years.

Also, patient 2 was described in the admissions Journal (October 2011) to be in good general condition. At regular physical examination were observed no abnormal airway. At the multidisciplinary conference before the transplant seems to have been agreed to patient condition was serious enough to warrant transplantation. Microscopic examination of the trachea removed showed that the operation was not radical, that is, tumor tissue remained. If the intention of the transplant was to try to cure the patient of his cancer, succeeded not. But being forced to leave the tumor tissue is not uncommon in advanced cancer surgery.

As we discussed in Section 11.3.3, there was no question of treating an immediate life-threatening condition due luftstrupsförträngning. However, it could be thought that transplantation could mean symptom relief and less risk of suffocation in the longer term – provided the synthetic trachea had been proven to work.

On microscopic examination, the patient had a slow growing cancer (section 4.1.7). The One of the experts we hired have found that "there is something remarkable that one has no formal evidence of residual tumor after completion of chemoradiotherapy before major surgery is performed. "

His assessment was that the patient's prognosis for survival (without surgery) was about three years. The Second expert found that a five-year survival rate of approximately 33 percent and a ten-year survival rate of approximately 10 percent reported in the largest compilation published [32]. would likely the chance of survival for the patient to be slightly lower due to the extent of the tumor.

Taken together, the two experts' assessments indicate a survival rate of at most a couple year. But here also should be emphasized that the estimates are very uncertain because the scientific the base is fragile and relatively long standing. A slightly brighter picture may be, for example, of a study of six patients, like the patient 2 before transplantation, not surgery without radiotherapy alone; their median survival was just over 6 years [33]. Although to some extent it is a speculation, one can not completely rule out that palliative measures or treatment other than transplantation would have led to a higher quality of life for patient 1 and 2 the time they had left to live, compared with what now came to be the case.

Patient 3 had a difficult luftstrupsskada caused by a previous operation of the home. Her quality of life was significantly impaired. The state, however, was stable in the sense that it was not dealing with progressive disease. There was still constantly a significant threat to life due to complications to the formerly luftstrupsskadan, mainly in the form of severe infections.

It appears to have Macchiarini been alone that took a position on whether the patient motivated the two transplants, at least the first of them. The purpose of the two transplants was that cure her, or at least relieve her respiratory symptoms. The surgery she underwent before the first transplant came, like the two transplants and their consequences in practice to aggravate her condition, impair her quality of life and pose additional threats to life.

Multidisciplinary conferences (MDK) offers the opportunity to collect several - though not totally independent - Assessments before a treatment. Such conferences are common in cancer care where many different specialists can be engaged. They are also well established in other disease areas (As a child heart surgery and transplants of heart and lung, just to take two nearby example among many). The value of MDK is considered to be so great that the National Board lifting until the percentage who face cancer treatment discussed at MDK as an indicator of quality of care.

Prior luftstrupstransplantationerna discussed patients 1 and 2 (but not patient 3) at MDK. At the MDK for the operations of patients 1 and 2 were specialists from at least six (Patient 1) and three (patient 2) clinics were present. There was a clear designated draftsman (Macchiarini), a detailed written documentation and the decisions taken appear to have been anchored among conference participants.

When we from today's perspective assesses the conferences seem to be three crucial points have been missing: access to key skills, critical examination of the evidence presented and discussion of other treatment options other than transplant the synthetic trachea. Despite the large number of participants at the first multidisciplinary conference, lacking key skills in the form of transplant surgery and transplant medical expertise. The cause is unclear.

The consistent picture we received from our interviews of participants in these MDK is that it does not heard any objections to the intervention itself. There was consensus on the indications – that patients' condition required surgery and artificial trachea seeded with bone marrow cells could be used. Details of how operations would be implemented were discussed. For the second operation is determined such that it would take place in Solna (with access to heart-lung machine) and not in Huddinge (as the first transplant).

No one seems to have asked critical questions:
How did the animal experimental data out?
How documented where the seeding of bone marrow cells would work?
Where doses of growth-stimulating factors secure?
If one were to choose transplant, was it wise to choose synthetic material?

The lack of critical examination made to conferences in practice came to legitimize a completely new treatment concept that was untested in materials, seeded bone marrow cells and the drugs used. In the current debate has Macchiarini fully correctly points out that decisions for the first two transplants were taken in consultation with other specialists at the hospital and clinic management was informed of what was planned. The conferences came in practice - Although not formally - dilute the responsibilities that would otherwise incumbent upon the operating surgeon.

Before Patient 3's two transplants were not carried MDK. Possibly it was due that such conferences are routine in cancer but not for other patients with complex diseases. But now it was an entirely new indication for transplant of a synthetic windpipe, a highly advanced and obeprövat intervention. Therefore, should the MDK have been arranged. It had was natural that at such a conference to critically examine the clinical course of the two previous transplanted patients. When the first transplantation in patient 3 failed, had it has also been set state with an MDK when it planned a new transplantation of synthetic trachea in the same patient. For our assessment of the issue of lex Maria Notification, see 11.6.

By e-mail correspondence with the operations manager at the Department of Thoracic Surgery shows that Macchiarini so late as June 2013 had advanced plans for further transplantation of synthetic trachea (possibly retransplantation of patient 1 or 3) [34], despite the fact that the hospital director in April 2013 taken a negative transplant operations.

In hindsight, many critics asked why they do not already before the first operation realized To transplant the synthetic material in the airways that are constantly exposed to infectious agent was judged to provide major clinical problem. Also, the idea of some day seeded bone marrow cells has come to be regarded as unrealistic. Why reacted none among them who participated in the multi-disciplinary conferences? In our interviews, several possible explanations put forward:
• Macchiarinis presentation of the patients, the surgical protocol he presented and his justifications for intervention appeared very convincing.
• Most people who participated in MDK was ignorant in the field. There was no particularly transplantation surgery and transplant medical skills.
• Those who still had some insights were so heavily involved in the development of regenerative medicine and airway surgery at the hospital and KI they consciously or unconsciously pushed away potentially negative aspects.
• Group thinking was pronounced (see below).

The MDK has legitimized operations. But they have not met the requirements to be imposed on such conferences. The intention is that different specialties constructively contribute according to their respective competence. It would have required that the group was independent expertise areas transplant surgery / transplantation medicine, regenerative medicine and treatment with unproven doses of growth-stimulating drugs.

Coordination.

As we described in Chapter 4, got gastro clinic coordination task at transplant Patient 1 and the patient was treated there during the weekends. This solution seems have been well motivated. As the operation developed, it turned out, however, that the absence of heart-lung machine Huddinge made that the patient exposed to unnecessary risk. Learning from past experiences. When operated patient 2 seems not to have collected sufficient information on the progress of patient 1 (or did not take sufficient account of the information they had) so that, when operating decision could take this into account.

Even more This concerned information on patients 1 and 2 face transplant in patient third New medical assessment (second opinion). Although we believe that the transplants mainly was considered to be research, it was still on hospitalized patients on the basis of a medical assessment of his state of health was proposed a radical untested treatment

with obvious high risks. Patients should be given the opportunity for an independent assessment of health status and whether the surgery was advisable or not in their case.

We therefore concluded that regulation of the possibility of new medical assessment was applicable even if the transplants constituted research. At an independent external assessment patient could have taken up both purely medical and ethical considerations and quality of life aspects.

11.4 During and after transplants

11.4.1 Drug Treatment

summary assessment

In connection with transplants used three growth stimulants such as so-called regenerative boosting therapy. We find that this concept was particularly weak during the building for use in humans. It was highly experimental and exposing patients to unknown risks. It can not be excluded that the use of one of the drugs (erythropoietin) may have contributed to the clot formations patients suffered.

As noted in Section 11.7, the hospital has violated the rules for the use of medicines in connection to the transplants. We take this up clinical non-legal views on drugs. Three compounds were used as growth factors to stimulate the formation of new cells in preparation of the synthetic luftstruparna. Two of these were approved drugs (but not just for this use), while the third (TGF-β3) was not approved for human use. The lack of knowledge about the possible negative effects of this third preparations, for example, if the could contain a virus components. Thereby subjected the patients to unknown risk.

The two drugs were given during the two weeks after the transplants were both approved MPA, but they were in far higher doses than is customary in humans. The lack of scientific literature on the effects and side effects when used at such high doses and the risk of serious side effects seem not to have taken into account. Even in conventional doses increases the of drugs (NeoRecormon; erythropoietin) the risk of clot formation (section 2.3). It can therefore not be ruled out that very high doses may have contributed to the clot formations patients suffered. To provide growth-stimulating drugs in high doses to a patient with residual tumor tissue (patient 2) also meant taking a risk.
The whole concept around these medicines boosting regenerative therapy in humans appears we have been very weak substantiated. It must be considered highly experimental. Manufacturers have distanced themselves from this type of use of their preparations (Section 2.3).

11.4.2 Clinical follow-up

summary assessment

A surgeon operates on many sources outside your own hospital goes out over the patient-physician continuity. This became particularly clear regarding patient 3 but was also later phases of Patient 1's care course. The lack of continuity meant a risk of impaired quality

of care. Macchiarinis very fragmented business with work in many parts of Europe and the US meant that he could not take full responsibility for following up their patients. From page läkarkollegornas one would have wished that he had been more available for the care of the transplanted patients or at least for advice. According to what has emerged in our interviews was among caregivers a great frustration about the lack of continuity of care and unclear ansvarsförhållan- the.

Of the records shows that Macchiarinis closest collaborators in the research laboratory entered as an adviser when complications appeared after transplants and Macchiarini was not available. The employee had no permit to work as a doctor in Sweden and his clinical interventions strikes us as strange. If other doctors at the clinic took responsibility for the decision was taken, however, need no formal errors have been committed.

We consider it unacceptable that health care is organized so as to make it possible for the patient charge physician to withdraw from its responsibility for the patient (the Swedish healthcare is generally flaws in this regard is no excuse).

We want to just point out that not Macchiarini could know something about the expected complications and how they would be treated because it involved a pioneering technology. Patients had every reason to feel insecure and mercy.

