APPLICATION FOR ETHICAL VETTING

For information concerning the application: see Appendix and Guidance, (www.epn.se)

IT IS NOT POSSIBLE TO USE THE ENGLISH VERSION OF THE APPLICATION.
IT IS NOT PERMITTED TO FILL IN THE APPLICATION IN ENGLISH, ONLY SWEDISH.

To the Regional Ethical Review Board in: Uppsala

Date fee paid:

Project title: AI for active drug disposal and monitoring

Information to be completed by the Regional Ethical Review Board

Application complete: Case number:
Request for additional information concerning the application: Requested information received:
Date of decision: Date processed:

The application concerns (also applies when an advisory statement is requested):

research in which only one responsible research body participates (5 000 kr)
research in which more than one responsible research body participates (16 000 kr)
research in which more than one responsible research body participates, but in which all the researchers or subjects of research have an immediate link to only one of the responsible research bodies (5 000 kr)
merely processing personal data (5 000 kr)
research involving clinical trials of medicinal products (16 000 kr)
changes to a previously approved application in accordance with section 4 of Statute (2003:615) concerning the Ethical Review of Research Involving Humans (2 000 kr)

If the board decides that the legislation concerning ethical review is not applicable to the study/research project, is an advisory statement wanted?

Yes: X No:
1. Information concerning the entity principally responsible for the research etc.

1:1 The entity principally responsible for the research
Name: Uppsala akademiska sjukhuset
Address: Sjukhusvägen 10, 751 85 Uppsala

1:2 Qualified representative for the entity principally responsible for the research
Name: Jane Doe
Professional title: Sektionschef Klinisk Forskning
Address: Uppsala Clinical Research Center, Uppsala Science Park, MTC, Dag Hammarskjölds väg 14B, 752 37 Uppsala

1:3 Researchers who are primarily responsible for the completion of the project (principal contact)
Name: John Doe
Professional title: PhD Computer Science
Address: Lägerhyddsv. 2, 752 37 Uppsala
E-mail: john.doe@it.uu.se
Telephone: --
Mobile phone: --

1:4 Location
Uppsala Akademiska Sjukhuset

1:5 Other participants
PhD students: Ricardo Alves, Kalyan Ram Ayyalasomayajula, Gustav Borgström, Maike Paetzel
Address: Lägerhyddsv. 2, 752 37 Uppsala

1:6 Applications/notifications to other authorities
None

Clinical testing of medicinal products
Not applicable

Cases concerning some kinds of genetic research
Not applicable

Certain research involving the irradiation of research subjects
Not applicable
2. Information concerning the project

2:1 Summary of the research project (programme)

For years, the number of trained nurses in the hospitals is decreasing dramatically. In many cases, nurses are responsible for so many patients that the day-to-day care cannot be ensured in case an emergency happens. The aim of this project is to contribute to the development of technical solutions to help the care-taking of nurses in a hospital environment. Specifically, an artificial intelligence (AI) was developed that can monitor and regulate the dose of pain killers for patients. In the study described in this application, the artificial intelligence which has been proven successful in lab studies, shall be applied in one floor at the Uppsala Akademiska Sjukhuset. In a double-blinded study, participants either receive their pain medication from a trained nurse or the artificial intelligence. Both have access to the medical history of the patient, his / her vitals from the live monitoring system and a live video feed. The data are stored in a centralized database within the hospital. Both the nurse and the AI are suggesting the pain medication dose to all patients participating in the experiment. For each patient, it is randomly chosen in the beginning if the dosage of the AI or the nurse will be applied. Neither the AI / nurse nor the patient are aware who is responsible for the pain medication.

Patients always have access to trained medical staff in case of need. During the daily ward round, the doctors ensure that the pain medication given by the nurse / AI is within an acceptable range. In addition, patients may always ask to see a doctor in case they do not trust the dosage given by the nurse / AI. Doctors can always overwrite the decision taken by the nurse / AI. In that case, the trial is stopped for that patient completely, independent if the nurse or AI has taken the decision before.

This research experiment will be a major step towards applying an autonomous pain medication monitoring system in hospital environments which will take a burden from nurses to allow them to focus more deeply on other tasks in care-taking of patients.

2:2 What is/are the primary scientific question(s) forming the basis of the design of the project?

(1) How much differentiation is in the dosage of pain killers given by the nurse and the AI?
(2) How often do participants call a nurse to ask for a higher pain medication dosage?
(3) How often do participants ask to see a doctor because they do not trust the decision of the AI / nurse?
(4) How often do doctors overwrite the decision of the AI / nurse?

2:3 State the results from relevant animal experiments

Not applicable.

