CLINICAL STUDY PROTOCOL

Tailored information about the coronavirus and the coronavirus pandemic for patients with chronic kidney disease

Protocol Identification Number: REK 144084/2020

SPONSOR: Akershus University Hospital, Lørenskog, Norway.

PRINCIPAL INVESTIGATOR: Ivar Anders Eide, MD PhD, Akershus University Hospital, Department of Renal Medicine, Pb 1000, 1473 Lørenskog, Norway.

CLINICAL STEERING COMMITTE: Anupam Chandra, MD PhD, Akershus University Hospital. Krystina Parker, MD PhD, Akershus University Hospital. Jon Anker Sarpebakken, The Norwegian Association for Kidney Patients and Transplant Recipients (LNT), Arve Nordlie, The Norwegian Association for Kidney Patients and Transplant Recipients (LNT), Pål Gulbrandsen, Prof., Akershus University Hospital. Kjersti Lønning, PhD, Oslo University Hospital Rikshospitalet. Willy Aasebø, MD, Akershus University Hospital, Gunhild Brørs, MSc, St. Olav Hospital. Tone Merete Norekvål, Prof., University in Bergen.

PROTOCOL VERSION NO. 3 - Nov 1st 2020

SPONSOR / PRINCIPAL INVESTIGATOR SIGNATORY APPROVAL

The study will be conducted in compliance with the Protocol and applicable regulatory requirements:

Willy Aasebø, MD, Head of Dept.	Ivar Anders Eide, MD PhD	01.11.20

Sponsor signature *Principal Investigator signature* *Date*

PROTOCOL SYNOPSIS

Investigation:	Tailored information about the coronavirus SARS CoV2, Covid-19, the coronavirus pandemic, the coronavirus infodemic and digital sources of reliable health information for patients with chronic kidney disease stage 4-5, using information videos followed by a teach-back method. The research questions is whether tailored information followed by the teach-back procedure improves health literacy and digital health literacy, reduce anxiety, maintain self-perceived health and lower the risk of Covid-19. We will utilize updated reliable health information at the LNT website lnt.no and the Norwegian Health Authority websites helsenorge.no, fhi.no and imdi.no. The teach-back method will be used in the intervention group only, which aims to ensure that key messages in information videos are presented in a way that the patient can understand, correct any misconceptions and show strategies to critically assess digital health information.
Target population:	Patients with advanced kidney disease (CKD stage 4 or 5).
Centre(s):	Akershus University Hospital, Lørenskog, Norway.
Study Period:	Estimated date of first patient enrolled: 07.12.20, and date of last patient completed: 31.12.23.
Main Endpoints:	· Digital literacy, measured by eHEALS. · Health literacy, measured by HLQ. · Degree of concern for Covid-19, measured by Fear of corona scale. · Self-perceived health, measured by EQ-5D-5L.
Design:	Randomized prospective open clinical trial.
Inclusion Criteria:	Age ≥ 18 years. CKD stage 4 or 5, including renal transplant recipients (defined as CKD5T). Written informed consent.
Exclusion Criteria:	Positive SARS CoV2 test prior to the baseline visit or at the baseline time-point. Cognitive impairment. Any reason why, in the opinion of the Investigator, the patient should not participate.
Sample Size:	n = 192, where we aim for inclusion of ≥ 50 patients with other native tongue than English or a Scandinavian language (Norwegian, Swedish or Danish).

LIST OF ABBREVIATIONS AND DEFINITIONS / EXPLANATIONS OF TERMS

Abbreviation	Explanation
CFS	Clinical Frailty Scale
CKD	Chronic kidney disease
Covid 19	Coronavirus 19 disease, which is caused by SARS CoV2
eHEALS	eHealth Literacy Scale, a subjective measure of digital health literacy
EQ-5D-5L	European Quality of Life Group (EuroQoL) 5 Dimension 5 Level scale of self-perceived health
HLQ	Health Literacy Questionnaire, a subjective measure of functional, interactive and critical literacy
LNT	The Norwegian Association for Kidney Patients and Transplant Recipients
Personvern	Institution Data Protection Officer (term not in regular use, thus replaced with “Personvern”)
PI	Principal Investigator
REK	Regional Ethical Committee
SARS CoV2	Severe acute respiratory distress syndrome coronavirus 2

