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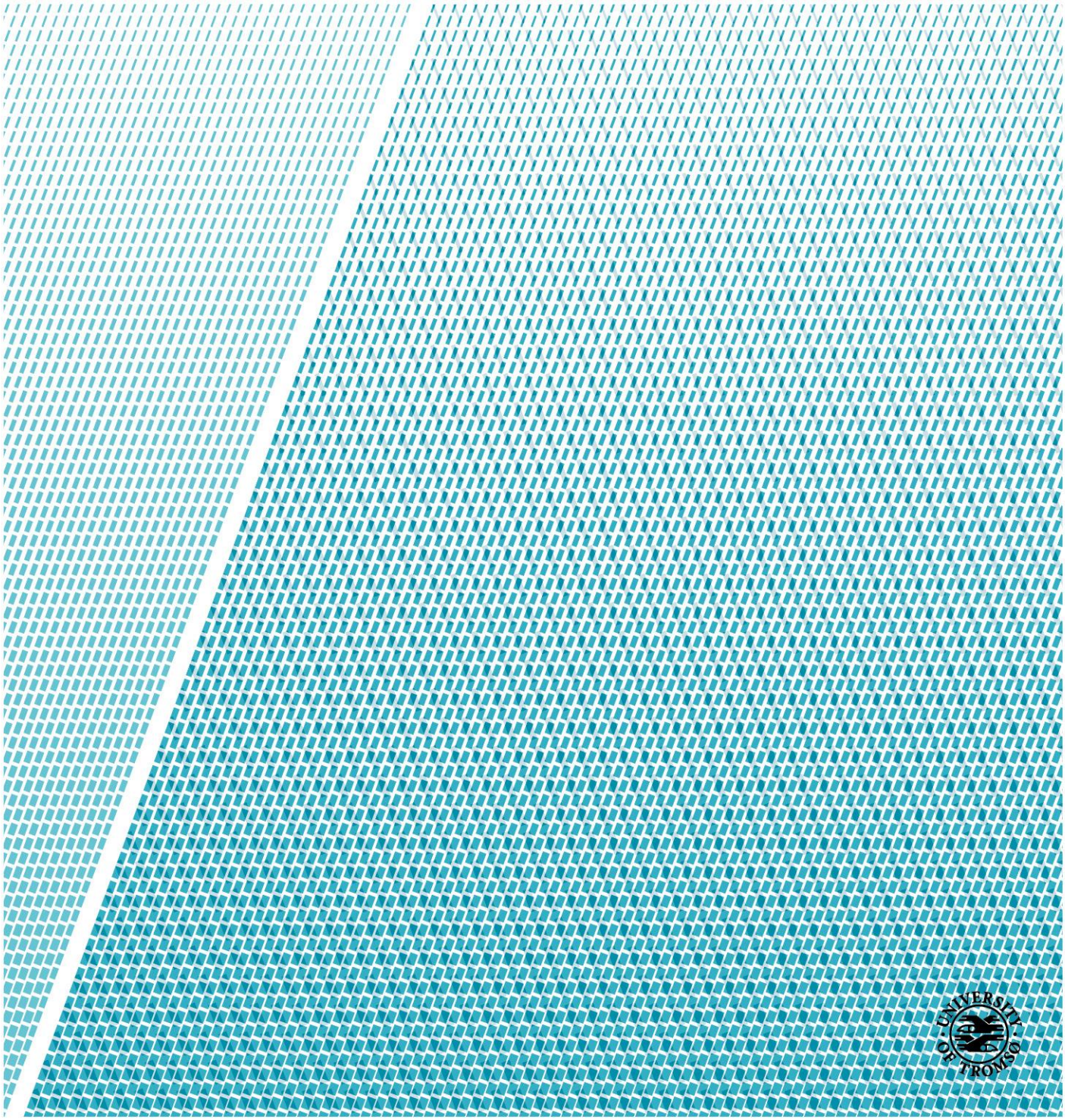
Research protocol

Monitoring adverse events caused by systemic anticancer treatment – Safer **Pe**rsonalized **C**ancer **T**reatment digital follow-up – **SpeCT**

HNF1626-22

Siv Gyda Aanes



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1 Background for the study

To reduce harm and improve patient safety in cancer care we need reliable and relevant measurements that reflect everyday clinical practice. This research is initiated to enhance patient safety and personalised follow-up for cancer patients by developing tools to monitor adverse events caused by immunotherapy as a widely used modern systemic anticancer treatment.