11.4.3 Attendance at operations

summary assessment

Staff from Harvard Apparatus were present at least, all possible, the transplantation (s). The records absence of consent from the patients. The presence of external people is another example how free Macchiarini reacted to the regulatory framework and the poor control over his hospital had activities. From a patient point of view, the presence of external persons and an invasion of privacy potential danger to patient safety.

The operations lasted several hours and it seems to have been many people come and gone. Macchiarini was only present during certain key moments of the first transplant and, according to oral information we received, it happened that during the day he appeared "plainclothes" in the operating room.

We have not been able to identify exactly what the people who were present at the transplants. However, we have gained access to a short video said to be taken during patient 2's transplant.

The film is marked "Copyright 2001 by Harvard Bioscience" and has in all probability taken by an employee at Harvard Bioscience. There is also information to suggest that

employees of Harvard Bioscience was present at the other transplantations.

Film Documentation from operations is possible under certain conditions. During the operation of patient 1 filmed the hospital's own unit Medical Imaging procedure. Applies the presence of external people must be informed consent should be obtained from the patient. The hospital has recently introduced a consent form where the patient gives written consent for the photo or filming, where the purpose must be specified. [35] We have in the three transplant patients' medical records not been able to find any equivalent document, nor the patients would have consented to the presence of external people.

There is no journal entry that verbal informed consent obtained. filming without first having obtained the permission of the patient must be seen as an invasion of privacy (We must, however, reserve the right for the company to have obtained concessions which are not documented in the records).

When external persons are present in the operating room, it is particularly important to safeguard patient safety. The external persons must not obstruct the operation work. In particular, the and their equipment does not pose the risk of infection. One should be particularly restrictive in allowing the presence of people who had contact with health care in other countries.

Professor Johan Thyberg have had contact with the hospital to search for possible contracts that would have existed between Harvard Apparatus and hospital. No such contract has not been found [36].

11.4.4 Measures for the autopsy of the patient 1

summary assessment

When one patient died, was initially differing views on the need for an autopsy, but the autopsy issue dissolved quickly in agreement. We believe that the autopsy brought important knowledge on graft and its effects.

In retrospect arose discussions on analysis of research samples. Those involved clinicians did an agreement on the management.

It has in the debate on Macchiarini encountered questions about the autopsy of the patient 1. The patient was treated at the Gastro Centre Huddinge when he died. Autopsies were assessed in the clinic not be keen. But then Patient 3's responsible doctor at the Department of Thoracic Surgery made proposals determined on autopsy, in consultation with the Gastro Centre. From the thoracic clinic side wanted to better understand the serious complications Patient 3 suffered and that caused very long hospital stay in the ICU [37].

According to a statement issued retrospectively approved patient wife autopsy and samples from patients were analyzed [38]. From gastro clinic site had before the autopsy decision no contact with the ENT clinic and you did not catch it there was no pressure from there to stop the autopsy [39]. There was, however, discussion of the analyzes of samples taken at autopsy. At a meeting with involved clinics (gastrointestinal, thoracic and ENT), it was agreed to proceed with the analysis at the hospital in what was considered to be clinical samples. However, there was research samples which does not record transferred [40] and sent abroad. It was agreed that these indefinite would not analyzed this in anticipation of a scientific analysis plan from KI (CLINTEC) [24]. No such analysis plan seems to have been established [8].

11.5 Organisation, responsibility

summary assessment

Macchiarini was active on both ENT and Thoracic Surgery. There was a lack of coordination between clinics which helped to Macchiarini could act very independently. The head of the ENT clinic had formal responsibility for appointment as Macchiarinis consultant. He took several well-justified measures to support and monitor the establishment Macchiarinis at the clinic, but these measures proved inadequate. Responsibility for the transplants were performed lying on the operating surgeon (Macchiarini) and the operations manager at the ENT clinic (patient 1) and Thoracic Surgery (patients 2 and 3).

The responsibility to comply with applicable regulations regarding health care was incumbent is primarily responsible physician. participants in the multi-disciplinary conferences that preceded the first two transplants had to Medical Consultants a limited professionally partial responsibility for the statements made. It does not relieve the patient-doctor in charge of his main responsibility for the actions taken.

Business managers had overall responsibility for the legislation was respected both there Macchiarini was employed (ENT Clinic), and where the business is conducted (largely in the Department of Thoracic Surgery). The head of the Department of Thoracic Surgery acted properly when the difficult issues surrounding transplants became obvious. From the ENT clinic struggled to accept, but the hospital director decided To Macchiarinis appointment as chief would not be renewed when it expired in November 2013. This decision was justified. Hospital withstood pressure from KI to extend the mandate.

Clinical Cooperation.

Cooperation between departments is essential when it comes to treating patients with complex diseases. While it can allow for very independent people as Macchiarini too freely move in the border zone between clinics. When a doctor employed at a clinic treats

patients at another clinic danger responsibilities become unclear. Most of those we interviewed have perceived Macchiarini as a very independent person. The hospital gave him much room to exercise their autonomy, something that probably contributed that the problems with his clinical activities were not discovered earlier.

Macchiarini that could operate on the thorax clinic without his business officer ENT clinic was informed (patient 3) must be regarded as unacceptable. This contributed not only the communication problem but also a poor decision for the patient 3's transplantation.

The academic influence.

One of the university hospital's strengths is that the College's expertise can be used to develop health and to conduct advanced care. Academy should also able to contribute with critical thinking based on the current state of knowledge. Regarding Macchiarinis clinical activities, we must conclude that the influence of the academic side contributed the vague steering, unclear responsibilities and fuzzy decision. Any critical examination were hardly from the academic representatives who were closely involved in Macchiarinifallet.

The operating surgeon's responsibility.

At university, many employment that is shared between the hospital and the academy, then usually the Academy as the main employer. To this to work, both the individual employee as operations management ensure that the arrangement do not go out of the quality of care and patient safety. Macchiarini had not only a Staff shared between KI and KS, he also had clinical activity in other countries. clinical researchers should of course have a good international network. But in Macchiarinis case led the simultaneous operations in the clinic, in the laboratory at Karolinska Institutet and at foreign clinics that his clinical efforts at Karolinska University Hospital was shattered. Continuity of care is particularly anxious regarding advanced therapies where skills are combined into a single or only a few people. For the transplanted patients burst continuity, something especially Patient 3 was, but to some extent also the patient 1. From a patient perspective, clinical activities elsewhere than in the home hospital in our opinion, be kept to a minimum.

Liability in the multidisciplinary conferences.

In multidisciplinary team meetings before the two first transplants were, as far as we could find, consensus that patients should be transplanted synthetic trachea. Of our interviews shows that many of the participants at the conferences considered that it had no responsibility (or limited accountability) for the positions made. In our view, participants in the treatment conferences to be considered medical consultants. They had as such a certain professional partial responsibility for the positions made. It does not relieve the patient-doctor in charge of his main responsibility for the actions taken.

Operations Manager's responsibility.

The head has a central role in the recruitment of staff with shared service where clinical activity is included. Related to the shared services department head at the institution responsible for the academic part. As discussed in the section on recruitment above, handled the recruitment of Macchiarini as clinical staff at the ENT Clinic far from satisfactory.

When the decision on appointment well was a time took the newly appointed operations manager more measures to ensure that Macchiarinis operations were conducted under controlled conditions (Chapter 3). A highly experienced employees, former operations manager, had overall responsibility for establishment of Paolo's clinical activity [41].

Two highly experienced professionals at the clinic would also support Macchiarini in his clinical work. These precautions seem operations manager have taken partly to support a colleague who had previous experience of Swedish health care, partly because he was shooting at the reference received unfavorable signals about how Macchiarini worked in Barcelona. These precautions despite we want to emphasize that operations

estate manager has overall responsibility for health care is patient safety.
Measures to control Macchiarinis clinical activity was, in our judgment,
both motivated and adequately designed. They appeared to still be insufficient for such a hard-driven employees who Macchiarini. The many uncertainties surrounding the licenses required was due to the contacts was so informal between the employees entrusted with to support Macchiarini and authorities. There are reports that in addition Macchiarini had their own informal contacts, which must be moved to another operations manager

Although spread information about support for Macchiarini to the clinic staff. but someone formal delegation was not. Whether delegation existed or not and what conditions,may have been, was the operations manager who had the final responsibility for Macchiarinis operations were conducted on a patient safely.

While transplantation of patient 1 was at the ENT Clinic, transplanted patients 2 and 3 at the chest clinic. Although Macchiarini was still employed at the ENT Clinic it was informed of the clinic is not the operation of the patient 3 until it was completed. Responsibility for the transplant was carried out low, except on Macchiarini, thoracic clinic operations manager. The head had been asked about the patient 3 was able to undergo surgery at the Thoracic Surgery [42,43]. He expressed some dissatisfaction with the information about the patient was so frugal [43] and he appears not to have been actively involved in the surgery decision [40].

Business managers in ENT and thoracic clinics took themselves with the problems of Macchiarini and his activities in the hospital. The head of thoracic clinic decided

Macchiarini that would not be allowed to continue to operate the clinic. The head of the ENT clinic suggested the hospital management that a "Accident Investigation" would be added to the light Macchiarinis business but seems mainly intended to have cooperation between the two clinics.

You can of course discuss if these initiatives could have been taken earlier (especially when facing transplant in patient 3), but our assessment is that the business manager at the Department of Thoracic Surgery acted properly when the difficult issues surrounding transplants became apparent.

Although they struggled from the ENT clinic's side came thoracic clinic's decision in practice mean that Macchiarinis surgical operations at the hospital ceased.

Head of Doctors' role.

In Macchiarinifallet the chief medical function had a very peripheral role during the time Macchiarini was employed at the hospital. Chief Physician's role is not regulated by law but each caregiver defines itself the mission's content. In our interviews, it has become apparent that the role of chief physicians and their staff have the Karolinska University Hospital is not unambiguous.

On the one hand, it was mentioned that the chief doctors can not be used to relieve the business managers their liability for patient safety, on the other hand, expects chief medical function to be more operational down to the patient level. For example it has been suggested that the chief doctor should lead multidisciplinary conferences for the advanced treatment.

We believe that the chief role of doctors should be completely unambiguous and known among hospital employees.

