External report on the Neo freezer malfunction

External review group, 2024-08-05

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To:

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Background and mission

On account of a closed valve over the 2023 Christmas break, Karolinska Institutet (KI) experienced a malfunction of the freezer infrastructure at Huddinge Hospital (Neo) that caused a thawing of 16 of the 19 tanks. An internal investigation has been conducted to ascertain the causes of the malfunction and propose measures to minimise the risk of something similar happening again.

In order to ensure that the internal inquiry would be reviewed and assessed impartially, an external independent review panel was appointed, tasked with verifying and auditing the information gathered and the conclusions drawn by the investigative team. The completed investigation was to be written up in a report (this one) with the team's observations, conclusions and proposals for remedial measures.

The external review group has long and broad experience of biobanking and biobank infrastructures from a wide range of aspects, including as principal and in terms of logistics, operations, quality systems and law.

Conclusions in brief

The external group is in agreement that the internal investigation of the freezer malfunction at Neo was conducted thoroughly and described adequately in the internal report. The group concurs with the internal investigation that the malfunction was caused by a number of failures rather than the isolated incident of the closed valve. The scale of the failures suggests a systemic flaw that the external report attempts to elucidate. What we call a systemic flaw spans an extensive chain of responsibilities, delegations, infrastructure, legal concerns and quality systems, including monitoring. The kind of substantial and critical activity as investigated in this report requires rigorous control that can only be maintained if the integrity of the entire chain can be ensured. As we all know, a chain is only as strong as its weakest link, and in this particular chain, multiple links failed. The storage of human cells and tissues carries a very great responsibility not only as regards preserving the trust of users but also, and not least, reassuring whoever has given their consent to the donation of biological material that its purpose, use and storage are managed in a manner that is both safe and in compliance with prevailing regulations, ethical and otherwise. Below is an itemised summary of the overall operational weakness that in the view of the external group must be addressed going forward. A more detailed analysis is given later in the report.

- The Neo-Biobank lacks a clear chain of responsibilities and clarity as regards who has overall responsibility and the responsibilities of the KI management.
- The Neo-Biobank lacks a quality management system.
- The Neo-Biobank does not meet the requirements of the Legal, Financial and Administrative Services Agency (Kammarkollegiet).
- The Neo-Biobank does not meet its legal requirements relating to documentation.
- The Neo-Biobank has a culture and organisation that is dependent upon and influenced by the competence, or lack thereof, of individual members.
- The Neo-Biobank operates in silos, leading to significant local differences in infrastructure support between campuses and among different buildings and departments.
- Benchmarking against other organisations as regards infrastructure management should be clarified.
- Measures to restore the trust of donors should be highlighted.

The work of the external group

The external group has perused and discussed the content of the internal report and conducted interviews with the affected researchers, the directors of Neo and Ana Futura, the head of the Facilities Office, the University Director, the Chief Internal Auditor at KI and the Dean of Campus South. Separate statements of opinion have been written by the group's legal counsel and international representative with a focus on legal aspects and quality management (see Annex 1 and 2).

Review of the internal report

Following a review of the internal report, the external group finds that the measures that were taken after the fact to be satisfactory. Mistakes made have been identified. System suppliers and investigators have written their own reports on their respective parts.

On reviewing the internal report, the external group finds the following:

- That information on testing the alarm and the alarm chain was lacking
- Filled nitrogen tanks should maintain their temperature for several days, but the report did not clearly explain that this was not the case as the nitrogen tanks were only partially filled every night.
- That there was no emergency standby service, which is required for this type of facility
- That a great deal of documentation was missing, which indicates that records were not kept properly. There was also insufficient documentation in the Neo steering group minutes and issues raised were not taken further; the chain of measures taken when problems were raised was also unclear: Did they reach the right person? Did the recipient understand that it was up to him/her to pass the problems on to the steering group to be acted upon and documented? This makes it impossible to know if the issues were taken further or not, or if they were taken up but the results not documented or acted upon. The steering group seemed to lack lists of measures taken, decision logs and follow-ups
- That on the move into the new building, the transfer from the Facilities Office was clear for the transferrer but not for the recipient, as it was done orally; there was no written transfer document or training
- That the project manager for the construction of Neo was not replaced and it is not clear why this was so; the internal report provides no information, probably on account of a lack of documentation, on when and how the decision was taken concerning how the Neo building was to be managed. It has emerged that other KI buildings with similar activities are managed differently, for example with operations teams and standby functions
- That the role of the heads of department vis-à-vis Neo is unclear.

Comments on internal proposals

The internal report proposes the following:

That the Neo freezer hotel be turned into a freezer facility like elsewhere at KI

The external group agrees.

