Self-Evaluation form for the Evaluation of Clinical Significance and Societal Impact of Clinical Research

ALF Panel 2

Introduction

The Swedish Government has commissioned the Swedish Research Council to evaluate the quality of the clinical research conducted by the regions[1] that are part of the ALF agreement. The content of the ALF evaluation is decided by the Swedish Research Council, based on guiding principles formulated by the National ALF Steering Committee. Accordingly, three international expert panels have been appointed to perform the evaluations:

- ALF panel 1: the quality of the scientific output
- ALF panel 2: the clinical significance and societal impact of clinical research
- ALF panel 3: the prerequisites for clinical research.

The purpose of the ALF evaluation is to enhance the quality of clinical research in Sweden, by reallocating 20 per cent of the ALF research funding based on quality, and to give feedback to the regions and highlight good examples.

The following instructions apply to the evaluation of clinical significance and societal impact of clinical research (ALF panel 2).

The assessment is carried out by a panel of experts. The expert panel will make its assessment based on the self-evaluation provided by the ALF regions, as well as the information provided at a hearing. At the hearing, the expert panel has the opportunity to ask supplementary questions to representatives from the ALF regions regarding the descriptions and accounts given in their self-evaluations. The self-evaluation and the hearing are also complemented by a background report, in which the regional context is presented. The background report also contains a glossary and explanation of definitions. (For more background information about the evaluation, please see Utvärdering av forskningens kvalitet i ALF-regionerna - Vetenskapsrådet (vr.se) (in Swedish) or Evaluation of research quality in the ALF regions - Vetenskapsrådet (vr.se) (inEnglish).)

[1] Sweden has 21 self-governing regional authorities known as regions (Swedish: *region*). Until 2019, these were known as county councils (Swedish: landsting). It should be noted that these regions are different from ALF regions, which are each a combination of a (regional authority) region and a university.

Instructions

Scope and objective

The self-evaluation consists of four assessment areas, called "scope" in Table 1. Each scope is associated with one or two objectives or desired states.

The self-evaluation questionnaire is organised according to the four scopes. The region and the affiliated university (i.e. the ALF region) are requested to answer the questions jointly.

Scope	**Objectives**
1. Clinical research and its impact on health care and public health	1.1 The ALF region works in a strategic, structured and planned way with clinical research to achieve an impact on health care and public health 1.2 The ALF region has appropriate and sufficient practices and strategies for keeping its clinical practice in line with the best evidence
2. Clinical research and education	2.1 The ALF region's clinical research is an integrated part of the education of healthcare professionals
3. Innovation and life science	3.1 The ALF region works in a strategic, structured and planned way towards innovation and life science development
4. Impact case studies	4.1 The ALF region is able to provide examples of the clinical and/or societal impact of clinical research conducted by researchers in the ALF region

Table 1. Note: definitions of concepts such as "public health" are given in the background report.

The questions in the self-evaluation are intended to capture the ALF region's daily practice, its systematic work and its long-term strategies, and not the practice of individual researchers. In your answers, please supplement the descriptions with examples to demonstrate and validate that the work practice or strategy is in effect and is working. Please do not only refer to an example, but also include a short description of why the example is valid. Please also refer to strategies and policy documents by e.g. web links and/or registration number (*Swe*: *diarienummer*) as well as page indications, if they will support and validate the description. (Referenced documents will not be assessed, but the region must be able to present the documents upon request.)

Previous ALF evaluation – reflections and remarks

The self-evaluation begins with a section where you are asked to reflect on the development of your ALF region since the last evaluation, taking into account the clinical significance and societal impact of clinical research. You are asked to describe any activities or modifications of structures and processes that you have introduced as a result of the previous evaluation in 2018. It may include actions taken as a result of comments and recommendations to your own ALF region or to other ALF regions, as well as inspiration from other ALF regions' structures and processes. This description will not form the basis for the panel's assessment, but the development of the ALF region will be

commented on in the evaluation report. (The expert panel will be given your reflections of the previous ALF evaluation, after the current evaluation is done.)

Format and timeline

The answers must be in English, in the “boxes” provided, and in accordance with the maximum length stated (e.g. one page of A4), in the font “Times New Roman” and font size 11. Please send the completed self-evaluation to: alf@vr.se by **June 3, 2022** at the latest.

If you have any questions regarding the evaluation, please contact alf@vr.se.

Self-Evaluation Form: The Clinical Significance and Societal Impact of Clinical Research (ALF Panel 2)

Name of ALF region: Stockholm

Reflections on the previous ALF evaluation

In this section, you are asked to reflect on the development of your ALF region since the last evaluation, with regards to clinical and societal impact of clinical research. This description will not form the basis for the panel's assessment, but the development of the ALF region will be commented on in the evaluation report.

a) In relation to the clinical significance and societal impact of clinical research, please describe your reflections on the last ALF evaluation, and whether any modifications have been implemented as a result of recommendations made by the panel.

The description should include how the ALF region's work has progressed with respect to:

(i) the ALF region's strategic work towards an impact on health care and public health, and

(ii) its work to keep clinical practice in line with best evidence.

The description should include new activities and modifications of routines and practices that are the result of recommendations made to the ALF region in question, as well as to other ALF regions. If knowledge transfer between the regions occurred during the evaluation process, this may also be included in the description.

Response: Max one page (A4).

The formation of a modern, integrated infrastructure for healthcare and research

The 2017 evaluation indicated that the Stockholm ALF region at that time was undergoing substantial changes, including a new university hospital building and the complete reorganization of its clinical structures. The evaluation concluded that it was thus too early to assess whether the reorganization would result in improved patient experiences and outcomes. An internal reflection was that the self-evaluation from the Stockholm ALF region had emphasized to some degree the results of our research at the cost of describing our system as such. We have carefully considered the 2017 evaluations (of Stockholm and the other regions) in our work during the past years.

The new hospital building for **Karolinska University Hospital in Solna** has now been completed together with the adjacent clinical research building **BioClinicum,** which provides access to strong research environments in immediate proximity to clinical care, with advanced infrastructure co-located with clinical and preclinical research groups. The clinical organization of the hospital is being continually fine-tuned, and the hospital's economy is now balanced. In 2020, Karolinska University Hospital and Karolinska Institutet (KI) were accredited the first **Comprehensive Cancer Centre** in Sweden. In the appraisal of the Centre the multidisciplinary ways of working at the hospital was highlighted as a particular strength, together with strong clinical research. In 2022 Karolinska University Hospital was ranked as the **8th best hospital in the world** (*Newsweek's ranking*) and has achieved a top 10 placing three years in a row. The data-driven approach to monitoring care was highlighted by Newsweek. **KI has been ranked as #7 in the world and #3 in Europe in life science and medicine** (QS 2021-22).

The reorganisation of care in Stockholm (including the new hospital) is part of a larger strategic plan for healthcare (*'Health Care of the Future')* that was initiated by Region Stockholm in 2012. We anticipate **shorter inpatient periods, more digital care contacts and a shift towards outpatient and primary care** as central parts of the care chain. Research and education need to follow patients flows, and the Stockholm ALF region has taken several steps to adapt to the new care landscape. Apart from the Karolinska University Hospital, seven other hospitals/care organizations in the region contribute substantially (approx. 20%) to the regional research activity (**Health Care Services Stockholm County, Danderyd hospital, Stockholm South General Hospital, Capio S:t Göran hospital, Södertälje hospital, Norrtälje hospital, Ersta-Sköndal and Stockholm Sjukhem**). **Five new university healthcare units** were established in 2021, four of which are located within privately operated hospitals. ALF research funding is distributed in part based on an algorithm between the RD&E committees, and in part based on open competition. In 2018 we adjusted the model used to distribute funding to the RD&E committees in order to follow the patient flows as the healthcare system transforms. **The Academic Specialist Centres** (est. 2016-2021) together with the Centre for Epidemiology and Community Medicine, Centre for Occupational and Environmental Medicine, and Centre for Health Economy, Informatics and Health Care Research Academic Primary Care Centre, and Centre for Psychiatry Research provide university healthcare outside of the hospitals. **The Stockholm Centre for Health Data** (est. 2019) serves as a regional single point of contact for providing a secure, coordinated process for health data access for research and innovation. **CLINICUM** is a new node for supporting clinical and translational research across the Stockholm ALF region.

The KI-Region Stockholm management group has appointed a specific work group responsible for **securing research and education in all parts of the Stockholm healthcare system**, regardless of public/private operation. The group is developing models of pre- and post-contract assessments of caregivers' ambition, capacity and performance with regard to clinical education and research, and re-allocates patient volumes when necessary. Keeping clinical care in concert with best evidence is a top priority. **The clinical leadership is ultimately responsible for implementing and monitoring best evidence, as is clearly expressed in the care contracts.** The Swedish Association of Local Authorities and Regions has initiated a country-wide national **knowledge transfer system.** The regional part of this program has been **fully implemented** in Stockholm. Each regional program group in the Stockholm ALF region has secured academic competence through its university representative. The **workplan** includes questions about research implementation and education. In addition, the Health and Medical Care Administration **specifically funds implementation support in healthcare and public health through five regional centers** .[2] The HTA-function has been reorganized and provided with an increased budget.

1. Clinical research and its impact on healthcare and public health

1.1 Strategic work towards impact

Objective: The ALF region works in a strategic, structured and planned way with clinical research to achieve an impact on healthcare and public health

a) Please provide an overview of how the ALF region works strategically with clinical research to achieve an impact on healthcare and public health.
The purpose of this question is to give an overview of the ALF region's strategic work to impact healthcare and public health. Specific aspects of the ALF region's work are to be included in question 1.1b, etc.

Aspects to be covered in the description:

(i) How the ALF region works to systematically implement results from clinical research, conducted by the ALF region and others, in order to achieve an impact on healthcare and public health.
(ii) How the ALF region works to systematically disseminate research results and best practice to: healthcare personnel, patient organizations, politicians and public servants, and to the general public.
(iii) How the ALF region monitors and evaluates its strategic work to implement clinical research results in order to improve healthcare and public health, and how the implementation of such results is followed up.
(iv) How the ALF region collaborates with other regions, universities and organizations (for example patient organizations) to improve healthcare and public health.

(In your answer, please supplement and validate the description by providing examples of the ALF region's systematic work, and refer to strategies and policy documents by web links and page indications, if available.)

Response: Max two pages (A4).

[2] (*Centre for Epidemiology and Community Medicine*, *Centre for Occupational and Environmental Medicine*, *and Centre for Health Economy*, *Informatics and Health Care Research Academic Primary Care Center*, *Centre for Psychiatry Research*,)

i. Systematic implementation of research results to impact healthcare/public health

The goal of the Stockholm ALF region is to provide best evidence healthcare (i.e. research based) throughout its entire system. Implementation of research results is secured **top-down** through the linear organization (described and monitored in care contracts), and **laterally** through the knowledge transfer system *and* implementation support. The **Life Science Strategy for the Stockholm region** and the **Research, Education and Development Strategy** (from 2021, developed in broad collaboration within the ALF Region) indicate strategic directions and areas in need of development. **Three political subcommittees** (The *Research Committee*, the *Innovation and Development Committee, and the Knowledge Transfer Board*) oversee the development of clinical research, life science, innovation and best evidence/knowledge transfer in Stockholm, including implementation of these strategies. The national knowledge transfer system consists of 26 national program groups, each responsible for specific disease areas (i.e. cancer, cardiovascular disease), and eight thematic groups including research/life science. **The *regional* level of the knowledge transfer system is now fully implemented** and provides a system for supporting best evidence (implementation, benchmarking, and follow-up of medical programs/guidelines) **across caregivers**. Coordination between the regional program groups is ensured by the Stockholm-Gotland Medical Council. **Each regional program group has secured academic competence through its representatives** from Karolinska Institutet (lecturer or professor). Of note is a **specific political board** (*The Knowledge Transfer Board)* responsible for structuring and supporting the healthcare leadership regarding best evidence/knowledge transfer. The Knowledge Transfer Board recently decided to strengthen the **Health Technology Assessment** (HTA) function in Stockholm (through increased budget and reorganization).

