The effect of a 6 month DiEtitian-TAILored nutrition intervention compared to usual care in patients with critical illness (DETAIL): a single center prospective intervention study.

Study protocol.

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1.0 Background

Malnutrition is common both in the ICU and the hospital in general (1,2). Thus, sufficient nutrition is of great importance to ICU patients, both during ICU stay, but also in the wards and after hospital discharge. Several clinical practice guidelines (3,4) have been published summarizing evidence from more than hundreds of randomized controlled trials (RCTs) to provide evidence-based guidelines regarding nutrition in the ICU.

However, nutritional research in the ICU has mainly focused on the early, acute period of critical illness. Recently, the focus has somewhat shifted to the post-ICU hospitalization period. However, the literature on post-ICU nutrition is still scarce (5). As in the ICU, competing work priorities is an important consideration, as nutritional therapy is prioritized less than other nursing tasks in the wards (6,7). In one of the few studies following the patient throughout the hospitalization from ICU to post-ICU ward, the ICU patient does not receive the energy and protein delivery recommended in guidelines and this persists after ICU discharge (6). Another study of post-ICU patients also found that the energy and protein intake was less than the measured energy expenditure and estimated requirements (7). Adequacy of nutritional intake in the post-ICU hospitalization period is highly dependent on the route of feeding, whereas patients with an oral intake have the poorest energy and protein intake (despite food fortification strategies and/or oral nutritional supplements) (8).

In Europe, we use the guidelines from the European Society of Clinical Nutrition and Metabolism (ESPEN) (9). A large systematic scoping review from 2019 found that adherence to these guidelines can improve clinical outcomes and quality of life, as well as reduce ICU and hospital length of stay and healthcare costs (10). ESPEN guideline on clinical nutrition in the intensive care unit state that energy needs could be calculated by using simple weight-based equations such as 20-25 kcal/kg/day. A recommendation of <70% (i.e. hypocaloric nutrition) of the estimated energy is preferred during the first week of ICU admission, with an increase to 80-100% (isocaloric nutrition) from the second week. Furthermore, ESPEN recommends that during critical illness, 1.3 g protein/kg/day can be delivered progressively (4). However, there is a lack of more specific weekly energy recommendations after the first week and during recovery post-ICU. For reference, recommendations for the general hospitalized patient are 30 kcal/kg/day and at least 1.2 g/kg/day (11).

A recently published cohort study investigated the protein and energy intake during the first week of hospital stay and the first year of recovery amongst ICU survivors (12). After 12 months, only 10% of 60 patients achieved the advised 1.2 g/kg/day protein target, whereas 28% reached the advised 25 kcal/kg/day energy target. Interestingly, during recovery, the proportion of patients using supplementation to increase energy and/or protein intake was only 15% at 3 months, 12% at 6 months, and 10% at 12 months. Overall, patients using dietary supplements had a higher protein intake at 3, 6, and 12 months and a higher energy intake after 3 months.

Apart from this study, no studies have collected information regarding nutritional intake in the ICU recovery phase. Additionally, no interventional studies with the purpose of

improving nutritional intake up to six months post-ICU admission have been performed. However, some studies have been done in other patient populations. A systematic review and meta analysis from 2022, including a total of 14 RCTs and 2438 discharged medical patients, found that nutrition support, including both oral nutrition supplements and frequent dietetic follow up, after hospital discharge increased daily energy and protein intake. It also increased body weight, and most importantly, improved survival compared to no follow-up. No differences were found in regards to readmissions and physical outcome (13). Additionally, the EFFORT II study, a large multicenter RCT is now planned to be conducted investigating the effect of continued nutritional therapy with dietetic follow-ups after hospital discharge in ward patients (14).

The aforementioned meta-analysis concluded that nutrition support to medical patients after hospital discharge can increase the patient's nutritional intake. However, in ICU patients, the effect of interventions to achieve nutritional targets in the recovery phase remains unclear. This study aims to address this evidence gap by determining if a standardized dietetic consultation during a six month period from ICU admission will result in an increased energy intake compared to no planned dietetic consultations.

2.0 Aim and outcomes

This study will document standard nutritional care of patients admitted to the ICU during the whole ICU and hospital stay, as well as their nutritional intake after discharge. Furthermore, providing frequent consultations with a registered clinical dietitian, the aim will be to improve nutritional intake during the same period.

2.1 Primary outcome

Mean energy intake in kcal/kg/day from day ten until six months (on four time points) after ICU-admission.