That a register be kept of all biobank material stored in KI's freezers

The external group thinks that it would be a good idea to keep such a register of sample collections, with information on who is responsible for each collection and where it is stored. At sample level,

this would be an almost impossible task unless all samples at KI are managed in a laboratory data system that is kept regularly updated as collections are topped up with fresh samples and as samples are used.

That deployment processes include risk analyses on several levels

The external group agrees that this would be both valuable and necessary.

That requirements be clarified and proper documentation ensured

The external group agrees that this would be both valuable and necessary.

That PT100 sensors be fitted to all freezers

The external group agrees that this would be necessary in order to continually monitor the temperature inside the freezers so that deviations can be detected early.

That common requirements be in place for facilities and equipment throughout KI

The external group agrees.

That transfers be improved and conducted both in writing and orally

The external group agrees but wonders who will make sure this happens in practice?

That responsibility for activity-critical systems be clarified and system owners appointed

The external group agrees.

That an Officer of Emergency Preparedness be instituted with a central service team operating across the university

The external group agrees that all activity-critical systems need access to an emergency standby system 24/7. Freezers that are kept closed maintain their temperature for many hours and so response times of at most a few hours are acceptable, depending on freezer type and temperature.

That a crisis organisation be established at central and local levels

The external group agrees but considers it more important to remedy systemic flaws so that further crises may be avoided.

That an incident reporting procedure be implemented

It is the external group's view that deviation management is an essential component of a quality management for facilitating continual improvement.

Other comments and proposals from the external group

It is clear from the interviews that the conditions under which researchers at KI work and the support they receive depends on their location and, possibly, departmental affiliation. Researchers who are able to store their samples under KI Biobanks receive a good service, with KI investing heavily in infrastructure. The support provided in other buildings depends to a large extent on the availability and competence of the staff. Neo lacks central professional support and sufficient financing to ensure such provision. There also seems to be a difference between the north and south campuses. Priorities and the level at which different issues are dealt with depend largely on the competence of individuals, so the lack of competence in key persons within specific fields can therefore lead to repeated disasters (malfunctions/incidents) not only in biobanking but also in

other parts of associated activities that need to work properly, such as data security and laboratory safety. KI would therefore need to review how resources and competencies are distributed with, for instance, a budget ring-fenced for infrastructure for the different buildings or per campus.

The strong influence of individual competence seems to be a matter of the internal culture at KI, whereby the university is to operate as an umbrella organisation under which control is decentralised and devolved to the departments and research groups. Unfortunately, such a culture falls short in the maintaining of common infrastructure and safety. KI will be taking a considerable risk if it persists with such a culture and organisation. It also emerged from the interviews that much of the examined work at KI is done in silos, and that a more interconnected process could be achieved with greater communication within each campus, along with overarching responsibility and leadership from KI.

The proposed solutions presented in this report are largely based on previous knowledge and experience of similar organisations both national (hospitals, universities) and international (e.g. BBMRI-ERIC, ISBER best practices and ISO 20387). KI should therefore perform some kind of benchmarking against other institutions to identify viable and effective tried and tested solutions. If would, for instance, be valuable to know how the requirement specifications for procurements surrounding the construction of Neo were drawn up.

KI lacks an overall quality system for the activities under examination, an omission that is dealt with in greater detail in Annex 2. Some form of quality system must be introduced to ensure the safety of personnel and the proper handling of infrastructure and equipment.

It is also apparent that Neo lacks a clear chain of responsibility and line organisation. Describing the organisational tree and lines of responsibility is part of a quality management system and is crucial to minimising the risk of issues falling through the cracks. The roles and responsibilities of the Facilities Office should be clarified, for example.

The external group has learned that because of KI's failure to meet its requirements, Kammarkollegiet will not recompense the losses caused by the malfunction. Kammarkollegiet has issued the same response after previous incidents, so KI should at the very least ensure that all resources insured via Kammarkollegiet meet its requirements.

Another observation is that -80 freezers and LN2 tanks share the same space in the Neo building. Given the dangers involved in entering an LN2 space, these two facilities should be kept separate.

Generally speaking, as has been pointed out earlier, documentation is inadequate, a failure that is commented upon in more detail in Annex 1 with a statement of opinion from a legal angle.

To ensure that remedial measures are actually carried out in order to mitigate the risk of any similar recurrence, KI is recommended to draw up a schedule for the follow-up of the measures decided upon. KI's Internal Audit can be tasked with adding this to forthcoming annual plans.

Annex 1 Comments from a legal angle

The lack of competence and records management at the university – a governmental authority – is a grave matter. Demands on proper documentation and administrative orderliness is essential to the running of such a body and to an open, democratic society in general. Additional targeted information and training activities should therefore be seriously considered. This also applies to written job descriptions and delegated responsibilities. Moreover, it would have been desirable for the internal report to have contained clearer references to the documentation requirements ensuing from applicable document management plan(s) and any other mandatory provisions.