Whether it concerns medical or clinical research must be patient safety in main room. This responsibility manage the physician's most important mission. The mission and responsibility should made clear, not least in the use of new untested methods.

Later in this chapter we take up particular patient safety issues surrounding the transplanted patients. In our view, patient safety should be one of the chief physician important mission, perhaps the most important.

One of the then head of the doctors endorsed the decision to operate patient 1 with reference partly to the Helsinki Declaration erstwhile section 35, and that it concerned health care with mandatory indication. As we have pointed out elsewhere in this chapter, we do not believe that this was an accurate assessment.

11.6 Assessment of what has happened in relation to the laws, regulations and international guidelines

summary assessment

Our overall opinion on the basis of the incidents is that the hospital lacked a good attitude to the health care regulations. As stated in the previous section, we believe that transplantation of the synthetic luftstruparna has provided clinical research. The hospital should have applied the Ethical Review Act. The lack of a research ethics review was crucial for the chain of events that led to the tragic outcome.

In connection with the ethics approval also required the permission of the MPA. No such condition there was not.

The hospital has also departed from the standards of health care. the management system is to some extent, been deficient. Lex Maria notification should have been made, in any case, after the operation of the third patient. The provisions on information and consent and new medical assessment not handled in a satisfactory manner.

Contacts with various licensing bodies were handled informally, usually through phone calls. The has given scope for divergent interpretations. We find it unacceptable that refrained from use formally correct ways to assess to what extent the conditions needed for different parts of transplant concept.

Legislation and state.

Our assessment of what has happened in relation to the laws and regulations is horizontal in nature and are also found in part in other chapters. relevant authorities naturally based on their responsibilities more formally decide on infringements of regulations occurred and what the consequences of these in this case may lead.

We have in previous chapters describe what we lean on our assessment and then come to that the present proceeding without a doubt been the research (which according to the Ethical Review Act also covers development on a scientific basis). It is the research organization that will be responsible for application to the ethics board is made. In situations where the university and health care are involved there could be a debate about who has this responsibility. Assessment, decisions and performing transplants, however, has taken place within the framework of the Karolinska University Hospital clinical operations. We therefore see it almost for granted that application for ethics approval based Ethical Review Act was a task for hospital / county council to gather before interventions began.

It can be a space of care to apply untested methods and conducting clinical innovation work. This does not mean that the doctor can deviate from the Ethical Review Act when criteria for research exists regarding the conducted business. There are different opinions how large the scope for deviation is. Medicinetikern Nils-Eric Sahlin and Counsel

Lena Wahlberg has in an article in Läkartidningen found that Swedish law gives a particularly limited (or no) room for the use of untested methods [44]. Swedish Medical Society and the Royal Academy of Science, in a joint report found that new untried methods of rule should be evaluated as a research project, but it should still be the ability to apply them to single critically ill patients when other treatment exhaustion [45]. Such considerations are not relevant when there is a clear aspects of clinical research, which we believe that it is done in the case of transplants of synthetic trachea.

Then comes the Ethical Review Act. These findings then controls largely what other rules applicable to these interventions. Operations with luftstrupstransplantationer and its conditions meant with great clarity not only medical positions needed to be done. Although other approaches

was necessary to consider, such as legal issues, and authorization from competent authorities.

Attempts to clarify these issues were insufficient. Being a part of this regulations may be perceived as difficult to access can not be taken as a lack of adherence to current regulations. An overall assessment of the situation in the hospital was in had been necessary. We can therefore based on these events do not free ourselves from the impression that the hospital lacked a good approach to health care regulations, at least in the context of more extraordinary situations in nursing work.

Virtually all the rules in the health field has the patient's best as a starting point and this focus is a cornerstone of the area lagreglerats whatsoever. You usually in this connection, that the patient is at a disadvantage in relation to health care through the weakness that the illness itself means and through the often low level of knowledge the patient has medical issues, compared with caregivers. As a result, the patient often does not assess the relevance of the medical measures proposed.

Therefore, a wide information and communication needs that must be met in order to be able to claim that the patient has and may exercise its option to self-determination.

We have previously noted that while legislation in the research field has a similar direction but in some respects, the regulation stronger. Ethical Review Act means the Unlike the health care law, that an independent authority will consider the reasonableness of the conditions for the participation of the patients in the part of health care constitutes research. Ethical Review Act's overall purpose is precisely to protect individuals and to provide a guarantee of respect for human dignity in research will be considered.

In Macchiarinifallet also responsible doctor had difficulties to make reasonable assessments of risks and likely course of care that you can normally do on the basis of science and proven experience. Therefore, there has been very uncertain and precarious

health care situation for the patient. In clinical research on patients care and research mixed together and goes partially into each other. A slippage the boundary between the places towards research-related elements in health care ethics are tested, contrary to the Ethical Review Act foundations.

If the business instead had been regarded as health care, would engagements with the good margin in conflict with the requirement of science and bereft of experience. We have previously explained for our view that the application of the concepts of vital indication, compassionate use, and last halmstråets basically could not legitimize the intervention was performed.

The synthetic trachea as such was a medical device, but in this context, when the product also must be lined with the bone marrow cells (containing a minor proportion of stem cells) to obtain the desired function, it became an advanced therapy medicinal products, in this case a so-called combination product. Necessary permits from the MPA was missing. The need for such permits had been under the MPA made clear to researchers and clinic managers when they sought advice from the Agency in 2011-2012. The lack of state must be considered as a serious deficiency.

Drugs were given in connection with the interventions to stimulate the formation of cells. One of these drugs lacked approval for use in humans. Pharmaceutical treatment should have been a part of the clinical trial for the synthetic trachea and represented thereby a departure from the provisions on clinical trials.

Health care legislation contains provisions of varying magnitude and a level of detail varies. It can be seen that if a health care provider not followed the rules in level of detail is of course to some extent violated the horizontal rules that this detailed regulation originates. So, for example, health care law and patient safety law demands hardly met if the National Board of Health regulations for management not been followed in all parts, or not been followed up adequately. In this case we see deficiencies, which are commented on in detail in the description of patient safety issues.

The management of the demands on the caregiver that the rules of lex Maria means has not been priority. These experimental surgeries could be described as a conscious risk-taking from hospital side with a clear departure from the science and proven experience. Lex Maria provisions fit less well in such a context, and the rules are not quite that simple apply. Should notification yet commented on, we want to emphasize that we assume that

the complications that arose after the first operation was not considered notifiable then the damage undvikbarhet with regard to current knowledge could not be assessed. The was initially a little knowledge to fall back on and lex Maria regulation was not seen as primarily relevant if it ever discussed. We share that view. It is therefore in some sense understandable that such notification was not made after the first operation. After the third operation was, however, in our view clear that a lex Maria notification

should be made in light of the experience which had accumulated.

The possibility of a new medical assessment (second opinion) in the Patient Act, transferred to the current conditions, would have meant that patients are given the opportunity to get an outsider physician's assessment of the issue of their current health condition, possible treatment options and of a synthetic trachea was really the only way to save the lives of patients in a short or longer term. The regulation was applicable even if the transplants mainly constituted research. One could argue that the assessment of patient 1 made in the USA - Proposing palliative care - meant a second opinion. The question is to what extent the patient was involved in the decision to consult the American expert. In any event took in this assessment did not consider the treatment option windpipe transplant.

Contacts with various licensing bodies were handled informally, usually through phone calls. It has room for divergent interpretations. Roughly speaking, one of the authorities - Medical Products Agency, Local Ethical Committee and Research Council Ethics Committee Chairman - understood that they responded to general questions and gave general advice, while from the clinic's understood that it had received the go-ahead to begin transplanting.

The three patients treatment housed also numerous legal questions. We can not see that such specific legal contacts have been made, either internally or externally.

Our conclusion is that it is unacceptable that the unofficial roads handle questions about any permission. It is also clear that from the official side had needed to be clearer in express requirements of formal applications. Macchiarini and his associates would have applied the Ethics Committee on research ethics approval. Although it had been a matter of pure medical condition would have been obtained from the MPA. The hospital's efforts to formally prepare for Intervention has been fragmented and inadequate.
We can therefore based on the incident does not free us from the impression that the hospital in connection with work with these transplants lacked a good approach to health care regulations.

Knowledge of the regulations.

At the two clinics involved seem knowledge of regulations and if professional recommendations have been limited. An obvious deficiency is more general that not all operations managers at the Karolinska University Hospital has been training in Good Clinical Practice. We believe that training is needed at all levels.

Professional guidelines.

In discussing the Macchiarini and his activities at the hospital The Helsinki Declaration's Article 37 (in the 2008 version of Article 35) invoked. it provides the possibility that the medical use unproven methods in single patients. Declaration also calls for research to determine the method's safety and effects. You can say the Helsinki Declaration's Article

37 gives considerable scope for the occasional patient using a new method without necessarily moving research.

One must remember, however, that the Declaration of Helsinki consists of recommendations developed by the World Medical Association and that it has no legal status (although many of recommendations are the basis for the Swedish Ethical Review Act). The declaration states also that doctors must follow the national legal framework, if it means greater protection for the patient than what is said in the declaration (Article 10). Full declaration permeated by the patient should not be exposed to unnecessary risks.

The other policy documents that were relevant are the recommendations of stem cell researchers international organization ISSCR. The document gives some room to under certain strict premises using unproven stem cell-based methods of care (see Chapter 7).

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Before the transplants took Macchiarini forward a written report. We believe that ISSCR's Guidelines for the use of untested methods of care followed in some respects. In the second followed respects they do not. We compare this to what happened in connection with the three transplants with what is stipulated in ISSCR guidelines (described in chapter 7).