2.2 Secondary outcomes

- 10-day, 30-day, 90-day and 180-day outcomes:
    - Nutrition intake
        - Protein intake
        - The amount of oral nutrition supplements, enteral and parenteral nutrition used
    - Nutritional risk including changes in weight (assessed by mNUTRIC score in the ICU and NRS-2002 in the wards and post-hospital)
    - Symptoms affecting nutritional intake and self-assessment of physical activity (assessed by the PG-SGA Short form)
    - Health-related quality of life (assessed by the EuroQol EQ-5D-5L and EQ VAS)
    - Frailty (assessed by the Clinical Frailty Score)
    - Resting energy expenditure and respiratory quotient (assessed by indirect calorimetry)
    - Physical performance (assessed by the Short Physical Performance Battery and the hand grip strength test)
    - Muscle mass (assessed by ultrasound)
    - Body composition (assessed by bioelectrical impedance analysis)
    - Mobility (assessed by ICU Mobility Scale)
- Energy and protein intake by location (ICU, ward and post-hospital discharge)
- Duration hospital stay (survivors and non-survivors)
- 6 months survival

- Cost per quality-adjusted life year (QALY)
- Cost per life year gained (LYG)

Additional analysis independently of which group the patients were allocated to will be performed on outcomes based on dividing the patients' regards to mean energy intake in kcal/kg/day from day ten until six months (on four time points) after ICU admission.

3.0 Methods

3.1 Trial design, setting and population

This study is a single-center prospective, unblinded interventional study and will include 300 critically ill patients from the general ICU at the University Hospital of North Norway in Tromsø. Recruitment will start in 2025 with tentative completion of recruitment expected in 2027. The study research team comprises dietitians, a research nurse, ICU nurse, intensivists and a gastric surgeon.

3.2 Sample size

Sample size calculation is based on earlier studies conducted in the same fashion with similar primary endpoint (15). Further, earlier studies in our own ICU confirm a comparable and acceptable confidence interval of 95% and coefficient of variation, in comparison to the referred study. This study calculated a necessary sample size of 120 patients in each group inflated with 20% to account for potential dropouts. Due to the slightly longer follow-up in our study, we calculate with 150 patients in each group to ensure a sufficient study size with up to 50% dropout assumed to be overestimated. With 300 subjects in total, this study has 95% power (two-sided p-value of 0.05) to an assumed acceptable difference of 15% difference in estimated average daily energy intake considered at the study's primary endpoint.

3.3 Eligibility, recruitment and consent

Patients aged ≥18 years who have been admitted to our ICU will be screened for eligibility. Absolute inclusion criteria is informed written consent. See detailed inclusion and exclusion criteria below.

3.3.1 Inclusion criteria

Patients in intensive care who meet all of the following will be eligible:

1. Admitted to the intensive care unit for >48 hours.
2. At least 18 years of age
3. Have one or more organ system failure (respiratory,cardiovascular or renal) related to their acute illness defined as:
    a. PaO2/FiO2≤300 mm Hg)
    b. Currently on one or more continuous inotrope/vasopressor infusion which were started at least 4 hours ago at a minimum dose of:
        i. Norepinephrine≥0.1 mcg/kg/min
        ii. Epinephrine≥0.1 mcg/kg/min
        iii. Any dose of vasopressin
        iv. Milrinone>0.1 mcg/kg/min)
    c. Renal dysfunction defined as:
        i. Serum creatinine 2.0–2.9 times baseline or
        ii. Urine output 0.5 mL/kg/hour for ≥12 hours or

iii. Currently receiving renal replacement therapy)

d. Currently has an intracranial pressure monitor or ventricular drain in situ
e. Permanent living address in Norway

3.3.2 Exclusion criteria

Patients will be excluded if:

1. Death is imminent in the next 96 hours or there is a current treatment limitation in place or the patient is unlikely to survive to 180 days due to underlying/chronic illness
2. Dialysis dependent chronic renal failure
3. Suspected or known pregnancy
4. Wheelchair user
5. Cognitive impairment in which intervention is considered not appropriate
6. Eating disorders

3.3.3 Screening and recruitment

Patients will be screened for eligibility through patient journals during the first 48 hours of admission to the intensive care unit. Screening will be performed by selected project staff members. Apart from the project manager, the members performing the screening are not affiliated with the ICU, and a dispensation for confidentiality to screen patient journals is needed.