Adverse events (AEs) is defined as an adverse outcome arising from medical care rather than patient`s underlying condition. AEs occurs twice as often in cancer patients compared other patients and most incidences are associated with systemic anticancer treatment (1). A widely applied method to identify and measure AEs is the Global Trigger Tool (GTT)- method, which uses a structured manual review of patient journals with triggers as indicators to signal potential AEs in hospitalised patients (2). Since 2010 all Norwegian Hospitals are obliged to measure AEs using the GTT-method. The Ministry of

Health and Care Services has recommended further development of the GTT method to more accurately measure AEs with automatic identifications and more disease specific models (3,4). Patient Reported Outcomes (PRO) and Outcomes Measures (PROM) have shown to better describe the patients` symptoms compared to reporting from health care professionals (5). A recent systematic review of 22 studies including PROMs in daily cancer care found that follow-up by PROMs had a positive effect on survival, symptoms, health related quality of life and patient satisfaction (6). Consequently, PROMs are seen as the preferred method and gold standard to gather information from the patients in studies and real-life, as they often give a more convincing picture of the patients' wellbeing and side effects from interventions and treatments (5). Studies have demonstrated that electronic PROs (e-PROs) as follow-up for cancer patients under chemotherapy treatment can reduce acute admission to hospitals, improve quality of life (QoL) and prolong overall survival with up to 7 months compared to follow-up by standard care (5,6). There are national recommendations for research to; a) increase quality and efficacy in health care; b) promote personalised, patient centred health; c) improve prediction and diagnostics; d) increase use of e-health; and e) increase innovation in clinical practice (7). To our knowledge there are no studies published on how e-PRO follow up affects rates of severe adverse events, QoL and survival of cancer patients receiving immunotherapy treatment. In our research we will study immunotherapy related AEs(irAEs) in real time and investigate if ePRO follow-up can reduce severe irAEs, influence QoL and perhaps also increase survival compared to standard follow-up of cancer patients.

In 2013, Nordland Hospital Trust (NLSH) in collaboration with SAS Institute (SAS) developed a modified half automated version of the GTT method, called Nordic Clinical Analytics Framework (NCAF). Here machine learning (ML)-methods make it possible to find records with positive triggers which then are manually reviewed to verify if the triggers represent a true AE. Previous research on this half-automated technology have shown that it can efficiently replace manual identification, saves time and resources identifying AEs (8). From 2017 the NCAF method has been used by all hospital trusts in Northern Norway, however it has some drawbacks. Firstly, technology to fully automate identification of AEs is not yet developed. Secondly, NCAF lacks cancer-specific triggers to identify AEs related to systemic anticancer treatment such as chemotherapy, immunotherapy and other targets therapies. This makes it difficult to both identify, compare, and monitor AEs over time for cancer patients (1,9-12). To develop an automated identification of AEs we need to identify relevant triggers, before incorporating them into the NCAF technology. Recently a few studies have validated cancer-specific triggers, nevertheless, none of these validated oncology trigger tools uses automated identification of AEs (9-12). Furthermore, validated triggers to identify AEs related to modern anticancer treatments such as immunotherapy do not exist today. Immunotherapy introduces a different type of autoimmune AEs that can affect every organ system and causes 15 % severe AEs. To prevent development of severe irAEs it is important with early detection, since they can be reversed