The **Precision Medicine Center Karolinska** is a new joint centre (KI/Region Stockholm) that provides a strong and nationally important infrastructure for the implementation of precision medicine. The Health and Care Administration organises support for implementation and quality improvement work through its **five regional centres**: *1) Academic Primary Care Centre/APC with eight Academic outpatient units/AVC, 2) Centre for Psychiatry Research 3) Centre for Epidemiology and Community Medicine 4) Centre for Occupational and Environmental Medicine, and 5) Centre for Health economics, Informatics and Health Care research/CHIS.* These centres are highly research-orientated and organised either as close collaborations or through joint management between KI and Region Stockholm and are designated to support healthcare and **public health work**. Specific capacity related to prevention, epidemiological oversight, and analytic competence is provided by the three latter centres, which are contracted to help implement Region Stockholm's **Public Health Policy.** CHIS is now also responsible for the upgraded HTA-work.

ii. Dissemination of research results

The Stockholm ALF region has a strong and vital clinical research culture, and there are numerous opportunities for staff, patients, politicians as well as the public to follow research results. ***Staff***: Three **hospital libraries** provide all caregivers (public as well as private) with access to scientific research articles (at the same level of access as the university). Supporting clinicians with access to evidence-based recommendations and clinical guidelines is a key task for librarians. There are numerous lunch seminars, webinars and lectures offered. An important part of securing staff competence (i.e. updated knowledge of the latest research and best practice) is a broad output of *Continuous Professional Development* courses, secured externally and/or are provided in-house. **During the pandemic, training programs for re-located staff were initiated within days**. Staff with research competence are key persons in providing such training. The *Stockholm Care Academy* is a specific forum for competence and development within the nursing sciences. Region Stockholm's HR system includes a planning tool for monitoring competence among staff (KOLL). ***Patients***: At the university hospital, all research studies require communication of a popular summary of the study results to study participants (in addition, see below under iv/Collaboration with patients) ***Politicians***: Three political subcommittees (*The Research Committee, The Innovation and Development Committee and the Knowledge Transfer Board*) closely follow the care organisations' work with regard to implementation of strategies, infrastructure development, ongoing research programs etc. ***Public***: The Stockholm ALF Region publishes about 400 press releases yearly and provides popular scientific communication through social media, the magazine *Medicinsk Vetenskap* (4 x 27 000 copies/y), the podcast *Medicinvetarna* (462 000 downloads), and

through a UK-based news platform *The Conversation*. Other examples include the collaboration between **Regional Cancer Centre Stockholm Gotland's council for patients and next of kin** and Cancer Research KI, which regularly organise (4/y) joint workshops with patient organizations, researchers and the general public. Another is the Covid-19 theme day organised by Karolinska University Hospital and Swedish Radio. Top researchers are very visible in regular and social media.

iii. Monitoring, evaluation and follow-up

Region Stockholm's **annual activity plan** identifies goals for healthcare and public health**,** as well as goals for research, innovation, and life science. Each caregiver's board elaborates and monitors goals at a local level. **Healthcare leaderships are followed up for key indicators and specific tasks related to all these goals**. The *Health and Care Administration* regularly follows the quality of care within all areas of healthcare (including dental care). A special **action plan** (part of our strategic work) was initiated in 2021 to ensure participation in research and education among all caregivers regardless of public/private operation.

The knowledge transfer system has developed a generic model for implementation and follow-up (regional gap analysis - action plan – communication - follow-up). Annual work plans for the regional program groups also include a **specific section on clinical research and education**. Karolinska Institutet in turn gathers all its representatives in regional program groups to allow cross-program benchmarking of research and education. During the pandemic this system proved to be extremely important as an arena for efficient knowledge sharing at a regional as well as at a national level. Currently, more than 20 different clinical COVID-19 best practice guidelines have been implemented based on collaborative work between academics and healthcare, facilitated by the knowledge transfer system. The healthcare in Stockholm is of very high quality, underscored by the fact that Stockholm has been granted almost 80% of permits for National Highly Specialized Care that have been included so far (certified national centres).

iv. Collaboration with other regions, universities, patients and organizations

National: Almost 60% of publications from researchers in the Stockholm ALF Region include a national co-author outside of KI-Region Stockholm. Region Stockholm is part of the national network for HTA-units and researchers are active in Cochrane and regularly engaged as experts by the Swedish Agency for Health Technology Assessment. The knowledge transfer system provides a strong framework for national collaboration on a broad range of topics. The Stockholm ALF region chairs *Genomic Medicine Sweden* (GMS), a national network including university healthcare, universities, industry and patient organizations devoted to implementing precision medicine. We also chair 34% of the national quality registries. The Stockholm ALF region takes active part in *ATMP Sweden*: a national network developing medicines based on genes, cells or tissue engineering (Advanced Therapy Medicinal Products) as well as in *Biobank Sweden*, a national collaboration between regions and universities to facilitate access to biobank samples. Researchers from the Stockholm ALF region are PI´s on 45% of the studies financed by the Swedish Research Council for Clinical Therapy Research - large grants which require the active involvement of at least four other healthcare regions in Sweden. **Patients:** Collaboration is extensive and a strategic goal. A criterion for achieving **status as university healthcare unit** is established patient/patient organization collaboration. All hospitals including Health Care Services Stockholm County have **structured models for patient collaboration.** At Karolinska University Hospital, patients are represented in the ethical committee and take active part in developing the research strategy. Patient or family representatives are also present at management groups at the clinic level and in a wide range of project groups at the hospital. The *Centre for Health Data* as well as *MedTechLabs* have patient councils, and the Academic Specialist Centres actively involve patients in their innovation platforms. **International:** Collaboration to improve care include e.g. (1) Mayo Clinic – long-standing collaboration within many areas of shared scientific, academic, and clinical interest; (2) European University Hospital Alliance - nine university hospitals in Europe share their expertise in healthcare, research, and education; (3) Cancer Core Europe an alliance of seven leading European cancer centres that combine scientific research with patient care; (4) Vaccelerate is the pan-European backbone for the acceleration of phase 2 & 3 COVID-19 vaccine trials. The Stockholm ALF region co-ordinates Sweden's involvement.

b) Please describe how the ALF region works strategically to identify and address research gaps and areas for clinical research

Aspects to be covered in the description:

(i) How the ALF region collaborates with other regions, universities and organizations (for example patient organizations) in order to identify research gaps.
(ii) How the ALF region works to encourage and facilitate multidisciplinary research.
(iii) How the ALF region works to encourage and facilitate clinical research aimed at addressing the identified research gaps.

(In you answer, please refer to the overall work practice or strategy of the ALF region, not the practices of individual researchers. Please supplement and validate the description by providing examples.)

Response: Max one and a half page (A4).

i. *Collaboration to identify research gaps*

A key component in identifying clinically important research gaps is the **collaboration with patients** in a healthcare system that is designated to meet all patient needs, including those for which there are no currently available treatments/interventions (i.e. research/knowledge gaps). Such healthcare must have systems in place to develop new knowledge when necessary. A key is a clinical culture in which ambition, ongoing systematic evaluation as well as reflective discussions are core components of the work culture, and in which students (next generation employees) are trained. The **pandemic** illustrates that the healthcare system in Stockholm has such capacity. Parallel to high pressure on the healthcare system during Covid-19, almost 300 applications to initiate studies have been submitted to the Ethical Review Board up until Sep. 2021 (43% of all applications in the country). Relevant results have been shared with clinical care locally, nationally, and internationally, as well as with authorities such as the Public Health Agency and WHO. An important asset of our clinical culture is our almost 2000 employees with a PhD (at Karolinska University Hospital a PhD is a requirement for a position as senior consultant). In addition to well trained staff and a reflective research culture in the clinic, other key components of 'gap identifying capacity' are, for example, access to research infrastructure (e.g. *SciLifeLab*, *BioClinicum*), research support structures, and competence provided through translational research platforms and programs (e.g. Centre for Innovative Medicine, Research school in Molecular Medicine, and Centre for Infectious Medicine).

Many research gaps are identified through **collaboration within clinical research communities**. Almost 60% of the publications from researchers in Stockholm include authors from other parts of Sweden. Likewise, collaboration with **patient organizations and representatives** is important**,** and is broadly implemented in regular clinical care, in regional program groups, at the Regional Cancer Centre, within specific research platforms (e.g. the Centre for Health Data, MedTechLabs), and within specific research projects focusing patient involvement (e.g. 'The Patient in the Driver's Seat: a multimethod partnership program on patient-driven innovations'). **Regional program groups within the knowledge transfer system** are specifically asked to identify knowledge gaps. The connection between the regional program groups and KI is assured by the university representative. Identified gaps are raised to a national level and/or handled regionally. **National collaborative initiatives** have led to targeted research calls (e.g. in 2021 when several regions formed a group which successfully lobbied the government to allocate designated vaccine research grants). Other examples of addressing specific research gaps are national as well as regional initiatives to allocate **funding for research in, for example, primary care and mental health**.

ii. *Encourage and facilitate multidisciplinary research*

The three regional universities KI, Stockholm University (SU) and the Royal Institute of Technology (KTH) have formed a strategic partnership – '**Stockholm Trio'** – devoted to promoting the interaction between their different disciplines. In addition to the regional ALF-agreement

between Region Stockholm and KI, Region Stockholm has also formed **strategic partnerships with both KTH and SU** with dedicated funding allocated to research gaps identified through the strategic partnerships. In this way, we have developed a grant program for collaboration built on a bottom-up approach where KTH, SU and Region Stockholm have one PI each.

At Karolinska University Hospital the organization is a matrix based on thematic medical areas combined with three function areas through which interprofessional and multidisciplinary teams are formed with the patient. **The thematic organization** promotes and strengthens interaction between disciplines, professions and the patient, which is also reflected in research collaborations.

SciLifeLab, located near KI and the Karolinska University Hospital, brings scientists together across traditional boundaries and **fosters collaborations with universities, industry, healthcare, public research organizations and international partners.** Karolinska Institutet is one of the hosts of SciLifeLab and facilitates its collaboration with clinical researchers within health care in Stockholm, especially in clinical genomics and clinical proteomics.

MedTechLabs is an interdisciplinary centre for medical technology research, financed by Region Stockholm, KTH and KI. The premises are in close connection with both KI and the Karolinska University Hospital, facilitating clinical studies. The clinical researchers are very active in the programmes of imaging, breast cancer and Artificial Intelligence, as well as bioelectronic medicine.

The Stockholm ALF region is leading in participation in European Reference Networks (ERN) and participates in 21/24 ERNs. The ERNs focus on complex or rare diseases and conditions and provide a governance structure for knowledge sharing and care coordination across the EU. The ERNs also provide clinical research opportunities, systematic patient involvement, and research collaboration networks.

iii. *Encourage and facilitate clinical research aimed at addressing research gaps*

Identified research gaps are continuously discussed at strategic level, and inform regional budget decisions, e.g. the specific **Precision Medicine Task Force** that provides the necessary infrastructure for personalized medicine, **the Centre for Innovative Medicine**, **MedTechLabs**. Important were the **20 M SEK extra funding from Region Stockholm for pandemic research** in the spring of 2020.

Research gaps identified in strategic work are prioritized in the grant application evaluations (together with novelty and clinical significance). Within the strategic program focusing **primary care**, awarded projects shall contribute to build academic competence, address knowledge/research gaps identified in primary care, and strengthen collaboration with the specialist level care. The Stockholm ALF region funds a **research school in family medicine and primary care**, and **extra positions as 'research-residents**' in family medicine (resident programs with allocated research time). Other initiatives include the **Research School in Health Science** in which a focus area is intervention and implementation research and **research positions for healthcare professionals** (e.g. nurses, physiotherapists, speech therapists, medical laboratory technologists, radiographers).

Nationally identified gaps are on the regular agenda in all national networks, and when necessary, **joint actions** are taken to address gaps. An example is the work that preceded a funding scheme focusing on **vaccination research** during the autumn of 2020. In this specific case, a group with participants from all ALF regions lobbied the national funding bodies to allocate specific vaccine research funding. In parallel, the Stockholm ALF Region reached out to potential applicants (national networks were required) and informed them about the upcoming funding opportunity. **During the pandemic resources were quickly reallocated to pandemic-related topics and many highly successful projects ensued.** KI also initiated the formation of interdisciplinary resource teams which have worked to promote and facilitate the establishment of relevant multidisciplinary, researcher-initiated projects internally at KI and in collaboration with the health sector and other higher education institutions. One example of successful KI/Karolinska University Hospital collaboration was the development of a treatment study for COVID-19 based on immune modulation, *ImmCoVA*, which already in July 2020 was approved to study the three immunomodulating drugs dexamethasone, IL-1-inhibition and IL-6-inhibition, while EMA approved the use of the latter two first in December 2021, at which time these three drugs were the only EMA approved immunomodulatory drugs. All other five major Swedish University Hospitals joined this.