However, the internal report does not make clear which risk analysis requirements are being referred to – i.e. exclusively the Ordinance concerning the Risk Management of Government Agencies (1995:1300) or other regulations?

It would have been desirable for the internal report to have described in more detail the differences between a freezer hotel and a freezer facility and whether such differences could have been instrumental in the malfunction, as well as an unclear responsibility for the facility, both perceived and real.

Just as the internal report notes, new biobank regulations have indeed not been issued, but both previous regulations (SOFS 2002:11) and drafts of the biobank act contain statements that could usefully have been given closer attention as they are of potential relevance to the biobanking of samples; see, e.g., prop. 2021/22:257 p. 87f, which also contains further considerations concerning the responsibilities of the principal and biobank manager.

According to the internal report, some of the sample collections came from the Stockholm Medical Biobank and are still considered its property. Whether, and if so, how this affected the incident, the responsibility and consequences were not, however, treated to any further analysis.

According to the internal report, many of the samples destroyed by the malfunction had been stored at KI under the provisions of the former biobank act; for example, by healthcare actors for use in research that had obtained ethical approval. If, and if so, how this is relevant to the internal report is not explained. For the record, according to the transitional provisions to the biobank act, the act is applicable to samples collected before its effective date.

KI is a government authority that operates under the regulations governing Swedish public administration, which also contain clear stipulations regarding management (operative representatives) and staff. However, the internal report lacks clarifications concerning both chains of responsibility and formal responsibility for the incident in question.

It is good that the internal report proposes that an option for a service agreement should always be included in the procurement of technical systems. However, such an arrangement is only possible if allowed by the prevailing regulations; the internal report does not state whether this is or is not the case, nor does it answer the question as to whether other applicable risk management regulations were in place.

There is no mention of whether KI has a special OEP (Officer in Emergency Preparedness) or crisis organisation as recommended by the internal report or how such a function is otherwise organised. This kind of function/organisation obviously needs to be established to deal with crises in the most effective way possible. According to the Ordinance concerning the Preparedness of Government Agencies (2022:524), certain such agencies are required by separate government decision to have an OEP tasked with initiating and coordinating the initial efforts to detect, verify, alert and inform in the event of peacetime crises.

Otherwise, the recommended measures outlined in the internal report are deemed to be well-considered and necessary, and have thus also been recommended by the external review group.

Annex 2 International evaluation with focus on quality management

The internal investigation report reveals the risks an organization faces when it fails to establish clear structures, responsibilities, controls, and improvement measures to protect its assets and the employees it houses. In the case of the Karolinska Institutet South Department group (KI Syd), the Neo freezer hotel experienced a malfunction of LN2 freezer storage tanks, resulting in immense property damage. Thousands of biobanked biological materials, collected and processed over decades, donated inter alia by the civilian population, were destroyed.
These samples were entrusted to the researchers of KI with the expectation of maintaining the highest quality and scientific due diligence. Unfortunately, the researchers and the framework provided by KI were unable to fulfil this obligation, leading to damage to KI's reputation and irritation among donors about whether KI or its researchers can properly manage the samples and data provided for research purposes.

Fortunately, no personal injuries have occurred at the Neo-Hotel to date. However, doubts have arisen as to whether this is guaranteed, after random interviews conducted by external investigators with the concerned scientists revealed a lack of enrolment training or planned refresher courses on how to handle safety measures at the Neo-Freezer Hotel.

Managing liquid nitrogen tanks for sample collections requires strict safety compliance, as non-compliance could lead to life-threatening events. Several risks can occur in a room with liquid nitrogen tanks. Liquid nitrogen rapidly evaporates and displaces oxygen in the air, leading to oxygen deficiency. In poorly ventilated areas, this can cause unconsciousness or even death by asphyxiation without warning. At around -196 °C, liquid nitrogen can cause severe cold burns and frostbite upon contact with skin or tissue. If liquid nitrogen evaporates in a sealed container, pressure can build up quickly and cause an explosion, making proper ventilation crucial to prevent pressure buildup. Materials exposed to such low temperatures can become brittle and fail, including seals and components of storage tanks or pipes in contact with liquid nitrogen. Inadequate maintenance can lead to valve and safety mechanism failures, resulting in uncontrolled leaks or system failures. Malfunctions or failures of alarm and monitoring systems observed over a long period, which have not led to proper and documented troubleshooting, are negligent.

The lack of documentation to instruct and train scientists on using the Neo-Biobank and safety measures is worrying, as handling samples and especially areas with liquid nitrogen tanks, are potentially life-threatening and inadequately managed by KI.

In addition to the weaknesses described in the internal report and the proposed immediate improvement measures, further suggestions for organisational development, can be made.

The proposal to develop the concept of "Neo as a freezer hotel" into a "Freezer facility" falls short. The Swedish Biobank Act (2023:38) clearly outlines regulatory requirements for sample collections. Consequently, an organizational unit that stores these samples (short term or long term) must be set

up and operated according to these regulations and should act as a biobank and be named accordingly.
The internal investigation report addressed the Swedish Biobank Act, stating that a structure must be established that meets these regulatory requirements, so it is advisable to establish a Neo-Biobank**.**

Prominent and well-organized biobanks at KI, such as the KI Biobank, Ana Futura, and Bio Medicum, serve as examples.

Eventually, a concept of a centrally governed but "Federated Karolinska Institutet Biobanks with dedicated areas" could be considered to consolidate expertise, competencies, and security concepts (24/7) in biobanking.
This approach would provide scientists with a service that meets administrative and QA/QC requirements for handling samples and data in biobanking processes, building and consolidating the necessary trust in the population for scientific or biomedical research.

An overarching quality management system (QMS) can and should be set up that follows the international standard for Biobanking, ISO 20387:2018 Biotechnology – Biobanking – General requirements for biobanking[1], which specifies requirements for the competence, impartiality, and consistent operation of biobanks, including quality control requirements to ensure biological material and data collections of appropriate quality. Quality is a clear requirement of the Swedish Biobank Act.

This international biobanking standard applies to all organizations performing biobanking, including biological material from multicellular organisms (e.g., human, animal, fungus, and plant) and microorganisms for research and development. Biobank users, regulatory authorities, organizations, and programs using peer assessment and accreditation bodies can use this standard to establish and verify the competence of biobanks through audits.

The ISO 20387:2018 standard, developed by the International Standardization Organization (ISO)[2] with input from more than 150 experts from 44 member countries, including delegates from the Swedish Institute for Standards (SIS)[3], sets a benchmark for international biobanking.

KI should seize the opportunity to improve the internal structures of the biobank concept and become a world leader in biobanks for research and development.
With the implementation of the standard, KI Biobanks can be guided in establishing, operating, and maintaining procedures that cover the entire lifecycle of biological materials and data while ensuring compliance with biosecurity and biosafety requirements, including risk assessments and derived measures implemented. All biobanking activities, processes, and procedures must be documented to ensure clarity and consistency.
Top management of the Neo-Biobank must be clearly identified within the KI organizational chart, holding overall responsibility. The governance structure must define the organization and management of the Neo-Biobank, its position within KI, and the relationships between management,

technical operations, and support services. Responsibilities, authority, and interrelationships of staff (scientific, administrative, service), managing, performing, validating, or verifying biobanking activities must be specified.
A dedicated governance body or advisory boards should provide guidance and advice on scientific, technical, administrative, and other relevant matters. Accountability for activities within its premises and addressing any liabilities arising from these activities are mandatory.

The Neo-Biobank must have staff with the authority and resources to carry out their duties, including implementing, maintaining, monitoring, and improving the QMS; identifying deviations; assessing the impact of deviations; and reporting to Neo-Biobank as well as management on the QMS's performance and improvement needs. The Neo-Biobank must ensure the availability and competence of administrative staff, premises, all equipment (in this particular case LN2 freezers), secured information systems, and support services necessary for biobanking activities. Documented procedures for staff management and compliance with relevant requirements are essential. Health and safety requirements must be established, documented, and maintained, with safety training levels determined through comprehensive risk assessments of materials, processes, and equipment. The Neo-Biobank must define and document the competencies required for staff and ensure they are competent based on education, training, demonstrated skills, and experience. Professional competence and training documentation must be maintained. Staff performing processes must undergo competence assessment according to established criteria, with regular assessments to ensure they retain necessary competence. Training must be documented, and new staff should receive appropriate orientation.

Neo-Biobank premises and environmental conditions necessary for biobanking must be documented and controlled, biosafety, and biosecurity clear chain of commands transparently available and supervised. Externally provided services from suppliers and all equipment (in particular, LN2 freezers) must meet biobank requirements, with procedures for handling, transport, storage, maintenance, calibration and alarm functionalities. Equipment must be taken out of service if compromised and isolated until verified to perform correctly.
By addressing these issues and adopting a comprehensive QMS, KI can prevent future incidents and uphold its commitment to high-quality scientific research and donor trust. Even beyond, KI should be eager to become a world leader in biobanks for research and development.
[1] ISO 20387 https://www.iso.org/standard/67888.html

[2]https://www.iso.org/about/members

[3] SIS https://www.iso.org/member/2101.html