• Written protocols were (although it had obvious shortcomings).
• Scientific justification for treatment was in the Protocol. However, information on preclinical Studies were missing, as well as the benefit-risk assessment.
• Description of alternative treatments were lacking in the protocol.
• There was a description of how to proceed in order to prepare the bone marrow cells would be used.
• Plan for monitoring and data collection to evaluate the effects of the interventions were. The recommendations also stress that evaluations should be objective; that question is currently being investigated among others by the Central Ethical Review Board of experts for misconduct research.
• Multi-disciplinary conferences were conducted before the transplant in patient 1 and 2 but not the patient 3; participants at the conferences had not sufficient specialist knowledge to assess whether transplantation of synthetic trachea was justified or not.
• mutilation was only partially anchored on the activity level (Macchiarinis business officer ENT clinic was not aware in advance of the transplant in patient 3 on the thorax clinic).
• We have identified some shortcomings in the processes for preview and access equipment; see separate texts.
• Written consent is documented regarding patient 1. We have separately described the shortcomings in information and consent.
• There was no plan to deal with possible side effects and to meet any need of psychological support.
• Plan for the disclosure of the results of the transplants were missing, but the intervention and the clinical course of patient 1 has been published in detail (the issue of misconduct continues to investigated), while the outcome for the patient, 2 and 3 only

briefly described in table form.

Overall, the Declaration of Helsinki and the ISSCR guidelines some room for use of untried methods for a few patients; from a fundamental perspective, luftstrupstransplantationerna at the hospital in this way be justified. Declaration of Helsinki speaks of national rules must be followed - this would apply in this case, for example, the MPA regulation surrounding tissue engineered products. As we noted above, it seems as if in several respects departure from Swedish legislation. The hospital appears to have relied only the Helsinki Declaration Article 37 - you have not inserted this article of the Declaration wider context.

In many respects ISSCR guidelines are not met.

Local rules.

It has been at the hospital lacking local rules for using new untried practices outside the clinical research. When introducing a new untested method often missing (or almost always?) risk analysis. Several of those we interviewed emphasized the need for a better system To quickly detect when new methods are too dangerous or otherwise at going wrong. Several have also considered that the chief doctor must be turned on when facing a fundamentally new approach. Section 11.12 below we describe the hospital's new initiatives in this area.

11.7 Patient

summary assessment

We have not had the ambition to shine through the entire hospital's patient safety culture and patient safety. Our impression is still that the hospital on the whole appear to have an adequate organization and working with the tools and models needed for an effective patient safety.

Macchiarinifallet, however, has revealed shortcomings in the management and control of the business. No risk analysis conducted for interventions and systematic follow-up was lacking. Patient safety must come first when new methods are introduced.

As we concluded in section 11.6, should the lex Maria notification having been made, in any case, after the operation of the third patient. A lex Maria complaint had resulted in the hospital conducted a case analysis.

Although Macchiarini had already quit his transplant operation, had a event analysis could identify more general patient safety issues. Possibly you could say that our investigation is now an unconventional form of event analysis. Based partly on interviews, and on the measurements of patient safety culture of the hospital

implemented, there is a great deal to suggest shortcomings in patient safety culture in the hospital. Our detailed audit has focused on the clinics where Macchiarini worked. openness to point out and correct the deviations are insufficient. It appears that there is a silence in culture Hospital clarified by Macchiarinifallet.

The review in Chapter 9 shows which tools are the most established in the work to reduce nursing injuries. The hospital appears at top management have a good knowledge of these methods and, most of them to enhance the safety of patients in the hospital.

Although the hospital worked with the methods that are available to enhance patient safety this event has still been able to occur. The question is whether some factor in patient safety broken or if there is an individual / individuals who caused or contributed to these extremely serious consequences.

In order to understand the underlying structures that may be relevant in the context, to understand how the overall patient safety culture is in the hospital and involved in clinics. One must also see how the collaboration between the hospital and KI impact on this process.

As we described in Chapter 9, two general views on patient safety into account.
• When looking at events in hindsight is a risk of erroneous conclusions and analyzes of causality and the key risk factors which are not understood [46]. All the alternative possibilities that existed at the time the decisions were taken and which then led to health damage must be clarified.
• There is rarely a simple relationship between the "human factor" and the errors committed. Human error should be seen as an effect of the vulnerability in the system deeper in the organization [47]. One secure system will contain latches and correction capabilities that prevents or at least hampers the various stakeholders in the care process doing wrong. Based on these two general comments will we report here the factors that are important in Macchiarinifallet.

Organisation.

We have not transparent how patient safety in general works at the hospital. But based on the material we had available, it appears that the hospital has an adequate organization and access to the tools and models needed. However, as the Swedish Accident Investigation Board previously noted in the investigation of a different treatment of injury, in that case still weaknesses in management and control of activities [48].

The conclusion is that the hospital management should better follow according to the National Board of Health regulations on quality management and patient safety in health and medical care [49]. Thus, the hospital should work for a more effective system for patient safety which systematically and continuously develop and secure the quality of care. This can only

done by that patient safety is put first when, for example introducing new methods, organizational and budgetary changes.

Looking at Macchiarinifallet we find that it does not adequately followed up his business. A management tool has not been used for the new surgical technique was introduced whether in relation to risk analysis or monitoring. Appropriate controls have not been made, either by person, underlying research or proven experience. It is important to position the group at the hospital is now preparing a program for the introduction of new untested methods, this fundamental perspective into their work.

Risk analysis.

In Macchiarifallet was never question of a risk analysis prior to transplant up. It was judged all three interventions as necessary - either because of the existence of vital indication or to other treatment was lacking ("compassionate use"). The fact that these names used infringed the need for risk analysis. Given that it was felt that the moving on health care (not research), the ethical permits and permission from the Medical Products Agency was missing, it had been extra set position with a risk analysis. The time was considered key which might also contributed to risk analysis never raised. Our assessment is that there were both respite and time for risk analysis.

Deviation, Lex Maria registration, event analysis.

The hospital has a strategy that isambitious that measures the number of abnormalities per employee and in this way encourage incident reporting. This view is, however, somewhat simplified and do not measure the quality of deviation management at the hospital. (See Chapter 11).

As described in section 4.2.1 was a lex Maria Notification of a patient Macchiarini surgery at the hospital, however, no deviation or lex Maria Notification concerning the transplanted patients. In Section 11.6, we have discussed the possible explanations that no notification.

There was, however, a notification regarding research misconduct (Chapter 6), which was the origin the great mass media attention. This is commented on elsewhere in this chapter. Cards can be mentioned that this notification was addressed primarily to KI and not to the hospital. Therefore handled not as a deviation in health care and hence as a potential lex Maria case.

Our interviews have revealed that there were several signs of Macchiarinis inadequate Managing Agent of the patients. Once notification of ERA came Macchiarinis this should be led to asked whether any research misconduct could have had clinical consequences. A dialogue with the complainants had provided a deeper understanding of the underlying problems, but this did not happen. On the contrary, challenged the plaintiffs action. From a patient safety is devastating if there is repressive signals in the system when failings

medical injuries or adverse events not mentioned. A culture of silence causes a danger that necessary security is not detected and corrected. Although hospital management actively oppose a Such a culture can still be found in the underlying system, driven by other employees and managers.

The regulations for the lex Maria is clear but may still have been difficult to apply the three luftstrupstransplanterade patients [50,51]. A Lex Maria notification has many advantages. For it First, everyone involved realizes that there occurred a serious health injury clinic management / chief medical attention; second is an external investigation, for the third takes a structured analysis that can lead to actions that promote safety. The investigation IVO performs after a lex Maria Notification is therefore often a support for the development of patient safety at the hospital / clinic.

Even taking into account the possible misalignment that one can make when considering a course in retrospect, should have been considered lex Maria registration, at least for the patient 3. If this occurred had probably been less negative impact of hospital management of Macchiariniaffären. Lex Maria notification was not made to be regarded as incorrect. A Lex Maria Notice had undoubtedly resulted in an event analysis. It could possibly able to see our investigation as a kind of external event analysis. But the normal routine is

the caregiver yourself doing an event analysis at preventable, serious health damage with potential implications for patient safety. The main thing is that the experience of Macchiarinifalletleading to the improvements and changes needed to increase patient safety at hospital.

Risk Individuals.

Section 11.2 is clear that we believe that there was a major lack Macchiarini hired both KI and the hospital. An efficient management system should have an effective filters and control systems for recruitment, particularly when key people are hired. Macchiarinis Clinical activity was not followed up in a structured way. Had this been more accurate had previously identified several risk elements in his clinical activity in terms of indication position (There are other doctors also participated), follow-up and continuity issues, documentation deficiencies, cooperation difficulties.

Patient Safety Culture.

We have not had any ambition to shine through patient safety culture throughout the hospital. Yet pointing our observations during the work on Macchiarinifallet that there may be considerable shortcomings. This is based partly on interviews, and on the patient safety culture surveys available. As reported in Chapter 9, there is great potential for improvement the ENT clinic, but particularly in the thorax clinic - the one that stands out from the national results is the overall safety awareness at the Department of Thoracic Surgery 2013 (index 43 compared the national index 57) and the self-reported patient

level (index 29 compared to National Index 53). An employee survey carried out in 2015 consistently gave a picture of less happy employees at the Department of Thoracic Surgery and less confidence in managers at various levels as compared with the hospital in general, which could indirectly affect patient safety [52].

These results should be assessed carefully as sources of error are many and the differences are not statistically processed. The response rate has been very low. This gives the uncertain response, but usually while indicating weak interest among employees for patient safety issues. results may thus point to the areas to which patient safety must be concentrated. At the Department of Thoracic Surgery work is under way to improve patient safety and some favorable results of the work has been reported [53].

Our interviews strengthens the view that there is considerable scope to improve patient safety cultureat the hospital. It is likely the only way to provide a safer treatment is to create a "resilient" system where the holistic approach goes before individual mistakes and where responsiveness to security issues permeates the entire business. A proactive and flexible approach needed to create a sustainable and safer system in the clinical activities at the hospital.

11.8 Possible causes contributing to developments

11.8.1 Groupthink and the bandwagon effect

summary assessment

In all probability contributed groupthink that warning in connection Macchiarinis employment is not taken seriously enough and that it is facing the transplants were not objections from Macchiarinis clinical colleagues.
The initial image of Macchiarini as highly successful appear to have created a bandwagon- effect, when the cart came rolling well so it was important to keep up.
The desire to be involved in the introduction of a pioneering medical treatment are among employees and managers made them less likely to make adequate risk assessments and to follow regulations.