We want to start data collection and the intervention in group 2 (described below) as soon after 48 hours of admission as possible, since optimal nutritional care in the early phase of critical illness may be of importance for the short- and long-term recovery. To achieve this, we want to screen the patients before 48 hours of admission. Since one inclusion criteria is an ICU stay of >48 hours, the estimated length of stay will be discussed with the treating physician. Eligible patients with an estimated stay of more than 48 hours will be given information orally and in written form within the first 48 hours after admission. Due to the plan of starting the data collection as soon as possible, the patients or next of kin get 24 hours to decide about participation. Information is given and consent obtained by one of two selected project members who are not involved in the patients' treatment.

If the patient itself is in a state in which an informed written consent is not possible to obtain, next of kin will be asked to consent on behalf of the patient. If the next of kin has given consent on behalf of the patient, the patient will be given information about the study and asked for a delayed consent as soon as possible. If delayed consent is not given by the patient, data collection will stop, and all data can be deleted if requested. The signed consent form of the next of kin will thus no longer be valid. If the patient dies without being able to give consent, the consent from the next of kin will stay valid. Both the patient and next of kin can withdraw from participation at any time.

3.4 Study plan

This study consists of one observational period followed by one interventional period with a non-randomized recruitment. The patients will be recruited to one specific group, either the observational group or the intervention group. Firstly, patients will be recruited to the observational group until 150 patients are recruited. Consecutively, patients will be recruited to the interventional group until another 150 patients are recruited. Follow-up time in both groups is six months from admission time, independent of ICU and hospital length of stay.

In the observational group we will collect data regarding the standard, usual nutritional care in the ICU, post-ICU in the wards, as well as post-ICU discharge. In the interventional group, the patients will receive dietitian-tailored nutritional treatment and guidance during ICU admission, in the wards and after discharge. We have chosen to not conduct an RCT due to the interest in collecting data regarding the standard care before implementing an intervention. A trial may increase the focus on the nutrition in standard care, giving a wrong impression of the actual standard care as of today.

Group 1: Observational group receiving standard care.
Group 2: Interventional group receiving dietitian-tailored nutrition.

3.4.1 Study levels

Independent of which group the participants are a part of, they can choose between three "levels" of participation (consent), whereas level A consists of registration of nutritional intake and assessments with screening tools and questionnaires, level B consists of physical tests and level C consists of blood tests. Level A is obligatory for participating in the study, while participation in levels B and C is voluntary. See detailed description of the included assessments and tests in each level in the "Data collection"-section. The participants can choose to participate in A, A+B, A+C or A+B+C.

3.4.2 Standard care

In the ICU at UNN Tromsø, a local nutrition protocol has been implemented prior to this study to ensure that nutritional intake is as recommended during the ICU admission. The protocol is developed according to ESPEN guidelines on Clinical nutrition in the intensive care unit (4), with the following recommendations on nutritional intake:

<u>Recommended energy intake/supply</u>

- The first week: a goal of 18 kcal/kg/day with the recommended daily increase:
    - First day: 10 kcal/kg/day
    - Second day: 14 kcal/kg/day
    - Third to seventh day: 18 kcal/kg/day
- From the second week: ≥ 25 kcal/kg/day

<u>Recommended protein intake/supply:</u>

- 1.3 g/kg/day with a progressively increase during the first three days in the ICU.

No specific nutrition plan is drafted when the patients are transferred to the wards. Further nutritional needs or plans are estimated/decided by the treating health personnel in the specific ward.

3.4.3 Intervention

In group 2, the dietitian will make an individual nutrition plan at study inclusion and follow-up every 24-48 hours throughout the hospital stay. After hospital discharge, the patients will be followed by telephone/video consult every 2-4 weeks by the study dietitian. The aim is to achieve an energy intake of at least 25 kcal/kg/day and a protein intake of at least 1.3 g/kg/day during the follow-up period.

3.5 Data collection

Data collection of all parameters will be performed on day ten, day 30, 3- and 6-month following ICU admission, independent of if the patient is still admitted in the ICU, has been

transferred to the ward or has been discharged. Patients transferred to other hospitals in the region will also be followed-up. Data collection will be performed in the same manner in both groups, regardless of location.

At enrolment, demographic data and information regarding the ICU admission and treatment will be collected. Furthermore, information of the nutritional intake and any use of medical nutrition therapy (oral nutrition supplements, enteral and parenteral nutrition) during the whole hospital admission will be collected. A detailed list of data that will be collected is attached to this REK-application in the file "Worksheet".

During admission, data will be collected through the digital patient journal system DIPS Arena and the electronic medical chart MetaVision. Direct information from the treating health personnel and the patient will also occur if there is missing data in these systems and when the patient eats itself. After discharge, the patients will provide the information during consultations either in the outpatient clinic or by telephone/video. The hospital's video-solution Whereby will be used for video interactions.