TABLE OF CONTENTS

1 INTRODUCTION

During the end of March 2020, the first wave of Covid-19 caused by the novel coronavirus SARS CoV2 hit Norway, and in particular counties Oslo and Akershus (1). This resulted in several hospitalizations due to Covid-19 in patients with advanced kidney disease at Akershus University Hospital, including cases of long-term hospitalization in critical care units and deaths. Reduced kidney function as well as frequent comorbid conditions in CKD patients, put this group at increased risk of Covid-19 (2). Moreover, SARS CoV2 enter human cells via endocytosis after binding angiotensin converting enzyme receptor 2, which is highly expressed in the lungs and the kidneys, and may in part explain the high prevalence of acute kidney failure in Covid-19 and the high mortality rate among these patients (3). Naturally, many CKD patients reported concern for Covid-19 and felt uncertain how to best deal with this new situation. With a new wave of Covid-19 currently sweeping across our region (1) and recent reports of increased morbidity and mortality during Covid-19 for CKD patients and transplant recipients (4), these groups of patients frequently report concern about their near future.

The severe acute respiratory distress syndrome coronavirus 2 "infodemic"

A coronavirus "infodemic" has accompanied the coronavirus pandemic (5), both internationally and nationally, supplying the public with abundant information on the SARS CoV2 and Covid-19 including what damage it can do, implications for the economy and how individuals and societies can fight it. Norwegian health authorities have used mainstream media and their own designated websites, to provide the public with updated reliable health information (1, 6, 7). However, this information is not equally accessible for all citizens (8). Moreover, some material published in mainstream media and several sources of information on the Internet present inaccurate or false information, speculations and myths put forward by unreliable sources (9). Several initiatives to reduce health misinformation and improve self-management are emerging (8). Improved digital literacy among health care providers and patients would likely empower them to cope better with the current situation and help fight prevalent misinformation. Most patients at increased risk of Covid-19 frequently encounter health care personnel. Thus, efforts by health personnel to provide these patients with accessible and reliable information on the coronavirus and the coronavirus pandemic could make them cope better with the current situation, especially if the information can be tailored to a specific target group, e.g. CKD patients (10). Knowing facts may help coping with stress and anxiety. Knowing how to critically assess health information may further reduce stress. Around the world, there are several ongoing epidemiological studies on associations between various factors related to health literacy and anxiety (11), including CKD patients. However, there is to our knowledge no clinical trial focusing on how to tailor Covid-19 information for CKD patients, how to improve digital health literacy in CKD, how digital health literacy affects mental health in CKD or whether improved digital health literacy lower the risk of Covid-19 (12). At present, Norwegian studies on experiences with and understanding of Covid-19 are scarce and limited to pregnancy and cancer management (13).

Health literacy in chronic kidney disease

Health literacy implies knowledge, personal skills and confidence to take action to improve health (14). Low health literacy is associated with medication non-adherence, a higher burden of disease and a higher mortality rate (15). Data on health literacy in patients with CKD are sparse and focus mostly on functional literacy, the ability to read and comprehend words and numbers (16). Other aspects of health literacy, like interactive and critical literacy are less studied in CKD. Interplay between health care providers and receivers are mostly studied for choice of renal replacement therapy (16). Critical appraisal of information is shown to be low in CKD patients (17), which is of particular importance in the current situation with abundant digital health information.

Digital health literacy implies ability to use communication technology to find, evaluate, create and communicate health information. It requires cognitive and technical skills and is influenced by motivation for and access to digital information (12). Patients with low digital health literacy are more prone to miss important information. Patients with low digital and low critical literacy are more susceptible to misinterpret available information (18). The national health authority websites has made Covid-19 information available in several languages (1, 6, 7). However, this information is practically inaccessible for patients with low digital literacy (12), and patients who do not speak English or Norwegian, must maneuver five steps on fhi.no before they can reach information in a language that they master (1).

Previous reports indicate that low-intensity intervention with tailored education targeted at specific patient populations may reverse unhealthy habits by improving knowledge and risk perception and promoting a healthy life style (19). This trial will investigate whether tailored education improves digital health literacy in a Covid-19 high-risk population like advanced kidney disease and make them cope better with current situation.

2 STUDY HYPOTHESIS AND OBJECTIVES, EFFICACY AND SAFETY ASSESSMENTS

2.1 Hypotheses

Hypotheses, based on existing data: Limited intervention with tailored information about SARS CoV2, Covid-19, the coronavirus pandemic, the coronavirus infodemic and input to critical assess available digital sources of health information for patients with CKD stage 4-5, followed by a teach-back method, will improve digital health literacy, health literacy, reduce anxiety, maintain self-perceived health and lower the risk of Covid-19.