1.2 Clinical practice in line with best evidence

Objective: The ALF region has appropriate and sufficient practices and strategies for keeping its clinical practice in line with the best evidence

a) Please describe the ALF region's systematic work to ensure that clinical practice and methods are in line with recent developments in research, as well as with national and international standards and best practice.

Aspects to be covered in the description:

(i) The ALF region's systematic work to phase out old methods (disinvestment).
(ii) How the process for implementation of new methods and phasing-out old methods is monitored and evaluated.

(The description could include the use of e.g. HTAs and quality registers, if applicable. Please supplement and validate the description by providing examples.)

Response: Max one page (A4)

i. *The ALF region's systematic work to phase out old methods (disinvestment)*

Healthcare leadership is ultimately responsible for disinvestment. In addition, the **regional knowledge transfer system** and the regional program groups described in 1.1 play an important role in monitoring/evaluating and the phasing out of old methods. Each program group provides a gap-analysis of their area based on regional healthcare data (e.g. quality indicators, quality register data, numbers of patients, age, socio-economic data, care givers, the professions who the patients meet). The coordinating body Stockholm-Gotland Medical Council has developed a generic model for regional gap analysis (analysis - action plan – communication - follow-up). An important regional resource in this process is the regional **HTA function** (recently reorganized and provided with an increased budget) that among other services organise systematic literature reviews of existing or potentially new treatments. The HTA provides support to the regional program groups (see above) but also accepts questions directly from healthcare personnel. **Example**: The regional program group Ear, Nose and Throat Disorders had observed a difference in the frequency of frenotomies (cutting the tongue band) in newborns between Stockholm and Gotland. A multidisciplinary work group was formed, the HTA provided a literature review, and based on this work a detailed care program for newborns aged 0-6 months (with the goal of reducing frenotomies) was implemented with key indicators for regular follow-up, resulting in a 50% decrease last year. More work on disinvestment is underway. A large research project is focusing phasing out "low-value care", and the Health Care Administration has commissioned a special report on the topic.

ii. *Monitoring and evaluating implementation of new methods and phasing out old ones*

Caregivers working in Region Stockholm are required to **adhere to recommendations and medical guidelines (clearly stated in care contracts and then monitored by the board for each caregiver),** securing patients' access to the best evidence care**.** National and regional guidelines and recommendations (e.g. those developed by the national knowledge transfer system) are all digitally accessible. Viss.nu provides knowledge support to health care professionals in primary care, and Kunskapsstöd för vårdgivare supports healthcare professionals in specialized care. Region Stockholm publishes an annual digital list of recommended evidence-based and cost-effective pharmaceuticals ('The Wise List'). Examples of monitoring models:

- **Cancer treatment:** Both Patient Care Bundles and Medical Programs have been developed nationally and regionally, and adherence to these is regularly monitored by the Regional Cancer Centres.
- **Psychiatry**: Region Stockholm has developed Patient Care Bundles that describe which assessment procedures and interventions are recommended for different conditions. Each clinic is regularly assessed for adherence.
- **Gap-analyses** performed by the regional program groups (see above)

Monitoring also occurs within the framework of the *National Quality Registries*. The Stockholm ALF regions regional registry centre **QRC Stockholm** is involved in regional and national monitoring of coherence to clinical practice within the national knowledge transfer organization, and patient representatives have participated in this work. QRC Stockholm supports 13 National Quality Registries and is responsible for data management in 12 of these. The variables are subject to yearly evaluation, and new variables are introduced after recommendations from the registries' steering committees. Variables are chosen based on their clinical significance and support in national and international clinical guidelines as well as in published peer reviewed research publications. The **Academic Primary Care Centre (APC) with its eight Academic outpatient units** form a network with all 220 primary care units in the region. The APC network is contracted to support the development of primary care in the Stockholm region. The centre provides academic competence in all relevant professions (MDs, physical therapists, nurses, occupational therapists) and assist in quality control (e.g. a special program to reduce the use of antibiotics) and CPD courses, whereby trainers and quality coordinators perform on-site visits and training. The work is based on quality management data and observed shortcomings, but also include the prioritisations made by the knowledge transfer system (the regional program group in primary care), as well as national and regional guidelines. Phasing out is one important aspect of this work (e.g. with regard to prescribing patterns). Patient representatives are involved at all levels, including development and innovation.

b) Please provide two examples of how clinical research performed in the ALF region has been used to develop the clinical practice in your region (e.g. by introducing new methods, treatments or to phase out old methods).

(The description should include references to examples of clinical practice implemented during 2017-2021. The research could have been carried out in collaboration with other regions.)P

Response: Max one page (A4).

Sepsis case-study: Accelerating detection and improving clinical care

Research: Sepsis is a major public health concern, with at least 40 000 new cases each year and a case-fatality rate of 20% in Sweden. Researchers from Stockholm recently presented the first validation of a fully-automated algorithm based directly on Sepsis-3 criteria capturing data from electronic health records, and showed its application in measuring sepsis incidence and mortality at Karolinska University Hospital. A model for early prediction of sepsis using artificial intelligence by machine learning models studying large amounts of clinical data (clinomics) is currently being developed. In parallel, a clinical sepsis alert system at the Emergency Ward, Karolinska University Hospital Huddinge, is being validated. **Impact:** The **national program group** for infectious diseases (chaired by one of the Stockholm PI:s) has developed person-centered and integrated clinical pathways for management of patients with sepsis. It is supported by a health-economic evaluation and is currently being implemented in Sweden. The digital infrastructure of the implementation has been developed by the two PI:s in Region Stockholm. The sepsis alert and sepsis surveillance systems contribute to sepsis being a case-study for personalized medicine at Karolinska University Hospital, whereby we will integrate matched multi-omics analysis (clinomics, transcriptomics, proteomics, genomics), to generate a feedback loop of research and implementation that accelerates discovery and clinical use.

When the crisis hits: The case of COVID-19

Research: In March 2020, a TASK Force COVID-19 expert group was formed as a rapid response to the first cases of COVID-19 infection (with experts in infection disease, intensive care and anesthesia, clinical microbiology, virology, virus epidemiology, imaging/diagnostic radiology, clinical immunology and hyperinflammation, epidemiology and outcomes research). Subsections of the taskforce **continuously summarized and reported** the global development of novel medical information, preclinical and clinical research initiatives, and implementation of best practice documents. In parallel, the TASK Force expert group together with the Center for Infectious Medicine (CIM) rapidly (within weeks) established a large **biobank** project aiming to routinely collect and subsequently make biobank material available for immediate and short-term preclinical and translational research. The Karolinska KI/K COVID-19 Immune Atlas project was conceptualized in March of 2020. The Immune Atlas (www.covid19cellatlas.com) was built as an open resource for broad research and educational purposes. It currently contains a presentation of the response evoked by different immune and inflammatory cells as it occurs in defined patient-groups with moderate and severe COVID-19 disease. It is based on in-depth analysis of innate lymphoid (NK cells (*Sci Immunol* 2020), innate lymphoid cells (*Clin Trans Immunol* 2021)), unconventional T cells (*Sci Immunol* 2020)), adaptive lymphoid (T cells (*Cell* 2020), B cells (*Clin Trans Immunol* 2021)), and myeloid (granulocytes (*PNAS* 2021), monocytes, DCs (*PNAS 2021*)) cells. Several other studies have been started and the results published. **Impact**: The subsections continuously provided information and provided healthcare with best practice documents which were implemented within infections disease, acute and intensive care, post-ICU care and in imaging. **Best practice documents from this group now provide the basis for national best practice guidelines and are used by the governmental National Board of Health and Welfare (Socialstyrelsen)**.

1.3 Progression over time

a) Number of on-going clinical studies

This question is not to be assessed in the evaluation, but instead provide a base-line for future evaluations.

Definition:

By **clinical study,** we refer to a research study using human subjects to study biomedical or health-related outcomes, intended to add to medical knowledge. In this context, only clinical studies that have passed ethical vetting (*Swe. Etikprövning*) are to be referred to. Both intervention studies and observational studies are to be included. By **on-going**, we refer to clinical studies that were either started or ended, or are currently on-going during 2021.

Question	**Number of clinical studies**
a. Number of on-going clinical studies (not counting studies done in cooperation with industry).	*1292*
b. Number of on-going clinical studies in cooperation with industry (regardless of who initiated the study).	*322*

c. Describe how the number of clinical studies has been calculated/estimated (e.g. does the ALF region employ a record of clinical studies). Max half a page
Stockholm has six Research, Development and Education (RD&E) Committees at the hospital/university department level - at the university hospital, at the other four teaching hospitals and at the Stockholm Health Care Services (SLSO), all of whom offer university healthcare. The six committees are assigned by the KI-Region Stockholm Management Group to keep a record of ongoing clinical studies (both academically initiated, and industry initiated). In November 2021 the committees were asked to report studies that were either started or ended, or ongoing during 2021.

2. Clinical research and education

Objective: The ALF region's clinical research is an integrated part of the education of healthcare professionals

a) Please describe the ALF region's strategic work to integrate research competence from clinical researchers into the education of healthcare professionals.

Aspects to be covered in the description:

(i) How students are trained to critically assess and interpret research articles and clinical research findings.
(ii) How students are trained in scientific research methods.
(iii) How the ALF region works to make students interested in conducting research.
(iv) How the ALF region works to engage clinical researchers in the tutoring of student essays.
(v) How the ALF region works to integrate student essays into clinical research projects and programmes.

(In your answer, please provide and describe examples of actions taken and outcomes achieved, if any.)

Response: Max two and a half pages (A4)

Strategic work

KI's Strategy 2030 and the Research, education and development strategy of Region Stockholm both stress the importance of research and education being closely interconnected. KI has developed a definition of research-based education which is used as a guiding principle in KI's first and second cycle education. The definition states that, in order for education to be research based, it is required that:

- Students are involved in ongoing research
- Teachers are active researchers and have a scientific approach which is related using relevant pedagogical methods
- The main topic and the content of the program is based on scientific methods and updated research results. The university actively conducts research within the main topic.
- The teaching is based on research in teaching and learning and builds on teaching activities which contribute to the development of the students' ability to understand, value, and use the processes by which scientifically based knowledge is created and constantly revaluated (the research process).

KI also works with the mirrored concept of **education-based research,** meaning that researchers who are involved in teaching and that teachers who are involved in research are of equal importance. Many researchers supervise and teach at third cycle level, but work is ongoing to increase the involvement at first and second cycle levels by making teaching, educational development and mentoring more visible. Stockholm's regional criteria for university healthcare units states that **each university healthcare unit should include at least one senior lecturer or professor with a combined employment position**, since it strengthens the link between research, education, and the clinical environment.

An important strategic goal in Stockholm is that the entire healthcare system – regardless of public or private operation – shall be accessible to research and education. Private care givers in

Stockholm are increasingly involved in providing clinical placements for students within all educational programs (close to 20% of student weeks). A new pedagogical internship programme has been launched in Region Stockholm. A pilot project comprising eight interns over two admission periods has been introduced. The interns will obtain formal education and perform research or development projects within medical pedagogy in clinical settings. The aims are to increase pedagogical skills among physicians and to improve the quality of clinical teaching.

i. Training in assessing and interpreting research

All courses within the program in medicine and other educational programs focusing on clinical care at KI, comprise critically assessment and interpretation of research articles. In addition, all the programmes have specific theoretical courses in research methodology, such as literature searches, scientific writing, critical appraisal, statistics, epidemiology, research ethics and evidence-based medicine. Many of the teachers involved these courses are clinical scientists.

The curriculum of the current 5.5-year medical programme includes a theme with progressive scientific learning outcomes, learning activities and examinations. Continued training to critically assess and interpret research articles and clinical research findings are included in all clinical courses and are discussed in relation to patient encounters and clinical decision-making in all clinical courses.