Below follows a description of the methods used to collect data regarding the primary and secondary outcomes. The descriptions are separated in the three levels as described previously (level A, B and C). See Table 1 for an overview of the methods used and the estimated time used on each method.

3.5.1 Registration of nutritional intake (level A)

From ICU admission until hospital discharge, the daily amount of energy and protein provided from oral nutrition, oral nutrition supplements, enteral and parenteral nutrition, as well as non-nutritional calories from glucose and propofol will be collected. Repeated 24-hour recall interviews will be conducted to gather information regarding oral nutritional intake on each collection time point (day 10, day 30, 3 or 6 months). At least two separate interviews will be conducted within a time frame of one to three weeks depending on the collection time point. If the variance of energy intake is greater than 10% between the two interviews, a third interview will be performed.

Estimated time on level A: 45-60 minutes on each measurement point. Patients can be followed both at the outpatient clinic or by video/telephone.

Table 1 Overview of the methods that will be used in the study

Level	Data collection	All locations/time points	Admission/inclusion	ICU only	Estimated time use for the study participant (minutes)
A	24-hour recall	x			30
	mNUTRIC Score		x	x	0
	NRS-2002	x	x		2
	PG-SGA Short form	x			3
	ICU Mobility Scale	x	x		0
	Clinical Frailty Scale	x	x		0

	Health-related Quality of Life (EQ-5D-5L)	x			5
B	Short Physical Performance Battery	x			15
	Hand grip strength test	x			5
	Indirect calorimetry	x			20
	Bioelectrical impedance analysis	x			5
	Ultrasound	x	x		5
C	Blood tests	x	x		15

3.5.2 Screenings and questionnaires (level A)

Screening tools and questionnaires will be used to assess the patient's nutritional status, clinical frailty, mobility status and quality of life. Nutrition risk will be assessed with Nutrition Risk Screening-2002 (NRS-2002) in all patients. This tool assesses changes in weight, body mass index, sickness and energy intake (16). Weight will be measured at least one till two times during the hospital stay in addition to the four collection time points. At follow-up after discharge, the weight will be measured in the outpatient clinic, or at home by the patients themselves. Additionally, mNUTRIC score will be used at inclusion and if the patient is in the ICU at the data collection time points. Both are validated tools in the hospital setting, the latter one is specifically validated for critically ill patients (16,17). The mNUTRIC Score includes SOFA and APACHE II scores which are screening tools aiming to predict ICU mortality (18).

The patient's mobility status will be assessed with the ICU Mobility Scale (19). Frailty will be assessed using the Clinical Frailty Scale, which is a validated tool to assess frailty based on factors such as physical activity and function. It is an ordinal scale with nine steps from very fit to terminally ill (20). Clinical frailty score pre-ICU admission will also be collected. A Norwegian translation of the validated questionnaire EQ-5D-5L (obtained by EuroQol), commonly used in the ICU patient group (21), will be used to assess health-related quality of life. The questionnaire consists of two parts; a screening of general health (physical and mental) and a VAS-scale to grade self-perceived health.

PG-SGA Short form will be used to assess the patient's symptoms related to food intake, as well as their physical activity level (22).

3.5.3 Physical measurements (level B)

Measurement of resting energy expenditure (REE;kcal) will be determined using indirect calorimetry. Indirect calorimetry is a non-invasive method considered the gold standard for determining REE (23). Measurements of REE with IC will be performed in mechanically ventilated patients by connecting the device to the mechanical ventilator circuit, and spontaneously breathing patients by using a canopy hood placed over the patient's head (24). We will use the Q-NRG® Portable Metabolic Monitor (Cosmed, Italy). The measured carbon dioxide production (VCO_2) and oxygen consumption (VO_2) obtained from the calorimeter will be used to calculate REE using Weir's equation. The respiratory quotient, which is the ratio between VCO_2 and VO_2, will also be calculated (24).

Physical performance will be assessed using the Short Physical Performance Battery test, consisting of a balance test, a chair stand test and a gait speed test (25). Additionally, the hand grip strength test will assess arm muscle function, and will be performed using a hand-held dynamometer (26). To assess muscle mass we will measure body composition and muscle mass using bioelectrical impedance analysis (27) and ultrasound, respectively. The first one will only be measured when the participant is able to stand and meet at the outpatient clinic where the device is. The analysis is done according to the device, inserting weight, height and age. Regarding the ultrasound, this can be measured by the bed-side and we will measure only one point at the thigh, according to a validated protocol (USVALID) (28).