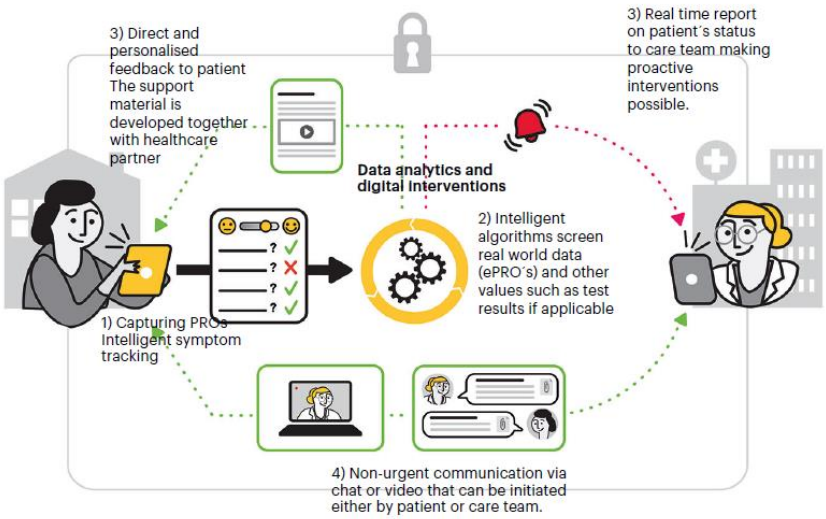

Figure 1: E-PRO follow-up with Kaiku Health

with timely intervention (13,14). Thirdly, NCAF only analyses hospitalised patients while most cancer patients receive ambulatory treatment, so monitoring AEs in an outpatient setting is essential to map the full extent of AEs.

As the first hospital in Norway, the Cancer Department at NLSH implemented ePRO follow-up as standard of care for all patients receiving immunotherapy from June 2021 by using Kaiku Health. The immunotherapy module is based upon reported irAEs in clinical trials of immunotherapy (15-17). Kaiku health is a web-based program for smartphones, I-pads and home computers, and by using ML algorithms the software screen, grade and alert for potential harm. Based on received treatment each patient gets a personalised follow-up symptom- and QoL-questionnaire (the European Organisation of Research and Treatment of Cancer, EORTC, recommended QoL-module called QLQ C-30(18)) sent out regularly. Filled-out questionnaires are submitted digitally to the Cancer Department which is able to see in real-time the patient's status, and directly identify possible symptoms. This makes it easier to respond immediately to potentially serious irAEs and prevent further impairment of the patient. At the same time as the health care professionals are alerted, the patient gets information on his/her own device about how they should react and what to do, and how their symptoms have evolved over time. Figure 1 illustrates how ePRO follow-up with Kaiku Health works in clinical practice.

From analysing the current methods and technologies used to monitor AEs caused by anticancer treatment, we intend in work package (WP) 1 to develop and validate a fully automated cancer-specific trigger tool to identify irAEs occurring in both hospitalised and outpatient clinical practice, called NCAF Oncology. In WP 2 we will study how the NCAF Oncology works in clinical care, and compare the incidence and development of irAEs between cancer patients followed by ePRO compared to standard of care. In WP3 we investigate how QoL in cancer patients evolves under immunotherapy treatment with follow-up by ePRO, and also compare overall survival between standard and ePRO follow-up.

1.1 Expected benefits

By developing novel technology relevant in clinical practice our ambitions are to develop and validate the first fully automated NCAF Oncology method to monitor irAEs specific to modern immunotherapy anticancer treatment both in hospitalised and outpatient settings, with the future purpose to measure and mitigate irAEs with use of less resources. The key **academic impact** is validated technological methods to monitor irAEs from systemic anticancer treatment that can be directly implemented in everyday clinical practice. Development of a fully automated NCAF Oncology can be used to develop similar technological methods to identify AEs in other medical specialties. Improvement of the NCAF allows further research on prospective warning signals and clinical support integrated in the electronic health record (EHR) to mitigate other AEs in cancer care. The use of ePROs and QoL-score provides personalized follow-up to the patients. It also gives healthcare professionals the opportunity to focus on the patient`s perspective at the same time as they can mitigate and prevent harm before it results in a severe irAE. Importantly, the patients are proactive in their own patient journey with more knowledge about their own symptoms and how to react on them. This encourages empowerment and safety to the patient and their family, and has proved to reduce symptoms such as pain, depression and fatigue and increase patient's QoL (6). It could also decrease the need for emergency admissions or unplanned visits/ phone calls at the outpatient clinic (5,6,15), which can be a burden to the patient, their family and the healthcare system. Knowledge about real time follow up and irAEs can be clinically relevant to better inform patients before starting new treatments. It may also provide information about when to end potentially harmful and high cost treatment, as alerted symptoms and/or decreasing QoL can signal toxicity or progressive disease (5,6,16,17).