The learning outcomes of the new, 6-year medical program, which is currently being implemented, have even more pronounced outcomes regarding scientific competence. Progression of learning activities and examinations over the program course are secured by a central coordinator with contact persons in individual courses and **learning outcomes for scientific competency are included in all courses**. The basic practical training in critical appraisal and interpretation starts early on during undergraduate education with e.g. workshops and journal clubs in which clinical scientists are involved. The students initially use simplified templates for appraisal of the scientific papers but also the templates from Swedish Agency for Health Technology Assessment and Assessment of Social Services (Swe: SBU). These activities are recurrent throughout the education. **Summative assessments of critical appraisal of abstracts to scientific papers are part of a final examination in the medical program during the research methods course, but also in the final integrated exam** (Swe. Integrerad slutexamination, IST).

During the mandatory degree project courses (Sw: examensarbetekurs) (the length of which varies between 10-20 weeks, 15-30 ECTS, between different programs, the medical program 30 ECTS), the students are invited to perform their degree research project in a clinical setting. Most of the medical students choose projects with clinicians as supervisors. Critical appraisal and interpretation of research articles is an integral part of these student projects. In addition, students' interpretation of findings is assessed when they have oral presentations of literature findings, which occur several times during their education. The same principles for teaching scientific competence are implemented on all educational programs focusing clinical care at KI (i.e. nursing, physical therapy, occupational therapy etc).

The quality of the work-based education is monitored by surveys to students as well as staff and clinical managers at the participating clinics. One of the questions in the survey addresses if the students have practiced using/discussed an evidence-based way of working. The question was rated lower than other questions in the survey in 2015-2016 and several actions were taken to improve this. Specific learning outcomes related to evidence-based care/evidence-based medicine are now specified in all courses which include clinical training, in order to increase teaching of and examination of an evidence-based way of working. These specific learning outcomes are also expressed in a way which causes students to actively work with evidence-related questions. Supervisors and other co-workers at the clinics should highlight evidence-based ways of working and be open to discuss evidence for treatments or other measures with the students. The students should also be included in quality and improvement work when possible. Following the introduction of these recommendations and an increased dialogue on the topic the rating score has increased from 64 in 2015 to 78 in 2021 (scale 1-100).

ii. How students are trained in scientific research methods

Students take theoretical courses in research methodology, such as literature searches, scientific writing, critical appraisal, statistics, epidemiology, research ethics and evidence-based medicine. Many of the teachers during these courses are clinical scientists. These skills are further trained during the degree project course, when students perform data collection, data analysis, write a publication-style report, give an oral presentation, critically appraise another student's report and give oral feedback. In addition, appraisal of scientific papers is integrated in several clinical courses.

iii. How the ALF region works to make students interested in conducting research

In the action plan linked to *KI Strategy 2030* one action is to stimulate research interest among students by offering research introductory and research stimulating activities and to improve the conditions for third-cycle qualifications.

KI offers two consecutive research introductory courses for medical students (FoLäk1 and FoLäk2) with 35 places yearly. These courses introduce the students to current cutting-edge research and research departments at KI, scientific theory, scientific history, basic molecular biology techniques, popular and scientific communication, manuscript writing, and they conduct two summer projects at KI labs. In addition, the KI Summer School in Medical Research is offered to first cycle students (43 places in 2022). Students enrolled in the KI Summer School are entitled to a research scholarship.

iv. How the ALF region works to engage clinical researchers in the tutoring of student essays

Senior lecturers and professors with combined employment or co-workers with adjunct positions at KI are central in engaging clinical researchers in the tutoring of student essays. Clinical researchers are encouraged to submit clinical degree projects to be included in a database from which the students can chose a project. Approximately 75% of the degree projects in medicine are supervised by clinical researchers. The Stockholm ALF region provides supportive funding for supervisors of medical student projects. However, to sustainably run a high number of degree projects it is important that supervisors themselves are willing to supervise when they have suitable student projects.

Several clinicians are also external examiners of student degree projects, which requires good subject knowledge, comprehensive research experience and understanding of students as novice researchers. Successful supervision of the projects is reflected in that almost 90% of the degree projects in medicine (at the medical program) pass at the first examination occasion. More proof that the reports are of high quality are students' presentations at national and international meetings, nomination to different prizes and short-listing to the *Undergraduate Awards*, a prestigious competition in which some of the world's foremost students participate.

v. How the ALF region integrates student essays into clinical research projects and programmes

Most of the teachers/supervisors are involved in teaching subjects related to their research and perform clinical research projects. In the medical program, at least half of the degree projects are part of larger clinical research projects. In this way, students become a part of the clinical research team and its community. Sometimes student projects are part of a pilot of larger projects/studies and when the project/study itself starts new students become involved. A 2-year prospective follow-up study reveals that many students continue to collaborate with their supervisors even after the degree project course; and 31% had submitted a scientific paper based on their degree project. In addition, 9% had been registered as PhD students and an additional 127 students (34%) were planning to register as PhD students (Möller R and Shosan M, BMC Med Educ; 17: 51 (2017, doi:10.1186/s12909-017-0890-7).

3. Innovation and life science development

Objective: The ALF region works in a strategic, structured and planned way towards innovation and life science development

Definitions:

By **life science development**, we refer to pre-clinical and clinical research, aimed at developing new medicines, treatments, medical devices and diagnostic methods.

By the **life science sector**, we refer to the life science industry as well as higher education institutions, and public actors at municipal, regional and national level, who work to promote public health. The sector includes research, higher education and innovation, as well as the development of new medicines, treatments, medical devices and diagnostic methods.

By **innovation,** we refer to a new or enhanced product, process or combination of the two, which is markedly separate from a former product or process.

a) Please describe the ALF region's strategic work towards innovation and life science development

Aspects to be covered in the description:

(i) Whether the ALF region has a life science strategy, and when it was adopted.
(ii) What actors/organizations are involved or engaged in the ALF region's strategic work towards innovation and life science.
(iii) How the work/strategy is monitored and evaluated.
(iv) How the ALF region works to enable and facilitate collaboration with the life science industry and other parts of the life science sector throughout the production cycle, from idea to product.
(v) How the ALF region collaborates with the life science industry and other parts of the life science sector concerning R&D infrastructure.

(Please refer to your life science strategy, if available, by web link. Please provide examples to demonstrate and validate the description.)

Response: Max two and a half pages (A4)

i. Strategies

The Stockholm-Uppsala region constitutes a strong cluster for life science; during the last decade the number of life science companies increased with 48%. Region Stockholm and KI work closely together and share the **high level of ambition**, as expressed both in **KI's Strategy 2030** and the **Life Science Strategy for the Stockholm region.** Region Stockholm first adopted an **Innovation strategy** in 2016 and an amended/updated version was launched in 2020. **Strategy for Karolinska Institutet's Research Infrastructure** addresses current and future needs of RI including specific challenges for clinical research. In May 2022, Region Stockholm allocated 10M SEK to a regional Life science office.

ii. Actors/organizations involved in strategic work

The **Life Science Strategy for the Stockholm region,** reflecting the national strategy, was developed in broad regional collaboration and adopted in May 2021, and now forms a framework

for regional strategic work. Numerous regional stakeholders, including Royal Institute of Technology, Stockholm university, Lif (the trade association for the research-based pharmaceutical industry in Sweden) and the pharmaceutical industry were included in the development of the strategy. The strategy draft was also circulated for comments and input to over 40 stakeholders in the region, including patient organizations, municipalities, and public actors at both regional and national levels. The **Innovation strategy** was developed stepwise: several internal and external workshops and dialogues, circulation of a draft strategy to >20 stakeholders (care givers, universities, unions, industry, patient organizations, municipalities, innovation hubs) and final revision before political decision.

iii. Monitoring and evaluation of strategic work

Implementation of the Life science-strategy is monitored through the work of **appointed work groups** which are responsible for specific **action plans**. A special **life science-coordinator** has been appointed, and representatives from relevant organizations are invited to take part. Region Stockholm is responsible for the **action plan *"Access to health care data"*** and KI is responsible for the **action plan *"Precision medicine"***. KI and Region Stockholm share the responsibility for the action plan *"**Research and education in all parts of healthcare**"*. Indicators related to the outcome of the implementation of the action plans are regularly reported in the region's budget follow-up process, and to political boards, to the KI-Region Stockholm management group, to KI Life Science Council, in the annual financial report of Region Stockholm, and externally to other stakeholders. Digital round table meetings are open to staff, patient representatives and external partners and gather large interest. In 2022, the action plan *"**Clinical studies**"* will be launched, aiming at facilitating large clinical trials in Stockholm. An EU-perspective is part of the work; Region Stockholm, Stockholm Trio (the three universities) and the City of Stockholm share a common office in Brussels. This collaboration recently provided a joint position statement on Health data. To further enhance consensus and alignment within life science, KI has established the **KI Life Science Council,** which gathers various actors (including the regional universities, the Region leadership, industry and the national life science office). Stockholm organises a yearly **joint problem-solving conference** at which healthcare, universities, industry, patients and politicians meet to discuss challenges and solutions in life science.

The implementation of the **Innovation strategy** is also monitored by indicators reported in Region Stockholm's annual budget follow-up process and described in detail in an **annual Innovation report** (Innovationsbokslut). The innovation system within Region Stockholm is organized a network embedded in all parts of Region Stockholm's areas of responsibility (health care, public transportation, culture and regional development) consisting of: (1) A regional innovation management group that is responsible for the coordination of wide-ranging innovation efforts (i.e. the **central node** responsible for driving the work); (2) A broad **innovation network** which gathers representatives from all companies and boards who work within or on commission for Region Stockholm; (3) **Local innovation hubs** at hospital/care giver level with different profiles. Caregiver boards are expected to actively support innovation. The **regional innovation fund** distributes 15M SEK annually to innovation projects (**project grants**), and an additional 4M SEK that is allocated to larger projects involving several partners (**strategic innovation grants**). Strategic innovation grants funds e.g. 5G development projects that involve multiple stakeholders including companies. Of note is the **patient involvement in the innovation process**; suggestions from patients are collected, clustered an analyzed yearly in a process coordinated by the Health and Medical Care Administration's Patient Board.

iv. Enabling and facilitating the production cycle, from idea to product

Facilitating contact and collaboration: KI and Region Stockholm are together involved in several **foundations and science parks** which work to promote collaboration between academia, businesses, the public sector and society (KI Science Park, Flemingsberg Science, Stockholm Science City, Kista Science City) and which together form the **regional innovation ecosystem**. These nodes work together to scale up guidance and to organize joint events in which connections between the life science sector and information and communications technology is encouraged and facilitated. KI Science Park and Academic Housing (the public real estate company) have together created a **community with more than 80 companies within the Solna campus** (Innomedicum). To facilitate access to the healthcare system for small and medium-sized enterprises (SME), the

innovation office at Region Stockholm (i.e. the central node described above) has established a **single point of contact for SMEs**. Incoming requests are forwarded to innovation leaders in the healthcare system to find a match. IDEAS is new joint project between KI and Region Stockholm (recently funded) aiming at expanding support to innovators outside academia.

All major caregivers/hospitals have local innovation offices (point 3 above), with somewhat different and complementary profiles. **Karolinska University Hospital and its Center for Innovation** have developed **Innovation partnership models** that are long-term collaborations in which businesses, researchers, clinicians and patients work together to continuously improve healthcare based on the needs of the hospital. A structured way of working has been developed whereby choice of procurement strategy is one important factor to ensure a future outcome for the hospital. The innovation partnership has for instance resulted in new technology being developed in cooperation between the neurosurgeons at Karolinska University Hospital and industry. The result is a newly developed navigation support using AR-technology for use in spinal surgery and is now tested in other fields such as when removing tumours in the brain. For 80–100 patients per year this has meant a shorter rehabilitation and less risk for secondary surgery. The Center for Innovation also **trains staff in innovation management**. Such training is now implemented (1) broadly in the entire region (with funding from the Regional Innovation Office), and (2) within European networks through the Healthcare Transformation Academy, an EU-funded project. Southern hospital provides training in **design thinking** regionwide. **Other example**: The innovation node at Health Care Services Stockholm County has developed an app ("Always Open") for digital care, now implemented in the entire region. The app now has 2.3m registered users in Stockholm (as compared with 25,000 before the pandemic) and the app is used for various purposes such as regular care visits, patient surveillance and triage, informing about available vaccination opportunities, booking services, notifications of lab results etc. Danderyd hospital is piloting 5G-platforms.