In Chapter 7, we have given a brief introduction to the phenomenon of group think and the bandwagon effect. One of the central components of groupthink is that dissent under-

pressed. In connection with Macchiarinis employment at KI and the hospital and during the next following the time came a few very serious warning. Groupthink may have contributed that signals are suppressed. Macchiarini have renowned great ability to convince Other. This seems to have strengthened the group thinking and contributed to his clinical activities are not critically reviewed until about two years into his job at the hospital.

A similar psychological concepts, studied mainly in the social sciences, is bandwagon-effect - once the carriage set in motion, it becomes increasingly difficult to question the movement. Yet difficult it is to completely drop out. The image of the extraordinary success that surrounded Macchiarini during his first time at KI and the hospital may have created a bandwagon effect - "everyone wanted to dance around the golden calf" that a few of them we interviewed put it. In our interviews, we have tried to get a grip on it could possibly be a culture in the hospital promoting groupthink. As we discuss in the next section are some indications of this. A culture where dissent crowding can have negative effects on patient safety culture among annnat (See Chapter 9).

It should also be noted that in such a large organization as the Karolinska University Hospital can hardly speak of a single culture - it is highly likely that there are several parallel cultures. The quest for coherence / groupthink probably varies greatly between the different activities. There is no doubt that a number of responsible and motivated people beyond Macchiarini saw this as a groundbreaking pioneer work that one for themselves and for the hospital's reputation wanted be involved in. This in itself understandable and good intentions, however, blinded ability to assess the risks and the desire to make a sufficiently thorough background analysis method.

11.8.2 Approach

summary assessment

In such a highly competitive environment that Karolinska University Hospital, it can occur in some places a culture of silence. There seems to be many informal leaders in healthcare, something that can make decisions and responsibilities unclear. Knowledge of and respect for the regulations that exist seem to vary within the hospital. It is not unusual to take a short cut in curves through informal contacts with the authorities. In Macchiarinifallet are such examples. From the hospital management has had ambitions to oppose a repressive culture. This work appears not have been fully reflected throughout the hospital.

Karolinska University Hospital has a long tradition of being regarded as the country's leading as well as medical research, which creates the risk of flaws and shortcomings are notn visible. There may be a need for further development of the hospital's work values. We reject references to historical examples of surgical pioneering efforts and wholeheartedly supports today strategies to develop new surgical techniques in ways that minimize the risks for patients.

General culture.

We have in our interviews raised the question whether there is (or has been) a particular culture at the Karolinska University Hospital, which would facilitate Macchiarinis transplantation or other similar events. Here we have got very different responses, which can depend on what function it had, at the clinic they worked but also on whether you

have worked in environments other than the Karolinska University Hospital.

Separately, we present our assessment regarding patient safety culture (section 11.7). We want this just highlight two phenomena that may have had some bearing on the assessment of Macchiarinis Operation:

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• In such a highly competitive environment that Karolinska University Hospital is in some places a Silence culture, they are wary of open criticism upward to avoid jeopardizing his position. Often it is associated with that employees are not loyal to the decisions made.
• Because there are so many who are heavily academically qualified and have their KI services associated with clinical service at the hospital, there are many informal leaders. Shared services can lead to conflicts of loyalty.

Cut corners.

As described elsewhere, there are examples of Macchiarinifallet chosen informal rather than formal avenues of contacts with the authorities. Some of them
we interviewed have seen this as a "contagion effect" from KI, which would have a culture that for reproduction curves ("cut corners"). KI appears to have developed informal channels of contact with the county leadership, ministries and agencies that are unusually open in comparison with other universities.

Whether this view is correct or not, we see that one of the involved clinicians page not enough strictly followed the regulations that exist.

Repressive culture? In the debate, the hospital's handling of the four notifying doctors interpreted that the hospital is a punishment culture. We have not been able to assess whether this is generally for the entire hospital but can state that in the early stage of notification of fraud in research (aimed at KI), primarily focused on the issue of the journal intrusion complainants' side. This can be from a medical legal perspective have been correct but it came to obscure the critical issues surrounding Macchiarinis transplant operations.

Both the former as the current hospital director says he worked hard against a repressaliekultur (with introduction of a visselblåsarfunktion 2015 in the example). It is possible that this work has not been full impact at the clinic level.

Values work.

When the former hospital director took office, he saw a great need to pursue work on values. This work was to be conducted from 2007 onwards. of our interviews to judge, there may be a need to further develop the work values, something that has already begun

on the chest clinic.

The historical heritage.

Several of the academic representatives we interviewed points out that a lot Some of today's advanced surgery based on the bold pioneering work, albeit at the price of initially high mortality. Two Swedish example is the brain surgeon Herbert Olivecrona and heart surgeon Viking Olov Björk, both regarded as pioneers in their respective fields. the one worked at the Karolinska University Hospital throughout his career, the other in parts.

Another example put forward is liver transplantation, where the mortality rate was high during the first years.

A comparison between luftstrupstransplantationerna and these historical examples are hardly reasonable. In Macchiarinifallet will be including the issue of how patients are selected for these engagement. We ask ourselves wholeheartedly behind today's strategy - to develop methods to animal experiments study and to practice the surgical technique on animals or in a simulator before embarking with operations on humans. With this strategy, the risks of the first patients was minimized.

11.8.3 Relations with KI

summary assessment

KI and the hospital has not had the same basic strategy for the hospital. While KI wanted wager the excellent researchers and top recruitment of employees with shared services, hospital management sought a system of continuous improvement with the aim of creating a credible and patient safety organization. At senior management level were consequently KI's backing of Macchiarini more wholehearted than the hospital.
KI has, for better or worse, a great influence on decisions taken within the hospital organization, influence which is probably larger than at other Swedish university.

When Macchiarinis research was criticized by notifiers and in the media. set hospital in our opinion, too favorably on the KI line in the defense of Macchiarini.

Different strategies.

According to the former hospital director acted KI always for their own purposes, which influenced relations between KI and the hospital. Hospital management tried to create a system for continuous improvement in order to create a credible and patient safety organization. KI had little understanding of this work. They wanted instead to invest in excellent researchers and recruit stars.

After the hospital director had previously perceived to have very good backing from the hospital Board, the change of chairman in 2013, KI received more feedback on their strategies in Hospital Board. As we also mentioned elsewhere (section 11.2.1), we estimate that Macchiarini fitted well into the CI strategy - he drew in large research grants and county council came to bet big money on him and his research.

Power relations.

Those we interviewed at the hospital has consistently described the KI large influence on decisions taken within the hospital organization, an influence which is probably much greater than at other Swedish University Hospital. We perceive that KI's prestige and big success, the institute's central position in the Swedish medical research, its economic muscle and powerful representatives have contributed to the large influence on the hospital's decision.

We find that the power relationship between KI and the hospital has been particularly evident in recruitment of Macchiarini, where KI side in practice come to decide that he would be recruited and that he would have a clinical appointment with placement at the ENT clinic. When Macchiarinis employment at the hospital ended, however, took the hospital decision, contrary to the objections of KI side.

We want to reserve us to the people we interviewed were employees of the hospital. They may have had a desire to reduce the hospital's role and power in Macchiarinisaken.

Different settings to Macchiarini. In the years 2012-13 was the relationship between hospital management and KI management increasingly strained. The main reason may have been to the hospital in January 2012 took over the future planning of the NKS project from the county administration. KI had in the previous organization had a major influence on the planning; This influence decreased now. At a meeting with KI's headmaster (and vice-rector at present) were hospital director upset criticized for this, but also to the hospital would have worked against Macchiarini. We see this as an example of KI's backing of Macchiarini been more wholehearted than the hospital, at least at senior management level.

The debate surrounding Macchiarini. Since the notifications were directed to KI's rector and the question of misconduct in Macchiarinis research, it was long KI who came to stand in the focus of the public debate. In a review of the available e-mail correspondence and other written material, it is clear that the CI sought to clarify that the institution had no responsibility for luftstrupstransplantationerna. KI searched (and thought to find) basis to the hospital's ethics committee approved transplants (e.g. [54]); in fact treated transplant question never by the Committee.

KI was set state that the hospital would be present at the press conference which the president unveiled his "acquittal" assessment of allegations of research misconduct. KI

also took the initiative a joint article, which the president and the hospital director in September 2015 both stressed that Macchiarinis transplants performed as life-saving health care, not as research [55].

New approach to hospital.

In the new business model for the hospital (2015) stresses the importance of a high degree of integration between healthcare, research and teaching. One of the basic principles of cooperation must be that patient safety is the top priority in the highly specialized care [56].

11.8.4 Economic conditions

summary assessment

We do not have transparent economic conditions around the patients, but notes that the care of the three patients at the hospital has required huge resources, both personnel economically. Two of the patients were the financial arrangements for the operations so unclear that they gave rise to disputes.

Regarding patient 1 and 2, economic conditions have not yet been settled five years after operations. For the first patient approved the hospital director to the hospital undertook to stand the costs of any complications after the procedure. For the second patient, issued KI Department CLINTEC a financial guarantee, an improvised solution when the patient already was on his way to the hospital. Lack of planning and Macchiarinis free approach probably caused time pressure. Therefore forced the hospital (and KI) to unconventional ad hoc solutions.

11.9 Notifications to Macchiarini

summary assessment

When the first notification of irregularities in Macchiarinis research submitted to KI had Macchiarinis employment at the hospital already completed. We believe that any research misconduct possibly influenced the transplanted patient care through the course of the first surgery the patient was described too positive. It led to not question that patient 2 and 3 would transplanted.

It was unfortunate that the focus initially was to be on the question of possibly unlawful intrusion record instead for on the important issues of Macchiarinis operations at the hospital. It has been perceived as a repressive action against the employees who complained of abuses.

We have not investigated allegations of research fraud - it makes other inquiries. However discusses we are the charges that may be of relevance to clinical practice, as

well as the notifications came to be treated by IVO and Drug Administration.

As seen in Chapter 6, reacted to the Belgian ENT Professor Pierre Delaere on the press releases if the first transplant of synthetic windpipe that KI and hospital sent out in 2011 before the Lancet article on the transplant published. He reappeared 2013-15 KI's rector with further criticism (seven emails, of which he had to answer to a) where he among other things, asked about the idea that stem cells could form a working trachea was "The biggest lie in medical history" [57]. Of documentary evidence we had access to it appears Delaeres criticism essentially have been handled within the KI system, but it has also reached the hospital side.

None of the addressees of Delaeres emails were decision-makers in the hospital and it appears unclear whether Delaere had fully realized that KI and the hospital are separate organizations.

When the first notification of research fraud / irregularities Macchiarinis research inlämna-

des KI in August 2014 had Macchiarinis employment at the hospital already ceased then close a year. Registration for KI's principal was among other erroneous clinical data on the transplanted patients. KI's investigator Bengt Gerdin found the basis for these allegations.

Now new studies underway in research fraud issue. We have not had visibility into these investigations, but if they would confirm that the articles contain inaccurate clinical information so the responsibility falls, except on Macchiarini, also his co-authors, several of whom are or have been active
in the hospital (and the two are among the complainants). From a medical point of view, their actions a moral dimension. The positive description of the process after the transplant patient 1 may have led to insufficient questioned the method when it was time to operate the two other patients. Four of the authors have withdrawn their co-authorship of the article on the first transplant.

The four notifying doctors had permission from the families of patients 1 and 3 from the patient himself to go into the records and retrieve information for their investigation of possible research misconduct. The also had approval from the Local Ethical Committee [58]. While the consent of relatives and patient obtained before doctors began their exploration of the records, came the decision of the Ethics Committee after they went into the records. This latter relationship pointed out by those who have been critical of the four notifying physicians. operations manager at the ENT clinic initially seems not to have been aware of consent from patients / relatives. He perceived it as a large-scale medical record intrusion and contacted the hospital Counsel [59].

Different forms of labor action, primarily warnings, were present. Whensince records became available online (via RetractionWatch) made the chief doctor and hospital Counsel Police reports of illegal journal intrusion. Assuming that the business manager not been informed of the patients '/ relatives' consent (There are conflicting data), seem initiative from ENT clinic management have been adequate. We find it unfortunate that the focus initially was to be on the question of any unlawful Journal intrusion rather than on the serious issues of Macchiarinis clinical operations.

10.11 Media

summary assessment

We are strongly critical of how the first transplant patient came to be used in marketing two universities, a hospital and individual surgeon. In at least one of the transplants Macchiarini planned to provide a media opportunity to film without the patient's consent. These plans were stopped by the chief doctors, in our opinion completely correctly.

As a result, we made different assessments of the substance, we are also critical of the hospital's argument in recent public debate, where the stubbornly defended transplants pure medical efforts and stressed that it did not circumvent any regulations.

The first transplant attracted much attention in the national and international media (Section 10.4). Macchiarini himself was remarkably active in its media contacts before surgery. Although one of the hospital's side made some efforts to try to control the media coverage, took the same time the opportunity to strengthen the image out of the Karolinska University Hospital Located in the front line. Even from KI-hand man offensive in its media presentation of the transplant. The patient was also presented at the Iceland University's 100th anniversary, when he already started to have problems from the graft. We are strongly critical of how this patient come to be used in the marketing of two universities, a hospital and individual surgeon.
We have found that patient 2 received attention in the media. A planned filming of the first transplantation of the patient 3 was canceled after the intervention of the chief physicians because patient lack of consent (Section 10.4). Patient 3 has subsequently attracted media attention in the negative context and not in the hospital initiative.

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In February 2012, visited a journalist from The New York Times Macchiarini and his activities in Stockholm, which resulted in a very positive reports [60]. In the report interviewed Patient 1. The journalist was also offered to participate in the international videoconference described in Section 3.4 [61], the latter a remarkable initiative because there discussed concrete patient with privacy sensitive data.

The Italian media attention in 2012 to Macchiarini been under house arrest because of accusations that he allowed some patients to go before the surgery queue [15]. This information became known Karolinska University Hospital but appears not to have

attracted the attention of the Swedish media. The case was soon down, but there are reports that it has recently resumed.

In the media storm that emerged around 2015-16 Macchiarini the hospital (as KI) consistently argued that the transplants were strictly humanitarian reasons, it has not moved on research and the relevant regulations are not circumvented. As shown in this report, we in many respects come to different conclusions. In the debate, from the hospital's use the concept of vital indication in a manner that we find to be misleading.

We question the the hospital's stubborn position in defense of transplants clean health care initiatives.

The hospital at first seemed to come off lightly than CIs of the media's scrutiny could possibly be because they kept a lower profile in the public debate. Macchiarini was never the same wholehearted backing from the hospital director as he had from KI's principal. Hospital also had a stronger de facto position in that Macchiarinis employment at the hospital was completed in 2013, while employment at KI was only completed In 2016.

11:11 Implications for clinical research and hospital coworker

summary assessment

Macchiarinis transplant operations have damaged the clinical research not only at the Karolinska University Hospital in Sweden, but also in general. To restore confidence in research require long-term, whole-hearted efforts. It has happened in the Macchiarini is in no way contrary to the bold and innovative clinical research. Such research requires ethics review and may well be combined with high patient safety. Many of the hospital's employees at various levels have been hurt by Macchiarinifallet. It has been in debate been an intransigence, even rancor, as many suffered serious ill of. This can be seen as a health and safety issue. It seems to us to indicate the location contradictions toned down and a "reconciliation process" begins.

From several quarters, we have heard examples of patients' willingness to participate in clinical research adversely affected by Macchiarinifallet. This view has also been in the public debate around Macchiarini. We have not had access to any solid empirical basis in this question. Whether it has been difficult to engage patients in clinical trials or not, we are of the perception of Macchiarinis transplant operations have been detrimental to the clinical research not only at the Karolinska University Hospital in Sweden, but also in general.

The confidence now eroded can, in our opinion, only be restored by patient safety is at the center, that ethical values are safeguarded and that the regulatory framework for clinical research followed strictly. This is in no way contrary to the bold and innovative clinical research. When patients died or have come to severe injury and accountability, it is obviously difficult to simultaneously speak of health workers as victims. We still can

not help but reflect on the many people work at the hospital and KI has been affected very negatively by what happened

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Macchiarini around.

It has been a debate intransigence, even rancor, as many of the hospital's employees have gone very badly off. This applies both to those who have been directly and more peripherally involved in Macchiarinis activities at the hospital. It has also affected those who raised the alarm about the problems which circumscribed his activities. Several of the employees who worked closely with patient 1 and 3 lived through periods of severe frustration. While other staff in the affected clinics (ENT and thorax), as we understood it, felt more contested than before.

It seems to us to indicate the location contradictions toned down and a "reconciliation process" begins. The hospital should process, analyze and remedy the damage suffered by individual employees, in terms of both personal consequences and the working environment. An improved working environment are of course a value in itself, but probably also indirect positive effects on patient safety.

12.11 hospital measures

summary assessment

Four initiatives from the hospital side, we find to be of particular relevance to fix the problems revealed in conjunction with Macchiarinis activity: A working group will work on the issues at the interface between healthcare and clinical research, a visselblåsarfunktion has been set up, hospital has begun examining Macchiarinis clinical activity beyond transplants and work
to strengthen patient safety has been launched at the chest clinic. We also note that the hospital and KI set up a joint panel for strategic recruitment.

In Chapter 12, we propose a number of other possible improvements.

We do not have an inventory of all measures which Macchiarinifallet (at least partially) may have been behind the new initiative from the hospital. However, we want this to highlight a few of the measures.

As we described in Chapter 10 are at KI guidelines for clinical and epidemiological research. We find, however, that this document does not provide any guidance regarding ethical issues or patient safety in clinical research. At the hospital, no guidelines for the application of new untested methods that are not subject

Research.

Recently, however, the hospital and KI jointly appointed a working group led by the hospital's chief doctor. For the problem areas that the group will work with belong the shared main responsibility, the interface between healthcare and research, the lack of documentation in connection with intervention studies and defective condition of the MPA and the Ethics Committee. [62] We find the initiative to be set location.

In 2015 established a hospital director visselblåsarfunktion at the hospital, where employees can anonymously provide information about possible abuses. This appears to be a intentioned but so weakly utilized tools. To get notifications come in this way would be interpreted that other channels to catch up on things that need to be addressed actually works well.

One possible interpretation to the contrary is that employees distrust visselblåsarfunktionen and not believe that a notification would be no changes or even could lead to repressive measures against the notifier, although the function is nonymous.

In Macchiarinifallet questions have arisen about his activities as a whole at the hospital and how safe the patient has been. The Principal has recently conducted an inventory of operations Macchiarini performed at the hospital in addition to the transplants. It has been tentatively identified 29, operations performed by Macchiarini, including the four transplants. A review of these operations have begun. We find no reason to also review some non-surgical interventions Macchiarini who attended (exemplified by a notification of unconventional therapy in a patient during ECMO [63]).

An improvement to strengthen patient safety has been launched at the chest clinic. we find this work indicate the position and suggests that the hospital management carefully monitors it.

In the light of the experience of Macchiairinifallet would the panel for strategic

strategic recruitments was added jointly by the hospital and KI in 2015, come to have a important function. It assumes that the group not only has a visionary role (with the risk of groupthink and the bandwagon effect) but also critically examined the function.