2 The student`s contributions into the project

The PhD student will be responsible for data collection, analysis and writing of all articles in WP1-3. For detailed plan of candidate's contributions see assigned tasks in project plan, section 5 *Project plan and overview of activities.*

3 Overall aim and hypotheses

3.1 Aim and objectives

The overall **aim** is to enhance patient safety and personalised follow-up for cancer patients by developing and implementing new technology to monitor AEs caused by immunotherapy as a systemic anticancer treatment in everyday clinical practice. To achieve this, we will focus on:

1) Improve the NCAF-methodology to include specific oncology triggers for more precise and accurate automated identification of irAEs.
2) Involving cancer patients more in their treatment by developing and implementing personalised e-PRO follow-up to reduce irAEs and improve patient outcomes in clinical practice.

To reach the main goal, we need to address the following **objectives** (O):

O1: Develop and validate specific oncology triggers with high sensitivity and specificity for fully automated identification of irAEs.

O2: Implement personalised ePRO immunotherapy follow-up for cancer patients and investigate the incidence and severity of irAEs.

O3: Implement personalised ePRO immunotherapy follow-up and investigate Health Related QoL (HRQoL) and overall survival compared to standard of care.

3.2 Hypotheses and research questions

We have identified the following hypotheses (H):

H1: We predict that the new developed NCAF Oncology can identify rates, type and severity of irAEs with high sensitivity and of relevance in clinical practice.

H2: By implementing ePRO as standard follow-up for cancer patients we predict that we can reduce the incidence of severe irAEs.

H3: By implementing ePRO as standard follow-up for cancer patients we predict that we can increase HRQoL and overall survival.

4 Materials and methods

4.1 Theoretical approach

Development of the NCAF is based on the GTT methodology created by Institute of Healthcare Improvement in 2006 (2). The modified NCAF uses ML technology with algorithms for indexed variables or free text, that will be further developed in this study (8). During the last years, a few different studies have validated cancer-specific triggers by manual review of patient records, identifying AEs related to cancer care (9-12). The ePRO software Kaiku Health is standard of care for cancer patients at the Department of Oncology at NLSH from 2021, using ML to interpret potential irAEs, and QoL by using the EORTC QLQ-C30 version 3.0 providing a QoL-score (19). QLQ is an integrated system for assessing the health-related QoL of cancer patients. In this study we will combine research with ML learning technology to create a fully automated identification of irAEs (WP1), investigate irAEs with NCAF Oncology in clinical practice under ePRO-follow up versus standard follow-up (WP2), and finally how ePRO follow-up influence overall survival and QoL (WP3).

4.2 Study design and methodology

A retrospective quantitative approach will be used to develop and validate new technology and methods since there is a need to control and check the outcomes, before we use an ambi-directional cohort study design to see how the new technology and methods perform in clinical practice on real

world data (20). The study is a multicentre study carried out at the Department of Oncology at NLSH in collaboration with The University Hospital of North Norway (UNN) and Helgeland Hospital Trust (HSYK).

The main inclusion criteria are above 18 years of age, cancer diagnosis as primary or secondary diagnosis according to the ICD-10 classification and receiving immunotherapy as systemic anticancer treatment reported with ATC codes for medications. Patient data will be collected from the hospitals shared EHR. Extracted information from patient records will be anonymised and stored within an encrypted environment at NLSH with restricted access only to certified study personnel, and kept for ten years. No data will be transferred outside the EEA.

The project is operationalised into three work packages (WPs) where cancer patients from all three hospital trusts will be included in one large cohort in WP1. In WP2 and 3 a prospective cohort will be compared to a retrospective cohort from WP1. Figure 2 under is an overview of the three WPs.

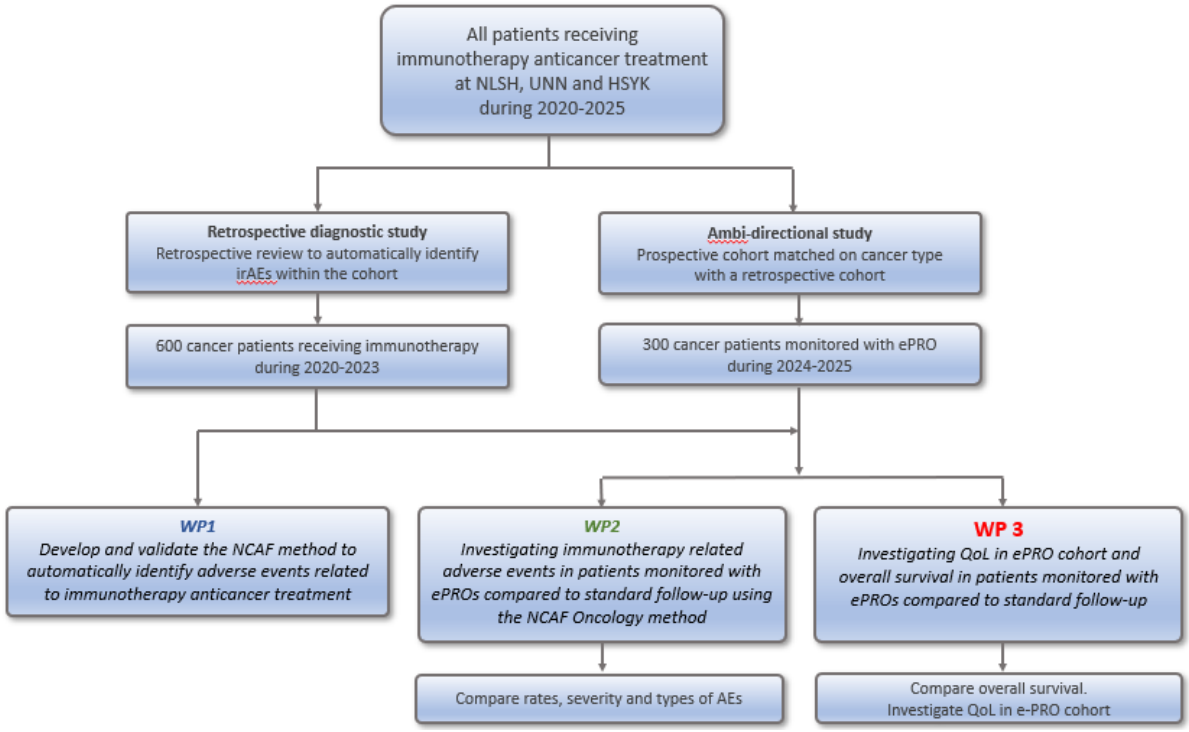

Figure 2: Overview of the three WPs

The specific methods, tasks (T), description of activities and the outcome deliverables (D) used for each WP are divided and specified in the tables below.

WP1: Automated identification of irAEs in cancer care
Target: WP1 is based on H1, with the aim to reach O1.
Method: Multicentre retrospective cohort study
Description of activities: 600 cancer patients treated with immunotherapy from 2021-2022 will be included and prepared for analytics in a separate technological environment. The use of corticosteroids, Infliximab or

Vedolizumab can be a common trigger for irAEs (14). By combining the ATC-code for these medications we may identify an automated trigger for irAEs. Text analysis and possible oncology triggers for irAEs will be used to develop logical stop-words and ML to validate automated triggers. The analysis is run again, matching with the code for procedures and/or ATC-codes. Different automatic triggers for irAEs will be tested and validated to identify algorithms for indexed variables and free text to investigate what increases the specificity, sensitivity and positive predictive values. Triggers with high enough precision will be included in the new fully automated NCAF oncology.

Tasks	**Deliverables**
T1.1 Data collection and set up for analytics	**D1.1** A data set of a valid study population with low selection bias ready for analysis and development
T1.2 Develop ML to identify triggers and irAEs	**D1.2** ML algorithms to identify irAEs
T1.3 Verify identification of triggers and irAEs	**D1.3** Report of triggers with high sensitivity and specificity to automatically identify irAEs
T1.4 Identify types of irAEs by using triggers	**D1.4** A fully automated NCAF Oncology to identify irAEs ready to test as a screening tool in clinical practice
T1.5 Write article about findings	**D1.5** Published article

WP2: Validation of the NCAF oncology methods ability to identify irAEs in clinical practice
Target: WP2 is based on H2 with the aim to reach O2
Method: An ambi-directional multicentre cohort study
Description of activities: 300 patients receiving immunotherapy and followed by ePRO during 2021-2025 from NLSH and HSYK will be included in a prospective arm. These will be compared to a retrospective cohort of 600 patients from WP1 including patients from UNN and HSYK with standard follow-up, receiving immunotherapy during the years 2024-2023, and matched on cancer diagnosis. The NCAF Oncology developed in WP1 will be used to identify rates, type and severity of irAEs in the two groups and tested in clinical practice to determine whether the method can be a clinical useful screening tool for AEs in cancer care.