2.2 Objectives

Primary objective:

- Digital health literacy, measured by eHEALS.

Secondary objectives:

- Health literacy, including functional, interactive and critical literacy, measured by HLQ.
- Self-perceived health, measured by EQ-5D-5L.
- Degree of concern for Covid-19, measured by Fear of corona scale

Additional objectives:

- Proportion of patients feeling overwhelmed by the amount of coronavirus information.
- Proportion of patients finding it difficult to get information about the coronavirus in their native tongue.
- Composite end-point of positive SARS CoV2 test, hospitalization and death regardless of cause during the first two years after the intervention.

2.3 Efficacy and Safety Assessments

In accordance with the primary and secondary objectives, we will evaluate the effect of tailored information followed by a teach-back method (20) on top of standard care. There are no risks related to participation in the study, hence no safety assessments will be made and there will be no safety evaluation after completion of the trial. During the first two year following inclusion we will record hospitalizations due to Covid-19, hospitalizations regardless of cause, deaths regardless of cause and positive SARS CoV2 tests from medical records at Akershus University Hospital.

3 STUDY POPULATION

3.1 Target Population, Number of Patients, Recruitment and Screening

The target population is patients with advanced kidney disease defined as CKD stage 4 or 5, including renal transplant recipients (defined as CKD5T), who receive health care at Akershus University Hospital. The sample size is set at n = 192, where we aim for inclusion of ≥ 50 patients with other native tongue than a Scandinavian language (Norwegian, Swedish or Danish) or English. Patients will be recruited from the Dialysis Unit, wards and outpatient clinic at the Department of Renal Medicine, Akershus University Hospital.

3.2 Inclusion and Exclusion Criteria

Inclusion Criteria:	Age ≥ 18 years. CKD stage 4 or 5, who receive health care at Akershus University Hospital. Written informed consent.
Exclusion Criteria:	Positive SARS CoV2 test prior to or at baseline. Cognitive impairment Any reason why, in the opinion of the PI, the patient should not participate.

4 STUDY DESIGN AND MANAGEMENT

Single center, prospective, randomized, open clinical trial investigating effects of tailored information about the coronavirus and the coronavirus pandemic for patients with advanced kidney disease, utilizing information at the LNT and Norwegian Health Authority websites, followed by a teach-back method, on top of standard care.

Study period: Estimated date of first patient enrolled: 07.12.2020. The anticipated recruitment period is 3-4 months. Estimated date of last patient completed: 31.12.2023, which also includes data management, statistical analyses, manuscript preparation and publication. The baseline and final visit CRFs will be dated.

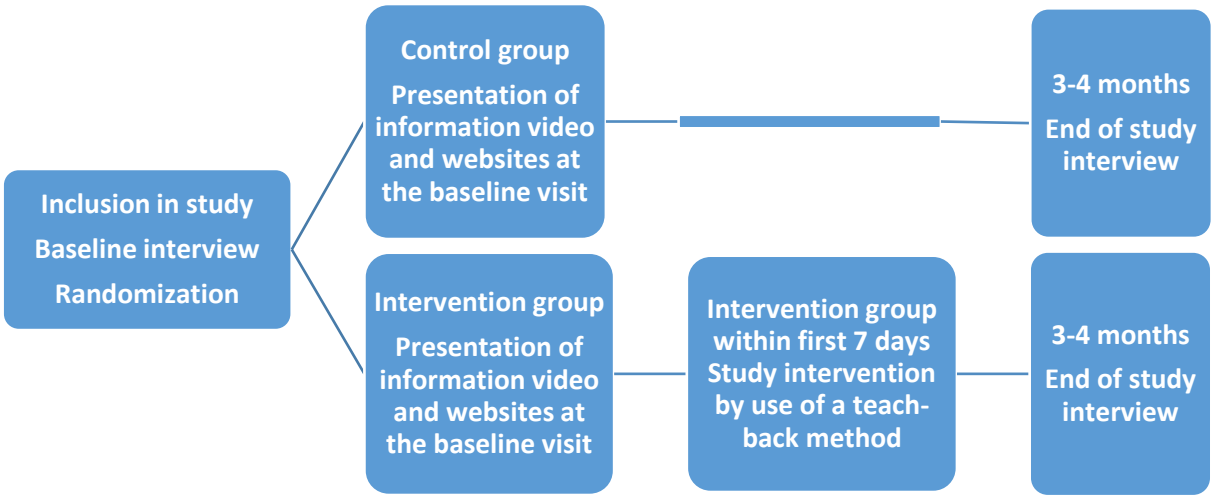
Study duration: Approximately 15 weeks. The effect of the study intervention (tailored information at baseline followed by a teach-back method within the next 7 days) is measures at the 3(-4) month final visit.