2:4 Give an overview of the examination procedures used, data collection and the nature of the data.

For each patient, the medical history is stored in a centralized database within the hospital. In addition, the video data and the vital functions are saved in the database. Both the nurse and the AI have access to the live data and the data history for all patients participating in the study. The data is stored for 10 years after the experiment has ended to ensure further development of the AI system and offline learning algorithms on the data.

In addition, it is logged which dosage both the AI and the nurse would give to the patient and which dosage was actually given to the patient. The system automatically logs how often the patient asks for a higher dosage of the pain medication and how the decision of the AI / nurse to this request was. The local nurses in the corridor manually enter if the patient asks to see a doctor and what the decision of the doctor about the pain dosage is. In case the doctor decides to overwrite the decision taken by the nurse / AI, the dosage given by the doctor is saved as well, but not made available to the AI / nurse. This data is only available for offline processing afterwards.
2:5 Describe how biological material that has been collected is to be stored in a biobank

Not applicable.

2:6 Account for the access to the resources needed during the implementation of the project

Uppsala Akademiska Sjukhuset is responsible for the medical equipment, the location and the insurance and training of the doctors and nurses who participate in the research project.

The responsible research team from the IT department is responsible for the development and supervision of the Artificial Intelligence.

2:7 Record-keeping, registering and processing of data

All data mentioned in section 2:4 are stored in a database located in Uppsala Akademiska Sjukhuset. The AI as well as the nurses involved in the project have access to the database during the experiment time. Afterwards, researchers involved in the project may further automatically or manually process the data to further develop the AI system. For this purpose, the data are stored for 10 years in the database.

2:8 Describe previous experience (your own and/or others) of the procedure, technique or treatment used.

The AI has been trained in an offline process on data collected in a previous experiment. In the offline training, the AI took the same decision as a trained medical doctor in 75% of the cases presented to the AI. In 20% of the other cases, doctors considered the dosage of the AI to lay within an acceptable range. In the remaining 5%, the dosage of the AI was too conservative. The AI never suggested a dangerous dosage for any patient.

3. Information about the participants in the research

3:1 How are participants in the research chosen?

All participants who are assigned to the floor in which the AI system was applied and who require 24/7 pain medication are asked for their consent to participate in the research study as soon as they are admitted to the hospital. Among those patients who give consent, participants are randomly chosen so we always have a maximum of 20% of patients within the particular floor who are participating in the research.

3:2 State the relationship between the researchers/the leader of the research and those people participating in the research

The responsible researchers and leaders of the research program are researchers from the IT department. They have no relationship and do not know the patients and the doctors and nurses involved in the project.
3:3 State the statistical foundation with respect to the size of the population(s) and/or material(s) studied

The AI system is applied in one corridor at Uppsala Akademiska Sjukhuset. All people who are assigned to this floor by the doctors responsible for admitting the patients are asked for their consent to participate in the research experiment. At each time, a maximum of 20% of patients at the corridor are supposed to take part in the research experiment. If more consent, patients are randomly chosen to participate in the project among those who consent. If less than 20% agree, all of patients who consent are chosen for participation. We aim for 100 patients in total. We cannot influence the specific population of participants, because this is dependent on the populations that seeks for medical care at Uppsala University Sjukhuset during the time of the experiment.

3:4 State if participants in the research may be included in several studies, either simultaneously or in another study or other studies closely linked to this one. If so, what kind of research?

Participants will not be asked to participate in other studies at the same time. They will not be asked to participate in follow-up studies.

3:5 What insurance cover is there for research participants taking part in the project?

The medical insurance of the patient covers for the participants, since the research is part of their treatment in the hospital. The nurses and doctors participating have the regular insurance from the Uppsala Akademiska Sjukhuset.

3:6 What financial remuneration or other benefits are participants in the research entitled to and when is this to be paid? (A more detailed description can be submitted as an annex)

Compensation for discomfort and inconvenience. Sum (before tax):

➤ None

Compensation for income from employment:

➤ None. The participants are in the hospital anyway and will receive paid sick leave for the duration of the study, if applicable.

Allowance for travelling expenses:

➤ None. Participants will receive help with their travel expenses to the hospital from the state as a regular part of their insurance, if applicable.

Exemption from costs of pharmaceutical products Exemption from other costs Which?

➤ None

Other benefits Which? When is compensation paid?

➤ None
4. Information and consent

4:1 The procedure involved and the content of the information that is given when subjects are asked to participate in the research

Each volunteer is informed that they might be treated by an AI under the supervision of a doctor. The information collected during the experiment will not be made public and will only be used for research purposes. After the trial is complete the data will be anonymized before making it public.