At KI, industrial collaboration has traditionally been de-centralized to the department level. Recently, KI has invested in a central *External Engagement Support Office* to create best practice support for industry collaboration and to manage large-scale umbrella partnerships. The **External Engagement Office** and **Centre for Innovation at Karolinska University hospital** meet regularly to share and triage requests from potential external partners.

Financial support: KI Innovations has established a strong life science **incubator** in the region and an **integrated innovation support** for ideas arising from academia. The Royal Institute of Technology and Stockholm university provides similar support, and works closely with KI Innovations. **Scale-Up** is a joint project between Region Stockholm Innovation, KI Science Park and KI Innovation providing funding and access to testbeds and thereby grow faster in the region.

Legal support: Immaterial property guidelines have been developed and published. Tailored advice for specific projects/collaboration is often needed, and both KI and Region Stockholm are currently discussing formats for expanding legal support for collaboration with industrial partners/companies.

Based on strategic decisions, **additional innovation platforms** for industrial collaboration have been formed. **MedTechLabs** is an **interdisciplinary centre for medical technology research**. Region Stockholm, Karolinska Institutet and KTH jointly manage the centre and provide basic funding for its research leaders. MedTechLabs have an extensive collaboration with industry and other partners on a project basis. Research projects are intended to achieve breakthroughs in their respective fields and to generate results that can benefit the healthcare sector within 5 years. An example of this is the program *Spectral CT and Endovascular Techniques* in which the next generation of Computed Tomography technology is being developed. The photon counting CT technology was developed by Prismatic Sensors AB, a start-up founded by a MedTechLabs' researcher, specializing in silicon detectors for photon counting CT. The start-up was acquired by GE Healthcare in 2020.The world's first silicon-based photon counting CT system is currently being tested in a clinical setting at MedTechLabs. **Precision Medicine Centre Karolinska** (PMCK) is an important strategic joint initiative within the Stockholm ALF region to create a center that facilitates the implementation of precision medicine into standard healthcare. By identifying organizational solutions for the integration of diagnostics, treatment and research, precision medicine can be moved closer to healthcare and thus closer to the patient. Within the context of industrial collaboration, the PMCK initiative is striving to create a common value proposition for

potential external partners. In this context, regular dialogue with the national Genomics Medicine Sweden (GMS) and the local Stockholm Center for Health Data initiatives, are held to ensure alignment and consensus of how to collaborate with industry in precision medicine. **The goal of PMCK is to significantly speed up the process for translation from basic research into clinical implementation**.

V. Collaboration regarding R&D infrastructure

The Stockholm ALF region currently works actively to increase access to its infrastructure for external/industrial partners. Today, businesses can access core facilities and infrastructure to some extent, but **several ongoing initiatives strive to increase this access.** One example is **Stockholm Life Tech,** a 3-year project that started in 2020 with funding from the European Regional Development Fund. The project owner is Region Stockholm, and project partners are Akademiska Hus, Flemingsberg Science, Karolinska Institutet, Karolinska Institutet Science Park, Karolinska University Hospital and Stockholm Science City. The purpose of the project is to further develop research and innovation infrastructures as well as making them more easily available for SMEs.

Access to data and samples: The Centre for Health Data (est. 2019) functions as a **single point of contact for access to health data.** The **Centre for Health Data** also has a **collaboration agreement with industry and provides testbeds** for projects in which companies and the region have joint interests. The Centre for Health Data also performs **real world data analyses** at the request of governmental agencies, and participates in regional, national and international activities related to health data. **CLINICUM**, with one central and local nodes, is a support structure for clinical and translational research. The two biobanks Stockholm's Medical Biobank and KI Biobank have formed a joint collaborative platform, **Stockholm's Joint Biobank Infrastructure.**

4. Impact case studies

Objective: The ALF region is able to provide examples of clinical and/or societal impact of clinical research conducted by researchers in the ALF region

Instructions

In this section, the ALF region is requested to provide three impact case studies, i.e. three examples where clinical research, performed by personnel employed by the region and/or the affiliated university, has made a significant impact (clinical and/or societal impact) beyond the contribution to academic research.

The **underpinning research** should have been performed (in full or in part) by personnel employed by the ALF region (i.e. by the region and/or by the affiliated university), and published in 2001 or later.

The **impact beyond academia** should have occurred during the period 2017-2021. The cases selected should have made a significant impact with regard to "clinical impact" and/or "societal impact", as defined below. (The three cases should be selected with regard to impact, not according to e.g. how the three cases complement each other.) Impact case studies provided in the previous ALF evaluation may be used if (i) there has been a change in impact beyond academia, (ii) the change in impact is explained in the description, as well as (iii) it is clearly stated that the case study has been used in the previous ALF evaluation.

Impact beyond academia is clearly distinguished from "output" and "outcome". "Output" refers to the underpinning research, i.e. the research publication(s). "Outcome" could (in this context) refer to a new or modified clinical guideline, whereas "impact" refers to the demonstrated effect on health on a specific patient group, arising from the modified clinical guideline.

An impact case study should be able to demonstrate the following:

- **Who or what** has benefitted from the results of the research (e.g. patient groups, end-users, government, or the wider public)
- The **type of impact** (e.g. improvements in health, quality of life, or reduction in costs)
- The **extent of the impact** (with specific references to appropriate evidence, such as reported benefits to health, quality of life, number of persons benefitted, or cost-benefit analysis)

Clinical impact refers to impact on health care. Clinical impact encompasses, for instance, impact due to new local practices for prevention, diagnosis or treatment of a particular disease, modification of recommendations for treatment or clinical practical guidelines, or modification of guidelines for phasing-out redundant methods (disinvestment). Clinical impact could also imply better decision-making, more clearly defined roles and responsibilities, or new policies relevant for clinical practice.

Societal impact refers to impact arising in other areas than in clinical practice, for instance with regard to public health and the quality of life in general, to public policy, to the reduction in public health costs, or to steps towards a more equal healthcare system.

4.1 Impact Case Study #1 – DETO2X-AMI: Phasing out oxygen support during myocardial infarction

a. Summary

Title of impact case study	DETO2X-AMI

	From (Mon YYYY)	To (Mon YYYY)
Period when the claimed impact occurred	**August 2017**	**Ongoing**
Period when the underpinning research was undertaken	**April 2013**	**December 2015**

Details of staff conducting underpinning research		
Name(s)	**Affiliation**	**Period employed by region and/or university (Mon YYYY to Mon YYYY):**
Leif Svensson (PI), MD, PhD Professor of Cardiology Senior consultant cardiologist	Södersjukhuset/KI SöS	Permanent
Robin Hofmann, MD, PhD (Coordinating Investigator) Senior consultant cardiologist	Södersjukhuset/KI SöS	Permanent
Nils Witt, MD, PhD Senior consultant cardiologist	Södersjukhuset/KI SöS	Permanent
Mats Frick, MD, PhD Professor of Cardiology Senior consultant cardiologist	Södersjukhuset/KI SöS	Permanent
Per Tornvall, MD, PhD Senior consultant cardiologist	Södersjukhuset/KI SöS	Permanent
Ellinor Berglund, RN, PhD Research nurse 50% Staff nurse ED Södersjukhuset	Södersjukhuset/KI SöS	Permanent
Morgan Karlsson, RN Head nurse, CCU Södersjukhuset	Södersjukhuset	Permanent
Anders Bäckman, RN Research assistant 50% Ambulance nurse	Centre for Resuscitation Science, Södersjukhuset/Ambulance Service	Permanent
Thomas Hermansson, RN Research assistant 50% Ambulance nurse	Centre for Resuscitation Science, Södersjukhuset/Ambulance Service	2010-2018
Lina Ljung, MD, PhD Senior consultant cardiologist	Södersjukhuset/KI SöS	Permanent
Thomas Nyström, MD, PhD Professor of Medicine	Södersjukhuset/KI SöS	Permanent

Senior consultant		
Per Svensson, MD, PhD Associate professor of Cardiology Senior consultant cardiologist	Södersjukhuset/KI SöS	Permanent
Tomas Jernberg, MD, PhD Professor of Cardiology Senior consultant cardiologist	Danderyd Hospital/KI DS	Permanent
Mattias Ekström, MD, PhD Senior consultant cardiologist	Danderyd Hospital/KI DS	Permanent
Rickard Linder, MD, PhD Senior consultant cardiologist	Danderyd Hospital/KI DS	Permanent
John Pernow, MD, PhD Professor of Cardiology Senior consultant cardiologist	Karolinska Hospital/KI Solna	Permanent
Linda Mellbin, MD, PhD Associate professor of Cardiology Senior consultant cardiologist	Karolinska Hospital/KI Solna	Permanent

b. Impact beyond academia

i. Description

Please provide a description of a case of clinical significance and/or societal impact to which your clinical research has made a substantial and distinct contribution.

Response: Max one page

Acute myocardial infarction (MI) remains the main cause of morbidity and mortality in Sweden and the world. Oxygen therapy has been provided to all MI patients for decades, despite the lack of high-quality evidence from randomized clinical trials in support of this strategy.
To address this issue, the DETermination of the role of Oxygen in suspected Acute Myocardial Infarction (DETO2X-AMI (NCT01787110)) trial included 6629 patients with suspected MI who were randomised to receive oxygen at 6L/min for 6-12 hours or ambient air, from 35 hospitals across Sweden. The primary endpoint of mortality[2] did not show any significant difference between the two study groups, leading to changes in treatment guidelines and clinical practice, restricting supplemental oxygen therapy to patients with hypoxemia only (<10% of all cases).

The DETO2X-AMI trial was initiated by Professor Leif Svensson and lead by Dr. Robin Hofmann (both from Södersjukhuset/Karolinska Institutet, Stockholm) who were responsible for the trial, including project management with on-site start-up meetings, ethical approval, project management, data analysis and reporting. Trial feasibility and safety was evaluated and confirmed during a 3-month pilot study at Södersjukhuset, Stockholm[1]. The main trial enrolled the first patient at Södersjukhuset in April 2014 and within less than 3 years 6629 patients were recruited with an average enrollment rate overall of 6 patients/site/month.

Clinical impact:
The results obtained had a significant clinical impact on both staff and patients. As routine oxygen therapy did not demonstrate beneficial effects concerning clinical outcomes,[2-8] analgesia, or health-related quality-of-life[9], healthcare personnel save valuable time (an estimated 6 minutes[10]) which can be used for treatments with proven efficacy or rapid transportation to the hospital, factors directly related to improved patient outcomes. Furthermore, patients are spared an uncomfortable, ineffective, and potentially hazardous treatment (hyperoxemia-induced adverse events).

In addition to improved healthcare guidelines (outlined below), extensive educational efforts were provided at all participating sites, half of all hospitals offering acute cardiac care in Sweden. These were provided both on-site and digitally and included ECG courses as well as workshops on clinical research methodology and scientific cooperation.

A further indirect clinical benefit is that use of the national cardiac quality-of-care registry SWEDEHEART as a trial platform increased the engagement of participating sites in more routine quality-of-care aspects. This was beneficial to hospitals reporting data, which in part is connected to reimbursement. Furthermore, participating staff included doctors, nurses, and assistant nurses from different specialties (emergency department, internal medicine, cardiology), both in pre-hospital and hospital settings. Study participation therefore improved interprofessional collaboration, which also improved cooperation in routine clinical practice.

Societal impact:
At the societal level, more restrictive use of oxygen leads to significant disinvestment for the healthcare system, estimated at around 5M SEK annually alone for patients with confirmed MI.[10] The Covid-19 pandemic has also demonstrated that oxygen is a limited resource that should be reserved for indications with proven efficacy, primarily patients with hypoxemia. Due to the large sample size with broad inclusion, extensive reporting of both the overall population and numerous important subgroups was possible, allowing for a more balanced assessment of patients.

ii. References – impact

When applicable, please provide reference (e.g. by web links) to relevant documents and/or names and contact details of stakeholders concerned who could verify the impact.