4.1.1 Flowchart

	Screening and Baseline visit	Within next 7 days	3 (-4) month Final visit	24 month follow-up
Screening for inclusion in trial	•			
Eligibility assessment and study enrollment	•			
Obtaining written informed consent	•			
Semi-structured interview	•		•	
eHEALS, a measure of digital health literacy	•		•	
HLQ, a measure of functional, interactive and critical literacy	•		•	
Fear of corona scale, anxiety / concern for Covid-19	•		•	
EQ-5D-5L, self-perceived health	•		•	
Question: Difficulty finding information in native tongue	•		•	
Question: Feeling overwhelmed by Covid-19 information	•		•	
Interviewer's assessment of Clinical Frailty Score	•		•	
Randomization	•			
Presentation of websites, including LNT information videos	•			
Study intervention (teach-back method)		•		
Medical record assessment	•			•
Charlson comorbidity index	•			

4.1.2 Study Visits, Assessments, Data Recording and Investigator Delegation Procedure

Three study visits will be performed as presented in the flowchart. The Investigators will conduct a semi-structured interview and fill in an electronic CRF, which will be dated to ensure correct follow-up time, and to correct for events occurring during the study period that might influence participant responses. Data will be recorded directly into the electronic CRF at the baseline and final visits.



At the baseline visit a semi-structured interview will be performed, followed by a presentation of the LNT website (21). By early December 2020 this website will contain 20 short videos with information tailored for patients with CKD and organ transplant recipients on the topics SARS CoV2, Covid-19, the coronavirus pandemic, the coronavirus infodemic and strategies to critical assess of available digital sources of health information. These videos also contain a short presentation of updates reliable health information sources at the Norwegian Health Authority websites fhi.no, helsenorge.no and imdi.no (1, 6, 7), included where they can find information translated to various languages and where they can find links to other reliable digital health information sources at these websites. The videos are created by the study group and will be filmed and edited at Akershus University Hospital. They will be made originally in Norwegian and English, followed by translation and dubbing to several other languages, similar to previous patient information projects at Akershus University Hospital (22). All study participants will be presented to this source of health information at baseline and asked to study it closely.

For patients randomized to the *control group*, the Investigator will present them with the information videos available at the LNT website (21) and the Norwegian Health Authority websites (1, 6, 7), which would be regarded as within the frame of standard care, although this service is seldom provided at present.

For patients randomized to the *intervention group*, the Investigator will take on a more active part and make a new appointment with the patient (a new study visit) within 7 days following the baseline visit, either as a regular meeting, a digital meeting (e.g. zoom) or a telephone meeting. The patient will be asked to seek information available at the LNT website and watch the information videos found at this website, plus seek information available at the Norwegian Health Authority websites, before the new study visit. At the study visit the patient will be asked to give a short resume of take home messages from these websites that he/she find useful in everyday life. They will be asked if they have any questions regarding the information presented at these websites, followed by a teach-back procedure, which aims to ensure that key messages are presented in a way that the patient can understand, correct any misconceptions and show strategies to critically assess digital health information. The patient will be asked to present their strategy to find updated reliable health information available on the Internet. The teach-back method aim to reveal topics where there is a need to further modify and/or repeat information to make it possible to understand for the patient.

For patients who do not speak any Scandinavian language or English, an Investigator who speaks the same language as the patient or a professional translator will attend baseline and final visits, plus the additional new study visit for patients randomized to the intervention group, to ensure adequate communication. The PI is responsible for providing appropriate training relevant for all study Investigators and has developed an interview guide. The PI has made a “delegation of tasks” listing of involved co-workers and their role in the project, and is responsible for updating this list. The PI will ensure that any new information of relevance to the performance of this study is forwarded to the clinical steering committee and any staff involved in the study. This is of particular relevance to Investigators who will perform interviews at study visits in another language than English or any of the Scandinavian languages. It is the PI responsibility to provide these Investigators with validated translations of questionnaires included in the interview. The Investigators will themselves translate the remaining part of the interview as they go along, which for this study most often will be the case for the Fear of corona scale

questionnaire. Please note that even though main language spoken at home and native tongue is recorded, ethnicity will *not* be recorded. Native tongue will *not* be used in subgroup analyses since this would not harmonize with the study purpose and patient concealment could become violated. The study design should ensure provision of tailored information regardless of the patients' native tongue or preferred spoken language.