4:2 How is consent to be obtained and from whom?

The consent is acquired in written form, from the patients that need constant pain medication.

5. Considerations in the light of research ethics

(Note: "nurse" denotes either an artificial intelligence- or human nurse, if not explicitly stated otherwise).

5:1 Describe the risks that participation might entail and possible complications

All dosages given by a nurse, may be overridden by a doctor. The two main problems for the patient are as follows, in decreasing order of immediate severity:

1. The patient may be exposed to higher doses than actually needed, where doses are regarded nonfatal, but may (or may not) lead to complications. A nurse may do miscalculations/ mispredictions, which leads to these complications; while a human nurse can be held accountable for his or her actions, an AI nurse cannot.

2. Second, a patient might feel the need for higher dosages to reduce pain. The latter problem might in turn result in the risk of being biased to never trust any nurses opinion (be it an AI or human nurse) as they might be overridden by a doctors opinion.

Field test speculation are solely based on lab tests and may be prone to unforeseen exceptions Generalizability is prone to statistical sampling error inherent to experimental design.

5:2 Describe the predictable benefit for the people participating in the research who are part of the project

The participants under the AI care receive constant care regardless of staff available.

- For the patient: The only part of the study where the AI nurse is involved is for medication; else, regular staff will see to the patient's needs. An AI nurse is trained to make accurate decisions that is based solely on what it has learned, so there is no risk of manually altering the AI nurse into worse decisions. The AI nurse is believed to make very accurate decisions as of sufficient pre-training before the study begins, that takes both the patient’s own experience as well as its actual health into account and make trade-off decisions based on those facts. If a doctor feels the need to override the decisions, it is guaranteed to learn from that decision, together with the outcome of that override. In conclusion, the AI nurse should learn to make the best available decision based on what they have learned by experience, thus maximizing the probability of a good decision.

- For the staff: Hospitals with employment problems, e.g., understaffed institutions, may ease the burden of their employees, that otherwise would have to keep track of every patient manually. Human nurses are relieved both from duties that the AI nurse may cover for them, as well of the stress from potentially making mistakes.
5:3 Carry out your own evaluation of the relationship between risk and benefit for participating research subjects

The worst overall thing that may happen for a patient in the long run is over-medication. This is a risk that may add complications that brings harm, short- or long-termed. As the AI nurse never will a patient take directly harmful (or lethal) doses, the long-term effect might be hard to track during a scope of this study. On the other hand, over-medication is a posed threat even for an experienced human nurse. As the AI nurse is supposed to do at least as well as its human counterpart, this is regarded as acceptable for this study, as the benefit will lead to a great help for both staff and patients at the hospital. The second worst thing is under-medication. This is a risk that may leave a patient in unnecessary pain. In the long run, this is may have effects on the patient health. The AI is however not expected to provide such severe under-medication, as it is taking the patient's own experience into account and only denies increased dosages when that poses direct threats to the patient. Again: this is also the case for human nurses, so this risk is comparable to current standards, while the benefit of the study will be relief for the staff meanwhile accurate medication is maintained for the patients.

5:4 In a broader perspective, identify and specify which ethical problems, such as risk versus benefit, can arise as a part of or as a result of the project

If successful, human nurses may see their expertise being replaced by the AI nurse. This might have an impact that biases the staff's view on the AI, especially for those who take vocational pride in their positions. Moreover, while the AI is ideologically intended to serve as an aid for hospital staff, other interests may view them as a way of replacing staff with an AI nurse, thereby cutting costs. We see a tradeoff: AI nurses may well enough provide with factual accuracy in medication, but cannot (presently) replace human presence for direct communication. Our conclusion is that the AI nurse for medication is still beneficial for everyone involved – maintained medication accuracy for patients + workload relief for hospital staff – so the benefit outweighs these ethical issues.

A subtle, but viable risk is the potential of patient not receiving the care they hope for, be it either by an actual error or if they think that their own wishes are not met, such that this may turn into a mistrust of AI nurses. This mistrust may thus be based on the feeling that, e.g., a denied higher dose of medication, is a result of the AI nurse doesn't meet their own desires. Also, in the rare occasion of a non-optimal decision that turns into even small complication, this lone event may seem very large even comparison to all the times a good decision was made. In the long run, a few patient might learn that AI nurses are bad, which will affect the society's view on them. As clinical AI studies are still rather new, there is no clear consensus about how to perform these tests such that this situations can be avoided. Therefore, this experiments must be performed as is, with these risks in mind, as the benefit of this study is believed to serve the society well.