Estimated time on level B: 45-60 minutes on each measurement point. Requires meet-up in the outpatient clinic.

3.5.4 Blood tests (level C)

Blood tests will be taken in both groups (if given specific consent) at the four main measurement points, as well as at inclusion. About 50 ml of blood will be taken on each blood test. In group one, the tests will be taken and analyzed on the same day as follow-up with the dietitian, , but the researchers will be blinded, thus not knowing the results until after the follow-up period of each patient. Only the affiliated bioengineers analyzing the tests will know the results, and will collect these results in a separate excel-file with study ID-numbers. After the follow-up period has ended, the patient and general practitioner will be contacted if there are any deviations from normal range. In group two, the clinical blood tests will also be taken and analyzed the same day as follow-up with the dietitian, but will not be blinded as the results will be a part of the assessment.

Estimated time on level C: 15 minutes on each measurement point, including waiting time. Requires meet-up in the outpatient clinic.

3.6 Statistics

For endpoints with several time points, statistics will be evaluated as the difference of repeated measures over time between the groups, applying a mixed model for repeated measures. Where appropriate, differences will be investigated with Student's t-test for normally distributed outcomes, and Wilcoxon rank-sum tests otherwise. As mentioned $p<0.05$ will be considered statistically significant. Calculations will be performed with Microsoft Excel and Statistics will be performed with Graphpad Prism (version 10).

3.7 Data management

All collected data will be stored on a dedicated data server at UNN. All study participants will receive an ID-number (linkage key) kept in a separate file from the collected data, securing de-identification. The project manager and project members responsible for data collection, will have access to the linkage key. Study inclusion will be documented for each study participant in the electronic journal system Dips. Additionally, in the intervention group, information regarding the treatment and advice given will also be documented in Dips.

Data may be transferred to our project collaborator in Sweden. These data will be deleted when the project ends. The linkage key will not be shared.

3.8 Communication and presentation

The results of the project are outlined to be published in two publications in international renowned open access journals. All publication will be done according to the guidelines of Open Access publication and Plan S. We further aim to present the results at

international congresses such as the congress for ESPEN as well as national congresses for anesthesiology, surgery, internal medicine, primary care, dietitians and nurses. Furthermore, we want the results to be communicated to the Norwegian Directorate of Health and the Norwegian Institute of Public Health, in which project members can contribute to future national groups working on nutrition recommendations of critically ill patients both during hospital stay and after hospital discharge. In collaboration with our user participant, we will choose the channels of communicating the results to the media and organizations for patients and next of kin.

4.0 Financing

The PhD-project is financed by Helse Nord RHF from 2025-2028 (project number HNF1745-25).

5.0 Ethical considerations

Informed consent will be gathered from all participants. In these studies, the participants have critical illness and most often temporarily reduced consent. It can be burdensome for next of kin to decide on questions about research participation in the acute phase. However, experience from previous studies shows that the vast majority of relatives are positive about research in the ICU. Substitute consent for persons with reduced consent competence follows the guidelines from the Norwegian national research ethics committee for medicine. Participation is voluntary and withdrawal is allowed at all times during follow-up, without further obligation.

Furthermore, there will be additional specific consent for both blood tests and additional physical measurements and tests.

5.1 Risk-benefit analysis

Participants in group one will have no direct benefits of participating in this study. They will receive standard treatment as other patients in the hospital. However, they will contribute with useful information that may improve the nutritional treatment of future critically ill patients.

Participants consenting to blood tests will be informed if these show abnormal results. In such cases, we will also inform their general practitioner about these findings. Participants in group two will receive individualized nutrition treatment and counseling from a registered clinical dietitian. These participants may improve their nutritional intake, physical function and health-related quality of life by participating.

We see few risks by participating in this project, apart from the burden that the participants may experience due to frequent follow-up and physical tests. Participants consenting to the physical tests and measurements have to meet in a fasting state (no food or drink intake that day). The appointment will be early in the day to prevent a long period of fasting. The physical tests may be exhausting. There will be an assessment whether it is safe to perform the test in advance, and the participants are free to abort the test if needed. Measurements of resting energy expenditure may feel claustrophobic for some participants. Thorough information of the measurement will be given to the participants prior to the measurements, and the measurement will not be performed if the participant is unwilling. The measurement can be stopped at any time point. Blood work may give pain in the incision site. All measurements, physical tests and blood work are performed by trained health personnel.

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