Response: Max half a page

Examples of international, national, regional and local guideline documents:

International guideline: European Society of Cardiology
Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal.

National guidelines: Swedish National Board of Health and Welfare
https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/nationella-riktlinjer/2018-6-28.pdf

Regional guidelines: Region Stockholm, knowledge for healthcare providers
Hjärt- och kärlsjukdomar - Kunskapsstöd för vårdgivare (kunskapsstodforvardgivare.se)

Local guidelines, Södersjukhuset:
Treatment recommendation (vårdprogram): Responsible: Mats Frick, mats.frick@regionstockholm.se

c. Underpinning research

i. Description

Please provide a brief description of results of clinical research in your ALF region that made an important contribution to the impact described above, and why these results were essential to the impact.

Response: Max half a page

The DETO2X-AMI trial proved that contrary to previously established treatment regimens for acute myocardial infarction (AMI), oxygen treatment is in fact without effect on patient mortality. This result was essential to the impact of the study, instantly changing the way in which AMI is treated. The primary endpoint was first presented by Dr. Hofmann as a late-breaking clinical trial at the European Society of Cardiology (ESC) congress in Barcelona 2017 and the findings were simultaneously published in the New England Journal of Medicine[2]. At the same meeting, the ESC treatment guidelines for oxygen therapy in patients with MI were changed, recommending a more restrictive use of supplemental oxygen for patients with hypoxemia only. As a consequence, cardiac societies across the world adapted their recommendations, including the American Heart Association/American College of Cardiology guidelines. These clear recommendations directly impacted treatment recommendations regionally, including hospital and pre-hospital care. At a national level, the Swedish National Board of Health and Welfare (Socialstyrelsen) changed their recommendations in 2018 (A34.01). Trial data has been presented at numerous international and national scientific meetings and to date a total of 14 scientific articles in high-ranking journals have been published.

ii. References – underpinning research

Please provide 1-10 references to publications to verify that your ALF region contributed to the underpinning research. For each publication, mark in **bold** the names of the authors affiliated to the ALF region at the time the research was produced. (The authors should also be specified in the summary above.)

Response: Max one page

1. **Hofmann R**, James SK, **Svensson L, Witt N, Frick M,** Lindahl B, Östlund O, Ekelund U, Erlinge D, Herlitz J and **Jernberg T**. DETermination of the role of OXygen in suspected Acute Myocardial Infarction trial. *American heart journal*. 2014;167:322-8.
2. **Hofmann R**, James SK, **Jernberg T,** Lindahl B, Erlinge D, **Witt N,** Arefalk G, **Frick M,** Alfredsson J, Nilsson L, Ravn-Fischer A, Omerovic E, Kellerth T, Sparv D, Ekelund U, **Linder R, Ekström M,** Lauermann J, Haaga U, **Pernow J,** Östlund O, Herlitz J, **Svensson L** and Deto2X–Swedeheart investigators. Oxygen Therapy in Suspected Acute Myocardial Infarction. *The New England journal of medicine*. 2017 Sep 28;377(13):1240-1249.
3. **Hofmann R, Tornvall P, Witt N,** Alfredsson J, Svensson L, Jonasson L and Nilsson L. Supplemental oxygen therapy does not affect the systemic inflammatory response to acute myocardial infarction. *Journal of internal medicine*. 2018;283:334-345.
4. Hofmann R, Witt N, Lagerqvist B, **Jernberg T,** Lindahl B, Erlinge D, Herlitz J, Alfredsson J, **Linder R,** Omerovic E, Angerås O, Venetsanos D, Kellerth T, Sparv D, Lauermann J, Barmano N, Verouhis D, Östlund O, **Svensson L,** James SK and SWEDEHEARTInvestigators DX. Oxygen therapy in ST-elevation myocardial infarction. *European heart journal*. 2018;39:2730-2739.
5. **Jernberg T,** Lindahl B, Alfredsson J, **Berglund E,** Bergstrom O, Engstrom A, Erlinge D, Herlitz J, Jumatate R, Kellerth T, Lauermann J, Lindmark K, Lingman M, **Ljung L,** Nilsson C, Omerovic E, **Pernow J,** Ravn-Fischer A, Sparv D, Yndigegn T, Ostlund O, James SK, **Hofmann R** and SWEDEHEART Investigators DX. Long-Term Effects of Oxygen Therapy on Death or Hospitalization for Heart Failure in Patients With Suspected Acute Myocardial Infarction. *CIRCULATION*. 2018;138:2754-2762.
6. **Nyström T,** James SK, Lindahl B, Östlund O, Erlinge D, Herlitz J, Omerovic E, **Mellbin L,** Alfredsson J, Fröbert O, **Jernberg T, Hofmann R** and SWEDEHEART Investigators DX. Oxygen Therapy in Myocardial Infarction Patients With or Without Diabetes: A Predefined Subgroup Analysis From the DETO2X-AMI Trial. *Diabetes care*. 2019;42:2032-2041.
7. Alfredsson J, James SK, Erlinge D, Herlitz J, Fröbert O, Dworeck C, Redfors B, Arefalk G, Östlund O, **Jernberg T, Mars K,** Haaga U, Lindahl B, Swahn E, Lawesson SS, **Hofmann R** and SWEDEHEART Investigators DX. Randomized comparison of early supplemental oxygen

versus ambient air in patients with confirmed myocardial infarction: Sex-related outcomes from DETO2X-AMI. Am Heart J. 2021 Jul;237:13-24.
8. Lindahl B, **Ljung L,** Herlitz J, Alfredsson J, Erlinge D, Kellerth T, Omerovic E, Ravn-Fischer A, Sparv D, Yndigegn T, **Svensson P,** Östlund O, **Jernberg T,** James SK, **Hofmann R** and SWEDEHEART Investigators DX. Poor long-term prognosis in patients admitted with strong suspicion of acute myocardial infarction but discharged with another diagnosis. *Journal of internal medicine*. 2021;290:359-372.
9. **Hofmann R**, Befekadu-Abebe T, Herlitz J, James SK, Erlinge D, Yndigegn T, Alfredsson J, Kellerth T, Ravn-Fischer A, Völz S, Lauermann J, **Jernberg T,** Lindahl B and Langenskiöld S. Routine Oxygen Therapy Does Not Improve Health-Related Quality of Life in Patients With Acute Myocardial Infarction-Insights From the Randomized DETO2X-AMI Trial. Frontiers in cardiovascular medicine. 2021;8:638829.
10. **Hofmann R**, Abebe TB, Herlitz J, James SK, Erlinge D, Alfredsson J, **Jernberg T**, Kellerth T, Ravn-Fischer A, Lindahl B, Langenskiöld S and DETO2X-Investigators. Avoiding Routine Oxygen Therapy in Patients With Myocardial Infarction Saves Significant Expenditure for the Health Care System - Insights From the Randomized DETO2X-AMI Trial. Frontiers in Public Health. 2022 Jan 12;9:711222.

d. Key processes and factors that facilitated the impact

i. Description

Please provide a description of the key processes and factors that you consider contributed to the impact, and whether the ALF region's practices and strategies have contributed to achieving the clinical and/or societal impact.

Response: Max half a page

The clinical and societal success of the DETO2X-AMI trial is based on several factors including:

1) The contribution of key individuals to the initiation, planning and execution of the trial and their access to the national SWEDEHEART network, which allowed us to perform a nationwide trial, and to rapidly implement into clinical practice the new guideline recommendations.
2) Well-established clinical and scientific cooperation among hospitals within Region Stockholm which encompasses almost a quarter of the Swedish population.
3) The ALF practice of distributing support for clinical research to individuals (research appointments, project grants) and departments (research nurses, individual research time, facilities, administrative staff).

The intimate collaboration between Karolinska Institutet (KI) and hospitals in the Stockholm region provides a unique opportunity to perform research on clinical treatment. KI's experience, scientific impact and infrastructure enables rapid distribution of results, particularly thanks to the departments of Communications and Public Relations. As the project described was performed as part of clinical routines for MI treatment, the new treatment guidelines could rapidly be implemented into clinical practice.

4.2 Impact Case Study #2 - *Slowing the course of accelerated aging through healthy living*

a. Summary

Title of impact case study	***Multidomain interventions to prevent cognitive decline and dementia: FINGER-model***

	From (Mon YYYY)	**To (Mon YYYY)**
Period when the claimed impact occurred	**01/2017**	**12/2021**
Period when the underpinning research was undertaken	**02/ 2001**	**12/2021**

Details of staff conducting underpinning research		
Name(s)	**Affiliation**	**Period employed by region and/or university (Mon YYYY to Mon YYYY):**
Miia Kivipelto, MD, PhD, Professor in clinical geriatrics, Director of Research and Development	Div of Clinical Geriatrics, Dept NVS, KI and Theme Inflammation and Aging, Karolinska University Hospital	Feb 2002-ongoing
Francesca Mangialasche , Assist. Professor in clinical geriatric epidemiology, senior geriatrician	Div of Clinical Geriatrics, Dept NVS, KI and Theme Inflammation and Aging, Karolinska University Hospital (KS)	KI: Jan 2008-ongoing KS: Jan 2020-ongoing
Laura Fratiglioni, MD, PhD, Professor	Ageing Research Center, Dept NVS, KI and Theme Inflammation and Aging, Karolinska University Hospital	Jan 2000 – ongoing
Anders Wimo, MD, PhD, Professor (emeritus)	Div of Neurogeriatrics, Dept NVS, KI	KI: Apr 1997-ongoing (emeritus) (adj professor Nov 2007)
Charlotta Thunborg, PhD, research coordinator	Div of Clinical Geriatrics, Dept NVS, KI and Theme Inflammation and Aging, Karolinska University Hospital	KI: Aug 2016 - ongoing KS: Apr 2019 - ongoing

b. Impact beyond academia

i. Description

Please provide a description of a case of clinical significance and/or societal impact to which your clinical research has made a substantial and distinct contribution.

Response: Max one page

The World Health Organization (WHO) estimates that approximately 50 million people worldwide have dementia, a number that will triple by 2050 without effective prevention and treatment strategies. Preventing dementia and Alzheimer's disease (AD) is therefore a global priority,

especially as available drugs have limited effects. Unfortunately, the failure rate in AD drug development is high and no new drugs have been approved in Europe since 2002. Until recently, the only well-established risk factors for dementia were age and genetic factors that do not facilitate the development of prevention strategies.

However, epidemiological studies carried out by the Aging team at Karolinska University Hospital and the Department of Neurobiology, Care Sciences and Society (NVS), Karolinska Institutet, have also identified various modifiable lifestyle and vascular risk factors enabling the development of FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) by Prof. Miia Kivipelto. This is the first randomized controlled trial (RCT) showing that it is possible to prevent cognitive decline using multidomain lifestyle-based interventions among at-risk elderly persons from general population. FINGER has caused a paradigm shift in that cognitive decline is no longer an inevitable consequence of aging, but instead a disorder that can be prevented using multidomain interventions. Besides effects on cognition, the FINGER-model also improved functional capacity and quality of life and reduced the risk of other chronic diseases (especially cardiovascular events and multimorbidity) and hospitalization.

FINGER is a continuously evolving concept. In a recent RCT entitled MIND-ADmini (Multimodal Preventive Trial for Alzheimer's Disease) the FINGER model was adapted for individuals with early AD at memory clinics in Stockholm, again with positive results and experiences. The FINGER model has also been adapted and tested worldwide, and Prof. Kivipelto has launched the *World-Wide FINGERS* network, the first global network of multimodal dementia prevention trials. It aims to adapt, test and optimize the FINGER model to prevent dementia across the entire continuum, from at-risk states to preclinical and prodromal AD, and in different geographical, cultural and economic settings, ultimately to facilitate implementation. WW-FINGERS has expanded dramatically since its launch in 2017 (45 countries from all continents are currently involved, see www.wwfingers.com).

Clinical impact
The clinical impact of the FINGER trial is exemplified not only by the cognitive benefit and improved quality of life of patients at risk of cognitive decline, but also by the development and implementation of WHO and local guidelines, ongoing at various levels and settings such as memory clinics, primary healthcare, municipalities and public health activities. The first WHO Risk Reduction Guidelines for cognitive impairment and dementia were developed and published in 2019 (with Kivipelto as co-leader and author). The guidelines are an important milestone and provide strong, evidence-based risk reduction strategies.

The Multidomain FINGER-based prevention program at the Memory Clinic, Karolinska University Hospital, Solna began 2020 and includes structured measures of risk factors and feedback, involving a multidisciplinary team. In parallel, an implementation study will assess progress. After the first phase, the program will be extended to 12 other memory clinics within the network of memory clinics in Stockholm. Support for implementation of the FINGER-based prevention program is included in the Inflammation and Aging R&D strategy.

An example of clinical impact in primary care includes STRONGER 60+, individualized FINGER implementation which is a hybrid implementation model evaluating both the process and its efficacy. FINGER dementia prevention was also part of the “Stockholm - International Capital for Cognitive Health” initiative which started in 2020. Educational activities are also continuously ongoing in collaboration with Karolinska Institutet, the Swedish Dementia Centre and FINGERS Brain Health Institute. Finally, the impact and potential for prevention are further highlighted by reports demonstrating declining trends of dementia incidence in Stockholm region.

Societal impact
Prevention as conducted in the FINGER trial has proven to be cost-effective. In a health economic simulation model, the FINGER intervention resulted in cost savings and a reduction in dementia cases based on a validated dementia risk score.

ii. References – impact

When applicable, please provide reference (e.g. by web links) to relevant documents and/or names and contact details of stakeholders concerned who could verify the impact.

Response: Max half a page

- **WHO guidelines**. Geneva: World Health Organization; 2019.Licence: CC BY-NC-SA 3.0 IGO. https://apps.who.int/iris/bitstream/handle/10665/312180/9789241550543-eng.pdf?ua=1
- **Global status report on the public health response to dementia.** (ref: Miia Kivipelto and Anders Wimo https://www.who.int/publications/i/item/9789240033245
- **Lidingö Träna Hjärna.** https://www.lidingo.se/toppmeny/kulturfritid/aktivsenior/tranahjarna.4.7eae984b178b3edbb9514b2.html
- **FINGER dementia prevention in Stockholm.** https://aldrecentrum.se/enskilt-projekt/finger-demensprevention-i-stockholms-stad/
- **Memory Clinic implementation.** Karolinska University Hospital. Coordinator Charlotta Thunborg (charlotta.thunborg@ki.se) and Alexandre Bonnard (Medicinskt ledningsansvarig, MU Aging) (alexandre.bonnard@regionstickholm.se)
- **STRONGER study.** https://www.stockholmssjukhem.se/aktuellt/nyheter/2022/deltagare-sokes-till-halsostudie-pa-stockholms-sjukhem Head of R&D, Stockholms Sjukhem, Elisabet Åkesson (elisabet.akesson@stockholmssjukhem.se)
- **World-Wide FINGER network.** https://wwfingers.com (contact: Miia Kivipelto and Francesca Mangialasche)
- **Partnership with Alzheimer Disease International:** https://www.alzint.org/news-events/news/adi-and-ww-fingers-renew-commitment-to-work-together-to-reduce-the-global-risk-of-dementia/
- **Swedish Centre for Dementia.** Wilhelmina Hoffman, CEO
- **The Melvin R. Goodes Prize for Excellence in Alzheimer's Drug Discovery.** This prize honors an innovative researcher who has made a significant and lasting impact in the field. USA, October 2021. https://news.ki.se/professor-miia-kivipelto-awarded-the-2021-melvin-r-goodes-prize-for-innovative-research
- **Dissemination activities.** These include popular scientific media publications (193 international, 39 national) and publishing a book about Brain Health and preventing memory impairment and Alzheimer's disease https://alzheimerfondenshop.com.
- **The Ryman Prize, New Zealand (2020).** An international award for the best work carried out anywhere in the world that has enhanced the quality of life for older people (by Prime Minister of New Zealand) https://www.rymanhealthcare.co.nz/the-ryman-prize/winners https://news.ki.se/professor-miia-kivipelto-wins-the-2020-ryman-prize
- **Life style training:** https://www.digitalvardochomsorg.se/lidingo-stad-satsar-pa-trana-hjarna-for-seniorer/ https://fbhi.se/first-finger-based-lifestyle-program-at-municipal-level-inaugurated-today-in-lidingo-stockholm/

c. Underpinning research

i. Description

Please provide a brief description of results of clinical research in your ALF region that made an important contribution to the impact described above, and why these results were essential to the impact.

Response: Max half a page

The results that made the greatest contribution to the impact of the FINGER intervention are as follows:

Identification of modifiable risk factors. Firstly, by using epidemiological studies, the team at ME Aging at KS and Dept of NVS, KI, were able to identify several modifiable lifestyle and vascular risk factors for dementia and AD such as high blood pressure, cholesterol and obesity at midlife, diabetes, low physical activity, smoking and sleep disturbances. Interactions with genetic factors, as well as possible underlying mechanisms through which lifestyle can promote resilience to brain pathology were studied and results showed that at least 40% of all dementia cases are related to modifiable factors and could be prevented, creating a clear prevention potential. Studies on secular trends of dementia occurrence also showed that the speed at which new generations of older adults develop dementia today is slower than what it was 25 years ago, likely a product of improved cardiovascular health and lifestyle in later-born cohorts, lending further support to the prevention potential.

Development of dementia risk score. Another significant achievement was development of the first Dementia Risk Score (CAIDE) to estimate the risk of dementia later in life based on easily available risk factors at midlife. The CAIDE dementia risk score can be used to target the interventions to those most at risk and is also a motivational and educational tool. It is still one of few validated risk scores and has been successfully used in clinical trials and in clinical practice.

Findings of prevention trials. Previous single-intervention failures stressed the critical need for a new multimodal preventive approach in the dementia field, whereby several disease mechanisms and modifiable risk factors are targeted simultaneously. FINGER is a Swedish/Finnish collaboration and is the first large-scale, long-term RCT to show that a multi-domain, lifestyle-based intervention can reduce the risk of cognitive impairment among those at-risk in the general population. FINGER used the combined 'finger model' consisting of a healthy balanced diet, physical exercise, cognitive training, social activities and vascular/metabolic risk management. Significant cognitive benefits (improved global cognition, executive function, processing speed and memory) were shown in 1260 at-risk older adults for the 2-year multidomain lifestyle intervention versus regular health advice (Lancet 2015). Of particular importance was the finding that this multidomain intervention benefits a large elderly population at risk of cognitive decline and dementia, irrespective of baseline characteristics. Persons with genetic susceptibility for AD (ApoE4 carriers) achieved clear beneficial effects. There were also several other beneficial effects beyond cognition highlighting the extent of the impact including a lower risk of functional decline, improved health-related quality of life, reduced risk of other chronic diseases and a lower risk of hospitalization.

ii. References – underpinning research

Please provide 1-10 references to publications to verify that your ALF region contributed to the underpinning research. For each publication, mark in **bold** the names of the authors affiliated to the ALF region at the time the research was produced. (The authors should also be specified in the summary above.)

Response: Max one page

1. **Kivipelto M**, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. The Lancet Neurology. 2006 Sep;5(9):735–741. (**IF 28.7**)
2. Ngandu T, Lehtisalo J, Solomon A, Levälahti E, Ahtiluoto S, Antikainen R, Bäckman L, Hänninen T, Jula A, Laatikainen T, Lindström J, **Mangialasche F**, Paajanen T, Pajala S, Peltonen M, Rauramaa R, Stigsdotter-Neely A, Strandberg T, Tuomilehto J, Soininen H, **Kivipelto M**. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER):a randomised controlled trial. The Lancet. 2015 Mar; 11;385(9984):1–9. (**IF 60.4**)
3. Rosenberg A, Ngandu T, Rusanen M, Antikainen R, Bäckman L, Havulinna S, Hänninen T, Laatikainen T, Lehtisalo J, Levälahti E, Lindström J, Paajanen T, Peltonen M, Soininen H,

Stigsdotter-Neely A, Strandberg T, Tuomilehto J, Solomon A, **Kivipelto M**. Multidomain lifestyle intervention benefits a large elderly population at risk for cognitive decline and dementia regardless of baseline characteristics: The FINGER trial. Alzheimer's & Dementia. 2018 Mar;14(3):263–70. (**IF 21.56**)

4. Kulmala J, Ngandu T, Havulinna S, Levälahti E, Lehtisalo J, Solomon A, Antikainen R, Laatikainen T, Pippola P, Peltonen M, Rauramaa R, Soininen H, Strandberg T, Tuomilehto J, **Kivipelto M**. The Effect of Multidomain Lifestyle Intervention on Daily Functioning in Older People. J Am Geriatr Soc. 2019 Jun;67(6):1138-1144. (**IF 5.56**)
5. Marengoni A, Rizzuto D, **Fratiglioni L**, Antikainen R, Laatikainen T, Lehtisalo J, Peltonen M, Soininen H, Strandberg T, Tuomilehto J, **Kivipelto M**, Ngandu T. The effect of a 2-year intervention consisting of diet, physical exercise, cognitive training, and monitoring of vascular risk on chronic morbidity—the FINGER randomised controlled trial, Journal of the American Medical Directors Association 2018;19(4):355-360. (**IF 4.67**)
6. **Fratiglioni L**, Marseglia A, Dekhtyar S. Ageing without dementia: can stimulating psychosocial and lifestyle experiences make a difference? The Lancet Neurology. 2020;19(6):533–43 (**IF 44.18**)
7. Ding M, Qiu C, Rizzuto D, Grande G, **Fratiglioni L.** Tracing temporal trends in dementia incidence over 25 years in central Stockholm, Sweden. Alzheimer's & Dementia. 2020;16(5):770–8. (**IF 21.56**)
8. Shireen Sindi, Thunborg C, Rosenberg A, **Wimo A**, Solomon A, **Kivipelto M.** Multimodal Preventive Trial for Alzheimer's Disease: MIND-AD$_{MINI}$ pilot trial study design and progress. Journal of Prevention of Alzheimer's Disease 2022;9(1):30-39. (**IF 4.67**)
9. **Kivipelto M**, **Mangialasche F,** Snyder HM, et al., World-Wide FINGERS Network: A Global Approach to Risk Reduction and Prevention of Dementia. Alzheimer's & Dementia 2020;1–17. DOI: 10.1002/alz.12123 (**IF 21.56**)
10. **Wimo A,** Handels R, Antikainen R, **Eriksdotter M… Kivipelto M**. Dementia prevention: The potential long-term cost-effectiveness of the FINGER prevention program. Alzheimer's & Dementia 2022 (in press) (**IF 21.56**)

e. Key processes and factors that facilitated the impact

Description

Please provide a description of the key processes and factors that you consider contributed to the impact, and whether the ALF region's practices and strategies have contributed to achieving the clinical and/or societal impact.

Response: Max half a page

Several key factors contributed to the clinical and societal impact of this project including the development of an innovative hospital platform termed "Aging", to integrate research, care and development, all of which facilitated implementation. The possibility to carry out translational research within a strong clinical infrastructure and with world-leading expertise (e.g. Centre for Alzheimer Research and Aging Research Center), as well as having a multidisciplinary clinical research team were also key factors central to our impact. Our streamlined operational model at the memory clinic of Karolinska University Hospital, Solna has further facilitated our achievements, as well as close collaboration with several key stakeholders and the active involvement of patients in qualitative research and advisory boards at all stages of the research.

Recent publications from the research group provide more detailed descriptions of important issues regarding the successful implementation of multidomain interventions to prevent cognitive decline and dementia, including an article from the patients' perspective:

- **Key considerations for successful implementation** of multidomain preventive interventions based on the FINGER and MIND-AD studies (including both Healthcare resources and infrastructure and person- and intervention-related factors)**.** Facilitators and barriers to implementing lifestyle intervention programme to prevent cognitive decline. Eur J Public Health. 2021 Oct 11;31(4):816-822.

- **Protocols supporting implementation and a user manual** for Brain Health Services. Multidomain interventions: state-of-the-art and future directions for protocols to implement precision dementia risk reduction. A user manual for Brain Health Services-part 4 of 6. European Task Force for Brain Health Services. Alzheimers Res Ther. 2021 Oct 11;13(1):171.
- **Experiences regarding guideline development**: Development of the First WHO Guidelines for Risk Reduction of Cognitive Decline and Dementia: Lessons Learned and Future Directions. Front Neurol. 2021 Oct 26;12:763573.
- **Patient experiences.** Experiences of Participation in a Multimodal Preventive Trial MIND-ADMINI Among Persons with Prodromal Alzheimer's Disease: A Qualitative Study. J Multidiscip Healthc. 2022 Jan 29;15:219-234.

4.3 Impact Case Study #3 - Time matters - saving lives before arrival at the hospital

a. Summary

Title of impact case study	***The Stockholm Stroke Triage Project – reducing the impact of severe stroke***

	From (Mon YYYY)	**To (Mon YYYY)**
Period when the claimed impact occurred	**October 2017**	**Ongoing**
Period when the underpinning research was undertaken	**October 2017**	**Ongoing**

Details of staff conducting underpinning research		
Name(s)	**Affiliation**	**Period employed by region and/or university (Mon YYYY to Mon YYYY):**
Michael Mazya, MD, PhD, Assoc. prof, Consultant neurologist	ME Neurologi, Karolinska US / CNS KI	Ongoing since 2009
Christina Sjöstrand, MD, PhD, Assoc. prof, Consultant neurologist	VO Neurologi, Danderyds Sjh. / CNS KI	Ongoing since > 20 years
Annika Berglund, RN, PhD	ME Neurologi, Karolinska US / CNS KI	Ongoing since > 20 years
Boris Keselman, MD, PhD, Neurology resident	ME Neurologi, Karolinska US / CNS KI	Ongoing since 2016
Einar Eriksson, MD, PhD, Assoc. prof, Consultant neurologist	ME Neurologi, Karolinska US / CNS KI	Ongoing since > 20 years
Niaz Ahmed, MD, PhD, Assoc. prof, Consultant neurologist	ME Neurologi, Karolinska US / CNS KI	Ongoing since >15 years
Staffan Holmin, MD, PhD, Professor, Consultant neuroradiologist	FO Neuroradiologi, Karolinska US / CNS KI	Ongoing since > 20 years
Ann-Charlotte Laska, MD, PhD, Assoc. prof, Consultant in internal medicine	VO Neurologi, Danderyd Sjh. / CNS KI	Ongoing since > 20 years
Mia von Euler, MD, PhD, Assoc. prof, Consultant neurologist	Medicinska fakulteten, Örebro Universitet	In Region Sthlm / SLL since > 20 years, but recently moved to Örebro

b. Impact beyond academia

i. Description

Please provide a description of a case of clinical significance and/or societal impact to which your clinical research has made a substantial and distinct contribution.

Response: Max one page

The most severe type of acute ischemic stroke (AIS) is caused by large artery occlusion (LAO) in about a quarter of AIS patients. Even if treated with intravenous thrombolysis (IVT) and managed at a stroke unit, prognosis in LAO stroke is poor; 19% of patients die by three months, 68% survive with disability leaving only 13% with an excellent, disability-free outcome.

In 2015, groundbreaking trials showed that the technique of endovascular thrombectomy (EVT) could double the proportion of patients with excellent outcomes, markedly increase independence in daily activities, and reduce disability. However, this treatment effect is highly time-dependent; ischemic brain turns to infarct at a rate of 120 million neurons per hour. In randomized trials, the median time from stroke onset to EVT was 4 hours.

The first EVT in Stockholm was performed in 2005 at the Karolinska University Hospital (KS), the regional provider of neuroendovascular treatment. Quality registers showed that 75% of patients requiring EVT were brought by ambulance to the nearest emergency hospital where they underwent diagnostic workup and were later transferred to KS. Compared to patients living nearby and brought to KS directly, those with a secondary transfer received EVT 60-90 min later, resulting in more frequent and severe disability.

In 2014, a new prehospital system was designed to facilitate identification of patients with the highest likelihood of needing EVT. Ambulances would be directed to KS immediately, without pre-processing at another hospital. Pilot calculations of local and multinational registry data led to the design of the A2L2 test for hemiparalysis, a specific clinical marker of severe stroke. This became part of the new three-step Stockholm Stroke Triage System: step 1 – stroke suspicion by ambulance nurse; step 2 – nurse performs A2L2 test; step 3 - if A2L2- positive, telephone consultation with stroke physician at KS, or if A2L2-negative, pre-notify nearest hospital. The teleconsultation was an essential design feature, aiming to increase triage precision.[6]

The new system was implemented in October 2017, as a region-wide project. All seven emergency hospitals in the region, three ambulance companies and the Stockholm county council IT department were involved. Furthermore, several inter-service groups were formed comprised of representatives from the above, responsible for tasks such as coordination, staff training, patient transfer coordination, quality assessment, safety and monitoring. During the first year, 2905 patients transported by first priority ground ambulances for suspected stroke in the Stockholm region were included in a prospective observational study.

Clinical impact

The first results, published in *JAMA Neurology* in April 2020, clearly demonstrate the positive effects for patients in that time from stroke onset to EVT dropped to a median of 2 hours 15 min, compared to 3 hours 25 min in the last year before the new system implementation. The new system had a 91% accuracy for directing patients to the correct hospital according to their need for EVT. Of all EVT patients, 70% were now brought directly to KS, compared to 30% the year before. The onset to EVT time in Stockholm was now one hour shorter than the Swedish national average (EVAS registry). Two years after initiation, we assessed clinical outcomes of EVT compared to the last two years prior to new triage implementation. Results showed significant increases in excellent, disability-free outcomes with the new system, as well as more patients attaining independence in daily activities. When analyzing the subgroup living independently before the stroke only, we saw 41% completely free from disability and 60% retaining their independence at three-month follow-up (versus 13% disability-free and 27% independent in the control arms of randomized trials of EVT). This paper was published in the journal *Stroke* in 2021. Initial results were communicated to key stroke stakeholders in the Stockholm region in January 2020 as a care quality report. Soon after, the Health Services Administration decided that the new triage system should receive permanent routine healthcare status. Regional pre-hospital guidelines were amended, and the A2L2 test with teleconsultation was mandated in all patients with suspected stroke symptoms, the onset of which occurred within 24 hours of assessment.

Societal impact

While formal health economic calculations have not yet been calculated within the project, it is highly likely that the findings have resulted in a significant reduction of societal costs. The Swedish Dental and Pharmaceutical Benefits Agency (TLV) calculated that thrombectomy performed according to the published randomized trials from 2015, in a Swedish setting led to reduced costs to society of 410 000 SEK per treated patient, due to a lower burden of functional impairment. It is

important to emphasize that thrombectomy in the new system in Stockholm is now delivered almost 2 hours faster than in the randomized trials (2 h 15 min versus 4 hours), with far better outcomes (see above). It should also be noted that the new system has not led to additional costs for the healthcare system, since there was no requirement for new staff or materials.

ii. References – impact

When applicable, please provide reference (e.g. by web links) to relevant documents and/or names and contact details of stakeholders concerned who could verify the impact

Response: Max half a page

Interview Reuters Health: https://www.medscape.com/viewarticle/928299?src=rss#vp_2

KI Press Release: https://news.ki.se/new-practices-improved-stroke-care

Article in Dagens Medicin: https://www.dagensmedicin.se/specialistomraden/hjarta-karl/battre-resultat-med-nytt-system-att-triagera-stroke/

c. Underpinning research

i. Description

Please provide a brief description of results of clinical research in your ALF region that made an important contribution to the impact described above, and why these results were essential to the impact.

Response: Max half a page

The main findings of this study are inextricably linked to the clinical and societal impact in that for every 100 patients with severe stroke, treated after implementation of the new triage system as part of the research project, an additional 10 now attain complete freedom from disability. One must consider that 17% of treated patients already had some degree of pre-existing disability before the stroke. If one examines the outcomes in patients without pre-existing disability, the new system led to freedom from disability in 41% versus 28% with the old system (i.e. 13 more patients free from disability of every 100 treated), which can be compared to only 13% reaching this excellent outcome in comparable, albeit younger patients, who did not receive thrombectomy in RCT control groups.

ii. References – underpinning research

Please provide 1-10 references to publications to verify that your ALF region contributed to the underpinning research. For each publication, mark in **bold** the names of the authors affiliated to the ALF region at the time the research was produced. (The authors should also be specified in the summary above.)

Response: Max one page

1. **Mazya, MV; Berglund, A; Ahmed, N; von Euler, M; Holmin, S; Laska, AC; Mathé, JM; Sjöstrand, C; Eriksson, EE.** Implementation of a Prehospital Stroke Triage System Using Symptom Severity and Teleconsultation in the Stockholm Stroke Triage Study. *JAMA Neurol*. 2020;77(6):691-699.*
2. **Keselman, B; Berglund, A; Ahmed, N; Bottai, M; von Euler, M; Holmin, S; Laska, A.-C.; Mathé, J; Sjöstrand, C; Eriksson, E; Mazya, MV**. The Stockholm Stroke Triage Project - outcomes of endovascular thrombectomy before and after triage implementation. Stroke 2022 Feb;53(2):473-481
3. **Almqvist T, Berglund A, Sjöstrand C, Eriksson E, Mazya MV.** Prehospital Triage Accuracy in Patients With Stroke Symptoms Assessed Within 6 to 24 Hours or With an Unknown Time of Onset. Stroke. 2021 Apr;52(4):1441-1445.

4. **Wiebert E, Berglund A, Sjöstrand C, Eriksson E, Mazya MV**. Sex Equitable Prehospital Stroke Triage Using Symptom Severity and Teleconsultation. Frontiers in Neurology. 2021 Nov 29;12:765296 – this won second place in a competition for best academic thesis, held by the Swedish Gender Equality Agency (Jämställdhetsmyndigheten)
5. **Keselman, B; Berglund, A; Ahmed, N; Bottai, M; von Euler, M; Holmin, S; Laska, A.-C.; Mathé, J; Sjöstrand, C; Eriksson, E; Mazya, MV.** Analysis and modelling of mistriage in the Stockholm Stroke Triage System. European Stroke Journal, accepted for publication on Jan 13, 2022.

The project has significantly contributed to one associate professorship (M. Mazya), one successfully defended PhD thesis (B. Keselman, https://openarchive.ki.se/xmlui/handle/10616/47711), and three successfully defended Medical Degree Projects (Master/Advanced level), by T Almqvist, E Wiebert, and M Sjöö, all of the above at Karolinska Institutet, under supervision by M. Mazya. One additional sub-project based on the new triage system will form part of an upcoming PhD thesis project by T. Almqvist.

*This publication reached an Altmetric Attention Score in the 98th percentile of all research tracked by the company.

d. Key processes and factors that facilitated the impact

i. Description

Please provide a description of the key processes and factors that you consider contributed to the impact, and whether the ALF region's practices and strategies have contributed to achieving the clinical and/or societal impact.

Response: Max half a page

The project is a classic example of the successful implementation of clinical research in practice. The idea was conceived by clinical researchers working daily with patients with acute stroke at Karolinska university hospital who were able to identify an unmet clinical need and clearly see the shortcomings of the previous care system, leading to unnecessary delays in time-critical treatment for patients with severe stroke. One factor particularly important for our impact was that the researchers involved were centrally placed in the organization of expertise and evidence-based best practice in stroke and neurological diseases within Region Stockholm, being members of the Stockholm stroke advisory board, which ultimately report to the Health and Care Administration. These vertical connections facilitated horizontal coordination with the regional prehospital chief medical officer, as well as chief medical officers for the three ambulance companies, as well as the departments of emergency medicine and internal medicine. A nurse/PhD (chair of the Stroke advisory board) played a pivotal role in the project, e.g. through organizing data collection protocols and training ambulance staff. Prehospital staff are key for identifying cases and signal to the hospital when potentially eligible patients are on their way, giving time for the team to mobilize and prepare for arrival.

Alongside the formal vertical and horizontal contacts and coordination, the project initiators worked extensively with the Stockholm stroke advisory board and the purpose-formed network group for prehospital triage (including representatives from stroke care at all emergency hospitals in the region), to facilitate dissemination. In parallel with the above, task groups were formed for technical implementation concerning prehospital electronic health records, ambulance staff training, quality follow-up, safety monitoring and research.