Tasks	**Deliverables**
T2.1 Data collection and randomisation	**D2.1** Data set of study population with low selection bias
T2.2 Analysing rates, types, severity of irAEs using the NCAF oncology	**D2.2** Report on rates, severity and types of irAEs and the NCAF oncology's ability to identify them in clinical practice including differences between ePRO follow-up and standard follow-up.
T2.3 Comparing rates, types, severity of irAEs between ePRO follow up and standard of care	**D2.3** Statistical analyses of differences between groups
T2.4 Write article about findings	**D2.4** Published article

WP3: Influence on QoL and OS of ePRO follow-up as standard of care
Target: WP3 is based on H3 with the aim to reach O3

Method: An ambi- directional multicentre cohort study	
Description of activities: 300 patients receiving immunotherapy and followed by ePRO during 2024-2025 from NLSH and HSYK will be included in a prospective arm. These will be compared to a retrospective cohort of 600 patients from WP1 including patients from UNN and HSYK with standard follow-up who received immunotherapy during the years 2020-2023, and matched on cancer diagnosis. HRQoL will be measured using EORTC QLQ-C30 version 3.0(18,19) included in the ePRO module. Overall survival will be compared using Kaplan Meier analysis.	
Tasks	**Deliverables**
T3.1 Data collection and randomisation	**D3.1** Data set of study population with low selection bias
T3.2 Report on new knowledge on reduction of severe irAEs caused by systemic anticancer treatment with ePRO follow-up	**D3.2** Report on new knowledge on reduction of severe irAEs caused by systemic anticancer treatment with ePRO follow-up
T3.3 Analysing difference in survival	**D3.3** Report on new knowledge on overall survival with ePRO
T3.4 Analysing HRQoL in ePRO patients related to irAE, progression of disease and death.	**D3.4** Report on new knowledge on HRQoL in the ePRO study group
T3.5 Write article about findings	**T3.5** Published article

4.3 Sample size estimation and power analysis

WP1 is a diagnostic study assessing whether the new NCAF oncology can be clinically useful as a screening tool for irAEs in cancer care. Sample size estimation is based on data from a metanalyses by Magee et al indicating that 16.6 percent of cancer patients experience severe irAEs (13). To achieve a minimum power of 80 % a sample size of 535 subjects will be required in order to detect a change in sensitivity from 0.80 to 0.90, based on a target significance level of 0.05 (actual p=0.040). Our proposed random sample of 600 patients receiving immunotherapy treatment from 2021-2023 should be more than adequate for the main objective of this study and should allow for possible subgroup analysis. Previous studies have shown that monitoring patients by ePROs reduces symptom burden (5,6), but no previous studies have investigated reduction in rates of AEs. WP2-3 should therefore be considered a pilot study and we estimate a reduction in severe AEs of 40 % to have a level of clinical importance. With an enrolment ratio of 2:1 and an alpha = 0.05 the project sample size needs approximately 300 patients monitored by the e-PROs and 600 patients followed up with standard care to reach a power of 80 percent. Today approximately 100 new patients yearly receive immunotherapy and are monitored by ePROs at NLSH and HSYK. With an expected increase in patients receiving immunotherapy our proposed enrolling 960 patients, where 320 are followed with ePRO, over a three

years period should be adequate for the main objective of the study. If insufficient participants are enrolled after three years, the inclusion period can be extended for additional 6-12 months.

4.4 Statistical analysis

Poisson regressions in Generalized linear models will be applied to compare rates of irAEs, severity level and categories of types of irAEs between the different samples. Poisson regression was selected as it accounts for variation of number of cases and length of stay. Adjustments of demographical variables will be done by including these as covariates. When evaluating the performance of the automatic oncology trigger tool, a retrospective physician lead review of the EHR will be set as gold standard. To evaluate the validity of the automatic oncology trigger tool we will calculated sensitivity, specificity and positive predictive value (PPV) with their respective 95 % confidence intervals (CI). The CI for sensitivity, PPV and specificity will be calculated using the Wilson score method and two-sided tests with a significance level set at 5 %. F1-score and area under the curve (AUC-ROC) are other performance metrics that will be used. The Kaplan-Meier estimate will be used to calculate overall survival between the ePRO and the standard of care groups in WP3.

5 Progress plan and overview of activities

The PhD will be carried out over 45 months from April 2023 – February 2027. The candidate will combine 80 % research with 20 % clinical work as an oncologist at NLSH. The PhD candidate is a member of the Cancer Research Group at NLSH and apply for enrolment at the PhD-program at UIT the Arctic University of Norway. Data are already routinely collected from EHR at the three hospital trusts. Data collection for all three WPs and record reviewing of patient record for all WPs have already been started in 2021 as part of a quality improvement and other research projects. Figure 3 shows an overview of milestones, assigned tasks and roles of the project.

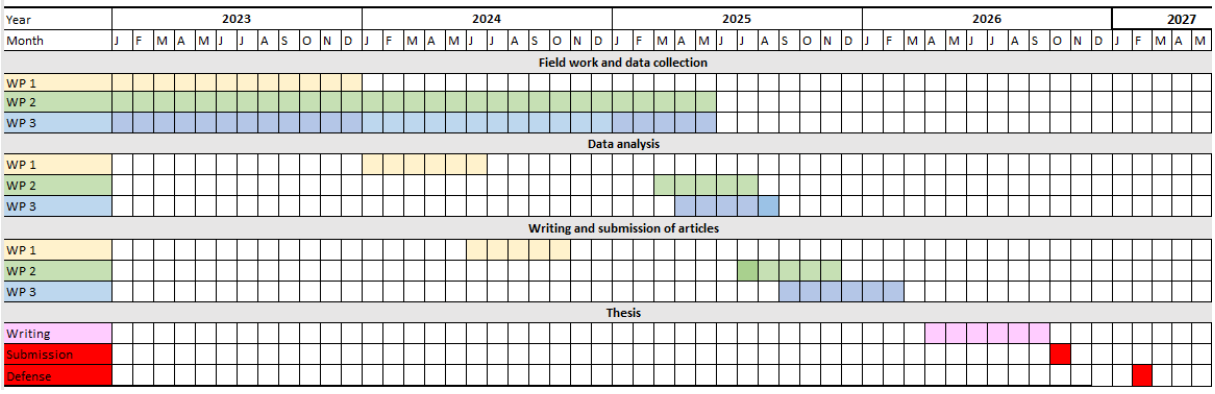

Figure 3 Overview project plan

6 Feasibility within the time frame

The Patient Safety Unit at NLSH have had two previous PhD projects evolving the automatic GTT-method and identifying AEs in cancer patients (1, 8). Knowledge and technology from this previous research on developing automatic measures are valuable and will be reused. The technology is already in use in Helse Nord, and new algorithms for the NCAF Oncology method will be developed by SAS Institute, Datavarehuset Helse Nord and technical personnel from NLSH, with separate external funding. Research related to validation and clinical impact is part of the PhD project. The project investigator and the PhD-candidate are both in clinical work at the Department of Cancer in NLSH and since 2020 responsible for developing and implementing the ePRO follow-up of cancer patients. As a result, some data is already available from the EHR and can easily be collected and analysed as discussed in section 5. The research will be linked to research groups both at NLSH and SHARE (Senter for kvalitet og sikkerhet i helsetjenesten) at the University of Stavanger (UIS), contributing with their broad experiences especially within healthcare research, patient safety and clinical oncology. Altogether the extended project group represent four out of five trusts in Helse Nord from both clinical and service departments with a broad national and international experience in relevant research and clinical oncology. We therefore argue that the feasibility of this research project is good.

7 Dissemination and publication plan

Findings will be disseminated in the academic field at national and international scientific conferences in cancer care, patient safety and technological development. The candidate and supervisors will disseminate the knowledge in teaching of medical students and healthcare personnel in Norway to enhance the knowledge of patient safety in cancer care. Offering our main results to media, patient organisations and the general public as articles, presentations, pod-, videocasts and blogs in social media as Twitter and Instagram will also be of high priority. The PhD-thesis will include three scientific papers published in open-source peer-review journals, with preliminary headings;

WP1: “Automated identification of irAEs in cancer care”

WP2: “Does ePRO follow-up reduce incidence of irAEs in cancer care?”