Finally, as an overall remark: when something "bad" happens that was caused by any AI, it is highly debated on who should be responsible. We believe that with AI's, we have for the first time in history created something that we may regard as more or less "intelligent"/autonomous. As a result, as no one but the actual AI is making decisions, we have come to a point where there is a vacuum of accountability.
6. Presenting the results

6:1 How are both the entity principally responsible for the research and research collaborators guaranteed access to data (to be stated when the research is an assignment) and who is responsible for processing data and writing reports?

The data is made available with names, ages and demographics anonymized (labeling the groups). The researchers are responsible for anonymizing the data.

6:2 How will the results be made publicly available? Will the study be sent for publishing in a journal or published in some other manner?

The data published is anonymized.

6:3 In what manner will the right to integrity of those participating in the research be guaranteed when the material is made public or is published?

Names will be omitted, demographics will be assigned labels and ages will be divided into age ranges.

7. Reporting the financial circumstances and dependencies

The purpose of the accounts to be given in points 7:1 - 7:3 is to clarify all direct or indirect circumstances that could possibly affect the researcher's relationship to the persons participating in the research (during the process of information, consent or implementation, for example).

7:1 When the research is an assignment

Name: IT department, Uppsala university
Principal contact: Johan Doe
Address: Lägerhyddsv. 2, 752 37 Uppsala
Telephone/mobile phone: --
7:2 Give an account of any financial agreements with a principal or any other financiers
(Name, amount)

Public funded research on a public funded hospital.

7:3 Give an account of the interests of the entity principally responsible for the research,
the principal researcher and of participating researchers

For the hospital the main interest is in reducing the need for nursing staff. For the researcher is to evaluate the performance of an AI when compared to a human. For the IT department is to showcase the research capability of the department

8. Signatories

Authorized representative for the entity principally responsible for the research who is the applicant in accordance with p. 1:2.

Place: Date:

Signature: __________________________________________________________

Clarification of signature:

Official title:

The undersigned researcher who is carrying out the project (principal contact) in accordance with p.1:3 hereby certifies that the research will be carried out in accordance with the application.

Place: Date:

Signature: __________________________________________________________

Clarification of signature:

Official title:
9. List of annexes

Documents which, in appropriate cases, are to be appended if corresponding information is not on the form, are marked with an x. Mark those annexes that are to be submitted with this application.

<table>
<thead>
<tr>
<th>Send with application</th>
<th>Annex nr</th>
<th>Description</th>
<th>Clinical testing of pharmaceuticals</th>
<th>Other research</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>The participating entity principally responsible for the research and collaborating researchers (principal contacts) for research involving the participation of more than one entity principally responsible for the research. For information see p. 1:5</td>
<td>x</td>
<td>x</td>
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<tr>
<td></td>
<td>2</td>
<td>Research plan intended for specialists. Also an annex intended for laymen, if needed. For information see p. 2:1 and Guidance to the research plan/protocol (programme).</td>
<td>x</td>
<td>x</td>
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<tr>
<td></td>
<td>3</td>
<td>Advertising material for the recruitment of research participants. For information see p. 3:1 and Guidance to the application p. 3:1.</td>
<td>x</td>
<td>x</td>
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<td></td>
<td>4</td>
<td>Written information for those who have been asked. For information see p. 4:1 and Information for research participants.</td>
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<td>5</td>
<td>Questionnaire. For information see p. 2:4.</td>
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<td>6</td>
<td>Standard EU form (as of 1 May 2004). Also applicable when changes are made.</td>
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<td></td>
<td>7</td>
<td>Summary of the protocol in Swedish</td>
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<td></td>
<td>8</td>
<td>User's handbook or product insert/product summary/IB</td>
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<td>9</td>
<td>Testimonial from operations manager or equivalent concerning resources and the safety of those participating in the research. For information see p. 2:6.</td>
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<td></td>
<td>10</td>
<td>CV of researcher (same as p. 1:3) with primary responsibility for completion (give an account of the competence of the researcher(s) that is of relevance to the study. Information in Guidance to the application p. 1:3.</td>
<td>x</td>
<td>x</td>
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<td></td>
<td>11</td>
<td>Description of remuneration given to research participants. For information see p 3:6 and Guidance to the application p. 3:6.</td>
<td>x</td>
<td>x</td>
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<td></td>
<td>12</td>
<td>Agreements with principals/financiers concerning, for example, terms of employment, grants/compensation awarded to the place where the research is conducted, to the principal responsible for health care, to the entity principally responsible for the research or to the researcher. For information see p. 7:2 and 7:3</td>
<td>x</td>
<td>x</td>
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Other annexes appended to the application: