THE MACCHIARINI CASE

Investigation of the synthetic trachea transplantations at Karolinska University Hospital

Summary
31 August 2016

INNEHÅLL

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.

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.

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.

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.

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.

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.

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.

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.

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).

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.

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.

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

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.

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.

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 question 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.

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 patient-safe 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.

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.

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

Restoring the trust in the clinical research demands long-term, 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.

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.

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.

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.