WP3:” Immunotherapy ePRO follow-up as standard of care in oncology – what difference does it make for the patients?”

8 Affiliation to research groups and cooperation with other institutions

The project is anchored at the Patient Safety Unit, in close collaboration with the Department of Oncology at NLSH, and the Cancer Research group at NLSH. All together the project involves four out of five health trusts in Helse Nord RHF and representatives from all collaborating health trusts are included in the project management. NLSH have a cooperation agreement with Datavarehuset Helse

Nord (HN) and SAS Institute (SAS) to ensure development of the NCAF to include oncology triggers for irAEs.

The project group has a broad national and international experience in research and enhancing patient safety. NLSH is leading nationally in the development of the NCAF using automatic trigger to identify AEs, contributing to two PhD degrees in patient safety. The project investigator has a PhD in patient safety in cancer care and is working 50 % in a post doctorial position at SHARE-UIS doing research on patient safety within the field of cancer care. In addition, two of the co-supervisors are working at SHARE. The centre is recognised as a nationally leading research centre in quality and safety in health- and care services with extensive international collaborations. Co-supervisor Dr Bates is an internationally renowned expert in patient safety, with special expertise in using information technology to improve clinical decision-making, quality-of-care and outcomes assessment in medical practice. This provide the project with important connection to Harvard and other internationally recognised collaboratives within healthcare- and patient safety research.

Project management:

- **Ellinor Haukland** (EH). PhD, MD oncology, Department of Oncology NLSH. Postdoc at SHARE-UIS. *Project investigator and main supervisor*.
- **Siv Gyda Aanes** (SGA). MD oncology, Department of Oncology, NLSH. *PhD candidate*.
- **Siri Wiig**. Professor of Quality and Safety in Healthcare Systems and Centre Director of SHARE-UIS. *Co-supervisor.*
- **David W. Bates**. MD, Professor at Harvard Medical School and SHARE-UIS. *Co-supervisor.*
- **Carsten Nieder**. MD oncology, Department of Oncology NLSH. Professor at UIT the Arctic University of Norway. *Co-Supervisor*
- Gerd Karin Bjørhovde. Dr.Philos, Professor Emerita of English literature. UIT the Artic University of Norway. *User representative.*
- Alexander Ringdal (AR), Technical support NLSH. *Project member.*
- Tonje Hansen. MD, PhD and Medical chief at NLSH. *Project member.*
- Ole Johnny Pettersen, Department of Internal Medicine HSYK. *Project member.*
- Hege Sagstuen Haugnes. MD oncology, PhD, Department of Oncology, UNN. *Project member.*
- Renate Elenjord. Pharmacist and Head of Research at Sykehusapotek Nord HF. *Project member.*

9 Financing

The project has received research funding from Helse Nord for the PhD candidate for 4 years research in 80 % position, and due to parental leave postphoned from 1st September 2022 until 1st April 2023. Technical personnel from NLSH Bodø is offered by NLSH and Datavarehuset Helse Nord. The Research Department at NLSH has funded external technical support from SAS Institute for WP1.

SAS Institute owns the NCAF technical solution and will be able to use the NCAF Oncology method when validated.

10 Ethical considerations

The project has been remitted for assessment to the Regional Committee for Medical and Health Research Ethics (REK) and categorised WP1 as quality assurance work and healthcare research, which do not require approval by the committee. Reference number 302945. As recommended from REK we have applied for exemption of confidentiality for the use of patient information for health service research. Reference number 319277 and 302945. WP2 and 3 has been assessed by REK after changes in protocol in 2024, reference number 711238, and will be registered in Clinical Trials when approved by REK. The Data Protection Official (DPO) at NLSH has assessed the study protocol and approved the project. Kaiku Health provides digital follow up according to recommendations of the GDPR and is after comprehensive risk assessment approved by the DPO at NLSH. Extracted information from patient records will be anonymised and stored within an encrypted environment with restricted access only to certified study personnel.

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