The PI or his designate will assess medical record for each patient at baseline and at two years follow-up. The following information will be recorded at the baseline visit: CKD stage, modality of renal replacement therapy where appropriate and chronic medical conditions to calculate the Charlson comorbidity index. The following information will be recorded at two years follow-up: Positive SARS CoV2 test, hospitalization due to Covid-19, hospitalization regardless of cause and death regardless of cause.

To ensure adequate responses, study interviews during a dialysis session should be performed during the first two hours of dialysis to avoid impact of cerebral ischemia towards the end of the session in some patients.

4.2 Storage of Study Documentation and Data Management

The PI will arrange for the retention of the patient identification list. Patient files shall be kept for the maximum period of time permitted by Akershus University Hospital. The study documentation shall be retained and stored during the study and for five years after study closure in accordance with FOR 2009-30-10 §8. All information concerning the study will be stored in a safe place inaccessible to unauthorized personnel. Registration of patient data will be carried out in accordance with national personal data laws. Data will be coded and entered into a computer database according to operating procedure for data management provided by The Norwegian Research Council. The study will be conducted in accordance with the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements.

4.3 Patient Withdrawal

All study subjects have the right to withdraw from the trial at any time and this will in no way prejudice their future treatment, in accordance with the Declaration of Helsinki. We plan to follow the patients for the entire duration of the study. Unless patients who choose to withdraw from the study specifically requests not to be contacted, every effort will be made in order to follow-up and complete patient evaluation.

4.4 Patient Confidentiality

The Investigators will ensure that the patient´s confidentiality is maintained throughout the study. The electronic CRF only identify patients by their randomization number. The PI will keep a separate log of patient codes and names. Akershus University Hospital provides a Study Monitor and any audits will be conducted with strict adherence to professional standards of confidentiality.

4.5 Study Amendments

Should it be necessary for the study protocol to be amended, the amendment will be notified to and sent for approval to local and national regulatory authorities (Personvern Akershus University Hospital and REK). The current Participant Information Form contains information about possible future amendments and need of a second consent before enrollment in future studies.

5 STATISTICAL CONSIDERATIONS

5.1 Determination of Sample Size

There is no previous data from trials to base any power analysis on for this study, thus it is appropriate to base sample size calculation on Tabachnick and Fidells formula $N \geq (8/f^2) + (m-1)$, where f^2 is set at 0.05, hence 160 patients need to complete the trial (23). With an expected drop-out rate of 20% the calculated sample size is 192. However, this estimate is solely based on mathematical principles and not patient observations. Thus, should concurrent studies performed on a related topic provide data on which we can base power analysis, we will ask REK for approval to adjust the sample size accordingly. In addition, we aim for inclusion of ≥ 50 patients with other native tongue than Norwegian, Swedish, Danish or English, as this is an important subgroup.

5.2 Randomization

At baseline, patients will be randomized according to a randomization scheme (ratio 1:1 for intervention vs control generated by a Statistician at Akershus University Hospital) and administered by a co-worker at Akershus University Hospital who does not take part in the study. The PI, or any other member of the study group, plays no role in the randomization process and will not be given access to the randomization scheme during the recruitment period. There is no blinding procedure (open clinical trial).

5.3 Statistical Analysis

All statistical tests will be performed using a 5% significance level unless otherwise stated. We will calculate delta values for efficacy variables (change from baseline to the final visit) for the intervention and control groups. The main statistical approach will be t-test for independents groups. For the composite end-point of positive SARS CoV2 test, hospitalization or death we will use odds ratio as the outcome measure.

Demographics and efficacy data will be summarized using means and standard deviations for normally distributed continuous variables, medians and interquartile range for non-normally distributed continuous variables and percentages for categorical variables.

Subgroup analysis will be performed according to (high vs low) educational level and modality of renal replacement therapy.

6 ETHICAL AND REGULATORY REQUIREMENTS

6.1 Ethics Committee Approval and Other Regulatory Approvals

The Protocol will be submitted and approved by the applicable competent local and national authorities before enrollment of patients in the study. The PI is responsible for informing these parties of any amendments to the Protocol as per national requirements.