References

1. Simon S. 20 most innovative surgeons alive today. http://www.healthcare-administration-degree.net/20-most-innovative-surgeons-alive-today/ . 2013.
2. Park A. Top 10 medical breakthroughs. Lab-grown body parts. Time Magazine, file://localhost/Users/kjellasplund/Desktop/Macchiarini%20KS/Debatt,%20media/Time%20Magazine%202012.html 2012.
3. Förslag om att rekrytera Paolo Macchiarini som gästprofessor i klinisk regenerativ medicin och kirurgi förenat med befattning som överläkare på 40% till Karolinska Institutet och Karolinska Universitetssjukhuset under 3 år med möjlighet till förlängning 2 år. Brev till KI:s

rekryteringsutskott. 2010-06-04.
4. Mejl från CLINTEC:s prefekt och ÖNH-enhetens chef till Macchiarini 2011-02-15.
5. Mejl från prefekten för CLINTEC och enhetschefen för ÖNH-enheten vid CLINTEC till KI:s rektor 2016-04-09.
6. Mejl från tidigare verksamhetschefen vid ÖNH-kliniken till Macchiarini 2012-02-20.
7. International videoconference – an important step to the transplantation. Icke-undertecknat referat (med all sannolikhet från Krasnodar) från videokonferens 2012-03-16 (möjligen feldaterat).
8. Mejlsvar från enhetschefen vid ÖNH-enheten, CLINTEC till utredningen 2016-07-14.
9. Uttalande 2016-02-29 om den internationella videokonferensen februari 2012.
10. Mejl från verksamhetschefen på thoraxkliniken till Macchiarini 2013-04-17.
11. Mejl angående Macchiarini från ÖNH:s verksamhetschef till sjukhusdirektören 2013-04-11.
12. Mejlkonversation mellan tidigare verksamhetschefen vid ÖNH-kliniken, enhetschefen vid ÖNH-enheten och CLINTEC:s prefekt 2013-04-09.
13. Mejl från enhetschefen vid ÖNH-enheten och prefekten, CLINTEC 2013-05-08.
14. Minnesanteckningar från möte med ÖNH- och thoraxklinikernas verksamhetschefer och deras närmaste medarbetare angående trachealtransplantationer och Paolo Macchiarini 2013-09-13.
15. Macchiarini P. Memorandum: Background to my recruitment at KI 2016.
16. Mejl från CLINTEC:s prefekt till KI:s rektor och forskningsdekanus 2013-10-04.
17. Minnesanteckningar från möte 2013-10-15 med beslutsfattare från sjukhuset och KI angående Macchiarinis transplantationsverksamhet
18. Mejl från verksamhetschefen på ÖNH-kliniken till sjukhusdirektören 2013-04-11.
19. Elliott MJ, De Coppi P, Speggiorin S, Roebuck D, Butler CR, Samuel E, et al. Stem-cellbased, tissue engineered tracheal replacement in a child: a 2-year follow-up study. Lancet 2012;380:994-1000.
20. Broström L. Karolinska blandar bort korten om fuskanklagelse, Dagens Medicin 2015-09-23, http://www.dagensmedicin.se/artiklar/2015/09/23/karolinska-blandar-bort-korten-om-fuskanklagelse/ .
21. Jungebluth P, Alici E, Baiguera S, Blomberg P, Bozoky B, Crowley C, et al. Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study. Lancet 2011;378:1997-2004.
22. Vetenskapsrådet. Beslut att avbryta utbetalning av forskningsbidrag. Dnr 521-2012-5956.
23. Gerdin B. Utlåtande i oredlighetsärende, brev till KI:s rektor 2015-05-13.

24. Nilsson M. Minnesanteckningar från möte angående obduktion och analys av prover från obduktionen av […], daterade 2014-03-10.
25. Betalningsgaranti från Karolinska Institutet till Stockholm Care AB för vård av patient 2. 2011-11-14.
26. Karolinska Institutet. Årsredovisning 2011, sid. 31, https://internwebben.ki.se/sites/default/files/null/arsredovisning_2011_0.pdf
27. Mejl från avidentifierad avsändare på Island till avidentifierad mottagare på Karolinska Universitetssjukhuset 2011-09-11.
28. Future of Organ Development: Alexander Seifalian at TEDMEDLive Imperial College 2013. YouTube-presentation. https://www.youtube.com/watch?v=DR4D24bDPaQ .
29. Heitmiller RF, Mathisen DJ, Ferry JA, Mark EJ, Grillo HC. Mucoepidermoid lung tumors. Ann Thorac Surg 1989;47:394-9.
30. Molina JR, Aubry MC, Lewis JE, Wampfler JA, Williams BA, Midthun DE, et al. Primary salivary gland-type lung cancer: spectrum of clinical presentation, histopathologic and prognostic factors. Cancer 2007;110:2253-9.
31. Zhu F, Liu Z, Hou Y, He D, Ge X, Bai C, et al. Primary salivary gland-type lung cancer: clinicopathological analysis of 88 cases from China. J Thorac Oncol 2013;8:1578-84.
32. Grillo HC, Mathisen DJ. Primary tracheal tumors: treatment and results. Ann Thorac Surg 1990;49:69-77.
33. Maziak DE, Todd TR, Keshavjee SH, Winton TL, Van Nostrand P, Pearson FG. Adenoid cystic carcinoma of the airway: thirty-two-year experience. J Thorac Cardiovasc Surg

1996;112:1522-31; discussion 1531-2.
34. Mejlkorrespondens mellan Macchiarini och verksamhetschefen på thoraxkliniken 2013-06-01.
35. Karolinska Universitetssjukhuset. PM Anvisning för samtycke till fotografering och/eller annan inspelning.
36. Mejl från professor Johan Thyberg till sju chefer vid KI och Karolinska Universitetssjukhuset 2016-07-05.
37. Mejl från verksamhetschefen vid thoraxkliniken till prefekten vid CLINTEC 2014-03-03.
38. Intyg från Dr Dessale Berhane 2014-02-25.
39. Mejl från professor i kirurgi vid Karolinska Universitetssjukhuset till utredningen 2016-06-04.
40. Mejlsvar från thoraxklinikens verksamhetschef till utredningen 2016-06-29.
41. Veckobrev från verksamhetschefen till ÖNH-klinikens medarbetare 2010-10-04.
42. Mejlkorrespondens mellan Macchiarini och verksamhetschefen på thoraxkliniken 2012-04-19–20.
43. Mejl från verksamhetschefen på thoraxkliniken till Macchiarini 2012-05-25.
44. Sahlin NE, Wahlberg L. Kliniskt bruk av oprövade metoder är juridiskt reglerat. Läkartidningen 2016;113:D4WS.
45. Kungliga Vetenskapsakademin, Svenska Läkaresällskapet. Rapport: Kliniska riktlinjer för användning av obeprövade behandlingsmetoder på allvarligt sjuka patienter. http://www.kva.se/globalassets/vetenskap_samhallet/halsa/2016/rapport-etikutredning.pdf .
46. Woods DD, Dekker S, Cook R, Johannesen L, Sarter N. Behind human error. Chapter 2: Hindsight. 2:a upplagan. Farnham, England, Ashgate Publishing Ltd; 2010.
47. Hollnagel E, Braithwaite J, Wears RLE. Resilient health care. Farnham, England, Ashgate Publishing Ltd.; 2015.
48. Statens haverikommission. Dödsfall på hjärtklinikens hjärtintensivavdelning N25 vid Karolinska Universitetssjukhuset i Solna, Stockholms län, den 17 oktober 2010. Slutrapport RO 2013:02 2013.

49. Socialstyrelsen. Ledningssystem för kvalitet och patientsäkerhet i hälso- och sjukvården. SOSFS 2005:12. http://www.socialstyrelsen.se/sosfs/2005-12 .
50. Socialstyrelsen. Socialstyrelsens föreskrifter och allmänna råd om anmälningsskyldighet enligt lex Maria. SOSFS 2008:28. http://www.socialstyrelsen.se/sosfs/2005-28 .
51. Patientsäkerhetslag. SFS 2010:659. http://www.riksdagen.se/sv/dokument-lagar/dokument/svensk-forfattningssamling/patientsakerhetslag-2010659_sfs-2010-659
52. IC Quality. Medarbetarenkät. Karolinska Universitetssjukhuset. Thoraxkliniken. 2015.
53. Mejlsvar från chefläkare Nina Nelson Follin till. 2016-07-06.
54. Tjänsteanteckning av tf universitetsdirektör, KI om tillstånd från etisk kommitté. Dnr 2-2184/2014. 2015-07-12.
55. Hamsten A, Samsom M. ”Vårt beslut vilar på saklig grund”. Dagens Medicin 2015-09-16, http://www.dagensmedicin.se/artiklar/2015/09/16/vart-beslut-vilar-pa-saklig-grund/ .
56. PM Ny verksamhetsmodell för Karolinska Universitetssjukhuset, daterad 2015-11-09.
57. Delaere P. Stem cells can regerate the windpipe and other (hollow) organs). Biggest lie in medical history? Opublicerat manuskript.
58. Regionala etikprövningsnämnden i Stockholm. Protokoll 2014-10-15, § 2, Dnr 2014/1532-31/1.
59. Mejl från verksamhetschefen vid ÖNH-kliniken till utredningen 2016-07-07.
60. Fountain H. A first: Organs tailor-made with body’s own cells. New York Times 2012-09-15.
61. Tidsschema: Visit at the Karolinska Institute/CLINTEC/ACTREM and Karolinska University Hospital in Huddinge. Visitor: Mr Fountain, New York Times. Date: Feb 14th & 15th, 2012.
62. Minnesanteckningar från KI-K Arbetsgrupp – Experimentell terapi, 2016-01-18
63. Call for investigation of possible research misconduct in below paper. Anonym och odaterad anmälan till KI:s rektor.

Chapter 12 Recommendations

12. Recommendations

From our mission from the Karolinska University Hospital: "Based on the facts presented will be investigation, make recommendations for improvements. " Our recommendations are focused on highlighting opportunities for improvement on patient safety, organization and procedures. The report's previous sections, we have clarified responsibilities when the hospital decided that moved Macchiarini and his activities at hospital. We have not had as primary objective to propose retaliatory measures against individual employees at hospital.

We are aware that some of our recommendations may appear to be obvious. But they based on findings of deficiencies found during Macchiarinis clinical operations. Some of the deficiencies have already been addressed in the hospital.

12.1 Management

Observation

• In Macchiarinifallet do not have quality management and patient safety (SOSFS 2005: 12)satisfactory.

Recommendation

• Hospital management should ensure that all clinics are good knowledge of the rules for management system and that the system is functioning. The implementation of the management system should monitored regularly. Hospital management should work proactively and systematically in patient safety (See 12.4).
12.2 The recruitment process

observations

• When Macchiarini recruited as chief physician at the hospital was the process flawed. One example is that you did not take sufficient account of unfavorable references.
• In recruiting Macchiarini acted hospital lacking in independence in relation to KI.
• The hospital did not have sufficient control over Macchiarinis operations at other hospitals. recommendations
• The recruitment process should be quality assured. This is especially true when it is relevant to employment of the key people on shared clinical and academic services, and when it is relevant to hire someone who has not previously well known at the hospital.
• For shared services, the hospital must make an assessment is independent of CI. This applies both to the hospital's needs that the applicant's qualifications and references.
• The hospital should have a system of strict control of the employees' activities at other hospitals, whether formally be regarded as secondary activities or not. This applies

particularly to people with shared employment.