6.2 Informed Consent

The PI and his designates is responsible for giving the patients full and adequate verbal and written information about the nature, purpose and risk/benefit of the study. They will be informed as to the strict confidentiality of their patient data, but that medical records will be reviewed for trial purposes by the PI in order to record data on SARS Cov2 tests and hospitalizations during two years of follow-up. It will be emphasized that the participation is voluntary and that the patient is allowed to withdraw from the study whenever she/he wants. Moreover, it will be emphasized that study participants need not respond to all questions. Participants need not give a reason for why they choose not to respond. Informed consent is mandatory before performing the baseline semi-structured interview in accordance with the national regulatory requirements. The study subjects must be provided with reasonable time to read and understand the Participant Information Form before giving written informed consent to participate in the study. We have included a shortened modified version of the CRF in Norwegian and English attached to The Participant Information Form, hence they will know what kind of questions they will be faced with. At the baseline and end of study visits the questions included in the interview will be handed out to them. Upon request the patient will be provided with a verbal translation of the Participant Information Form in the patient's native tongue (if other than English or any Scandinavian language), as described in section 4.1.2. The PI is responsible for keeping a list of all study subjects including in the study. In the electronic CRF a study participant will be identified by the randomization number only.

7 TRIAL SPONSORSHIP, FINANCING AND PUBLICATION POLICY

The Renal Department at Akershus University Hospital is the sponsor for this study. The study group will apply for external funding, but no funding parties will be allowed to play any role in study design, data collection, data analysis, interpretation, manuscript preparation or the decision to submit.

All personnel who have contributed significantly with the planning and performance of the study (Vancouver convention 1988) may be included in the list of Authors. International guidelines for authorship will be adhered

to persons designed as Authors. They have to qualify for authorship by participating sufficiently in the work to take public responsibility for the content. It emphasized however that only those who entirely meet with these criteria will be listed as Authors. The findings of this study will in due course and by mutual agreement be published in a scientific journal.

8 REFERENCES

1. www.fhi.no Norwegian Institute of Public Health website
2. Williamson EJ, Walker AJ, Bhaskaran K et al. Factors associated with Covid-19 related death using OpenSAFELY. Nature 2020; 584:430.
3. Wiersinga JW, Rhodes A, Cheng AC, Peacock SJ and Prescott HC. Pathophysiology, transmission, diagnosis and treatment of Covid-19. JAMA 2020; 324:782.
4. Jager KJ, Kramer A, Chesnaye NC et al. Results from the ERA EDTA Registry indicate a high mortality due to Covid-19 in dialysis patients and kidney transplant recipients across Europe. Kidney Int 2020, ePub ahead of print, doi:10.1016
5. Giddens, A. What's next? Covid-19 and the future world order. Invited lecture at UiO, Sept 17th 2020.
6. https://helsenorge.no/
7. www.imdi.no The directorate of integration and diversity website
8. Basch CH, Hillyer GC, Meleo-Erwin ZC et al. Preventive behaviors Conveyed on YouTube to mitigate transmission of Covid 19: Cross-sectional study. JMIR Public Health Surveill 2020; 6:e18807.
9. Zarocostas J. How to fight an infodemic. Lancet 2020; 395:676.
10. Donald M, Beanlands H, Straus S et al. Identifying the needs for self-management interventions for adults with chronic kidney disease and their caregivers: A qualitative study. Am J Kidney Dis 2019; 74:474.
11. https://clinicaltrials.gov/
12. Norman CD, Skinner HA. eHEALS. The eHealth Literacy Scale. J Med Internet Res 2006; 8:e27
13. https://nornesk.no/forskningskart/NIPH_experiencesMap.html Norwegian Institute of Public Health Report.
14. Nutbeam D. Health literacy as a public health goal. Health Promot Int 2001; 15:259.
15. Berkman ND, Sheridan SL, Donahue KE et al. Low health literacy and health outcomes: an updated systematic review. Ann Intern Med 2011; 155:97.
16. Fraser S, Roderick PJ, Casey M et al. Prevalence and associations of limited health literacy in chronic kidney disease: a systemic review. Nephrol Dial Transplant 2013; 28:129.
17. Dahl KG, Andersen MH, Urstad KH et al. Identifying core variables associated with health literacy in kidney transplant recipients. Prog Transplant 2020; 30:38.
18. Taylor DM, Bradley JA, Bradley C et al. Limited health literacy in advanced kidney disease. Kidney Int 2016; 90:685.
19. Lancaster T, Stead LF. Individual behavioral counselling for smoking cessation. Cochrane Database Syst Rev 2017; 3: doi: 10.1002.
20. www.teachback.org
21. https://www.lnt.no/
22. https://www.youtube.com/watch?v=W_1qJoX866Y
23. Tabachnick BG, Fidell LS. Using multivariate statistics. Pearsons New International Edition 2013.