12.3 Regulations, guidelines and ethics

observations

• In our investigation has revealed a number of examples of deviations from the regulations that exist. This may be due to lack of knowledge of the regulations but also in a free approach to rules.

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• In conjunction with the transplants, the recommendations of the international stem cell researchers organization ISSCR only partially followed.
• The County Council's R & D Director has initiated training on current regulations, still in its infancy.
• At Macchiarinis transplants have representative (s) for his commercial partners been present, unclear on what premises.

recommendations

• The hospital - and county - should ensure that all relevant staff are trained in the regulations which may be relevant at a university hospital. It is of particular importance to business managers are solid and up to date knowledge of the regulations. This should include
- Legal framework for patient safety
- Regulations regarding the rights of patients (and their families)
- Regulations concerning research ethics
- Regulations regarding clinical studies and advanced therapies
• The MPA should be invited to discuss the regulations on pharmaceuticals (including stem cells) and medical devices when used in medical care and the clinical research. This can occur, for example, seminars with business managers.
• There should be at the hospital for clear guidelines governing the conditions under which external people can participate in clinical activities. The guidelines should specifically consider issues of patient privacy, informed consent and patient safety. Applies to commercial operators should participation contractually regulated.
• Whether the course in research ethics is compulsory in the Institute's graduate or not, you should hospital require that personnel engaged in clinical research undergone training in clinical research ethics.

12.4 Patient

observations

• Risk analysis was not performed before transplantation with synthetic trachea began. Our impression is that risk analysis is rarely done when the new methods introduced at

the hospital.
• The last patient measurement hospital conducted indicated major differences in patient safety between the clinics. Thoracic Surgery stood out as particularly problematic. Efforts to strengthen patient safety at the Department of Thoracic Surgery in progress.
• National Commission of Inquiry came in 2013 with a comprehensive report prompted by a death at the heart clinic. Limited sections of the report have a bearing on patient safety at the hospital at large.
• Although we have not examined in detail the system deviation happens, it is our impression that focused the number of reported anomalies rather than on the quality of reporting and good feedback.
• It has raised questions about Macchiarinis business in general at the hospital. Although his technical skills are not questioned, there have been doubts about the indications for some of the surgical procedures. He has also been involved in the treatment of patients with ECMO ("artificial lung") supplied to the cells and growth factors in the trachea - although this treatment has been questioned.

recommendations

We have not had the ambition to shine through patient safety in the hospital in general. But Macchirinifallet has revealed shortcomings in patient safety culture and patient safety work possibly also applies elsewhere than at the two clinics surveyed.

• The hospital management should develop its quality review of patient safety at the hospital. To the extent that deficiencies are found, work should be developed on the basis of current knowledge regarding successful patient safety ("resilient" organization that is proactive, adaptable and focusing more on the correct and effective processes and less on discrepancies / errors). Patient safety culture must be characterized by informality, openness and questioning.
• In the clinical and device level, the entire set of methods available to strengthen patient safety exploited. It should work proactively to systematically involve various clinics / units in outreach / prevention work on patient safety.
• An improvement to enhance patient safety in progress at the chest clinic. Hospital management should carefully monitor this work.
• Risk analysis should be routinely performed when new methods are introduced in health care. This is especially true if you want to apply new methods in which HTA (Health Technology Assessment) can not be used or has difficult to interpret the information, and when the new method is not part of a research study. To support such a risk analysis, a specific advisory function established under the model that are at the university in many countries (for example, Leiden, The Netherlands [1]).
• The system for reporting deviations should be reviewed. The focus may need to be changed from volume to quality and timely feedback / action of the relevant incidents.
• Head of Doctors' responsibility and role in patient safety should be very clear.
• The hospital has recently launched a review of Macchiarinis surgical operations, in addition transplantations. There may also be reason to review some non-surgical

interventions he took part in, such as the contested therapies in patients during ECMO ("Artificial lung").

12.5 Clinical decision making

observations

• Introduce two of the transplants were conducted multidisciplinary conferences (MDK). These worked unsatisfactory. In practice, they came to legitimize interventions.
• Introduce the other two transplants (in the same patient) was no MDK.
• In our investigation, we have seen examples of groupthink and the bandwagon effect of multiple decision levels.
• There was a lack of coordination between ENT and Thoracic Surgery.
• There was confusion concerning patient responsibility in caring for the operations. Macchiarinis scattered in many countries walked out of the doctor-patient continuity of care.
• They had not compiled the experiences of previous surgery (e) the patient (s) when decided to proceed with the transplant series. recommendations
• MDK must be quality assured. MDK should be a forum for critical medical and exchange of knowledge and experience which the relevant competences are represented. Deliberations and decisions must be well documented and responsibilities clear.
• When MDK (and other clinical decision making) be revised, should take into account current knowledge in terms of groupthink and the bandwagon effect.
• There should be clear procedures for the coordination of major operations (or other therapies) where several departments are involved.
• The operations manager is responsible for the patient-physician continuity of care. This becomes particularly enter the state when it comes to highly specialized care where expertise is concentrated in single or a few individual (s).
• When a fundamentally new method introduced should follow the effects and side effects patient to patient so that you have access to the experience of previous patients in making clinical decisions.

12.6 Clinical Research

observations

• We do not Macchiarinis, the hospital and the NIER's assessment that luftstrupstransplantationerna are considered to be medical and not as clinical research. The hospital stands by this view risk the continued slide in the application of regulations governing clinical research.
• Ethical Review Act also refers to "development on a scientific basis", which seems be less well known in the hospital.
• The hospital has been repeatedly invoked the Helsinki Declaration in support of its view that research ethical review was not required. It does not appear to have taken into

account the Declaration of Helsinki overall appeal to doctors primarily have to stick to the national legislation.
• The events surrounding Macchiarini has negatively affected the respect of clinical research.

recommendations

• In the hospital and began KI-out internal guidelines for untried methods, should particular emphasis on ensuring that the ethical review the law and drugs regulations.
• Patients / users is a resource in the planning and implementation of clinical studies. their role can be formalized through the concept of the Patient Research Partners.
• To avoid the risk of slippage in the implementation of regulations governing clinical research should Hospital review its position on the question of whether luftstrupstransplantationerna would have Ethics reviewed or not.
• Several of our recommendations in other sections designed to strengthen ethics when new methodsintroduced in health care and to preserve the respect of clinical research.

12.7 New untested methods

observations

• The hospital has so far been lacking a system for introducing new methods, proven or untried.
• A working group with participants from both the hospital as KI, led by chief medical officer, has been formed with duties include reviewing the hospital's rules on the borderline between healthcare and clinical research.

recommendations

• One of the objectives of the new initiative should be to establish a clear structure for how new untested methods to be applied at the hospital. Special ethical competence should be tied to this structure (the Ethics Committee that currently exists at the hospital has a different focus).One may consider introducing a special feature for "orderly introduction and orderly REJECTION "which will consider new and obsolete methods (see also 12.4).
• When the instructions for a new structure for new untried methods should be designed specifically take into account the recommendations recently arrived from the Swedish Society of Medicine and the Royal Academy of Sciences.
• With the large research responsibilities Karolinska University Hospital, should be a default setting be that new, previously untried methods evaluated in clinical research projects and thus undergo research ethics review.

12.8 Cooperation with KI

observations

• There have been clear cultural differences between the hospital management and the KI management in the view of how they want the hospital to be developed.
• In Macchiarinifallet there have been examples of that hospital too kindly set up at KI initiative and, later, on the defense of Macchiarinis business. recommendations
• NKS (New Karolinska Hospital) has an ambition to develop in close cooperation with KI. Cultural issues becomes important, not least at a senior management level. It seems to be crucial that the two sides cooperate on an equal level. At the joint decisions must division of responsibilities between the hospital and KI be clear. Otherwise, lack sufficient transparency in investigation the complex relationships between KI and the hospital to come up with concrete proposals on how relations should be developed.

12.9 Economy

Observation

• We have not deepened ourselves in the economic conditions, but can confirm that in respect Two of the patients have been confusion about the payment of health care. These cases are still not finished.

recommendations

• The hospital, together with Stockholm Care as soon as possible to make a financial clearance for patient 1 and Patient second
• The hospital can consider making a thorough review of the economic conditions around transplants.

12:10 Employees

observations

• Self-employed people can be a great asset for healthcare. But Macchiarini was too large space to act independently. Unclear responsibilities and lack of coordination made this possible.
• There may be repressive environments in the hospital that can lead to silence culture where criticism suppressed. Both the former and current hospital management has taken steps to counteract such a culture.
• Many of the hospital's employees at various levels have been hurt by Macchiarinifallet. It has the debate has been a relentlessness that many suffered serious ill of. This is a safety issue. recommendations
• Several of our other recommendations designed to reduce the scope for such independence which can lead to lack of patient safety.
• The hospital management should continue to work to counter the repressive elements, especially in patient safety.
• The hospital should process the contradictions Macchiarinifallet created. Special

expertise may need to be hired to support such a "process of reconciliation".

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References

1. Leids Universitair Medisch Centrum. Good Research practice & integrity. https://www.lumc.nl/research/grp-and-integrity/grp/

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List of Persons interviewed in alphabetical order

Jan Andersson, professor, direktör för forskning och innovation, Stockholms läns landsting
Martin Birchall, Professor and Chair of Laryngology, University College of London
Gunnar Björck, överläkare, ÖNH-kliniken, Karolinska Universitetssjukhuset
Tommy Björk, ordförande, Lungcancerförbundet STÖDET
Viktoria Björk, Strategic manager, Karolinska Trial Alliance, Karolinska Universitetssjukhuset
Mikael Blom, ekonomiansvarig, Stockholm Care AB
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Carl M Hamilton, ordförande, Cancerföreningen PALEMA
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