Intensive Care of Elderly: What do They Wish for Themselves?

NCT05149040

Study protocol and Statistical Analysis Plan

06.06.2021 (version 3, IBM approval)

Project Description

1. Project Title

Treatment preferences of very elderly Norwegians in the event of acute life-threatening illness, and family members' ability to predict these treatment preferences: A self-administered survey.

2. Background

Very elderly patients (aged 80 years and older) are a large and steeply increasing patient population in western intensive care units (ICUs), but the overall benefit of intensive care for these patients remains controversial [1, 2]. Will ICU admission improve survival and quality of life, or will it prolong suffering and delay natural death? In case of medical uncertainty, crucial significance is attached to the patient's treatment preferences, but less than 1 in 4 very elderly ICU patients retain decision making capacity [3]. Therefore, information about the patient's likely will is frequently sought through a family conference.

Knowledge regarding the very elderlies' life sustaining treatment (LST) preferences is scarce and has recently been rated as number two of top-ten research-topics by a broad panel of experts [4-6]. To our knowledge, so far no survey instrument for this purpose exists.

Research addressing the accuracy of proxy statements by family members has only shown low to moderate correlation [7, 8]. Both internal and external validity of the existing research addressing proxy accuracy is limited.

3. Study design

The overall goal of this project is to improve critically ill very elderly patients' ICU trajectories by bringing forth knowledge about their treatment preferences, their family members' ability to predict their wishes, and by directing attention to confounders of shared decision-making under uncertainty.

3.1. Research questions:

- Which preferences do very elderly people have regarding LST in the event of acute illness warranting ICU admission?
- How accurate can close family members predict the treatment preferences of a temporarily incapacitated very elderly patient with acute life-threatening illness?
- Are there factors that impact on very elderly patients' LST preferences, and on the ability of a close family member to predict these preferences?

3.2. Preregistration:

We plan to preregister the proposed study on www.CinicalTrials.gov.

3.2. Protocol:

Choice of method: This study has an exploratory design and aims to investigate decision-making processes regarding choices where the informants can't be exposed to an experimental decision due to both the nature of the choice and seriousness of the consequences. Despite its well-acknowledged weaknesses, hypothetic scenario-based survey research emerged as a suitable approach based on a mapping review of the medical literature and on transferred knowledge derived from decision-

making research in other fields where decisional stakes are high as for example in criminology, economy, and politics [9-12].

We plan to develop and to validate a survey instrument and to conduct a self-administered survey of Norwegian residents aged 80 and older and a close family member who likely would act as a proxy in an event of acute illness.

Target population and sampling frame: Due to ethical concerns regarding exposure of very elderly patients to hypothetical treatment choices which they in real life would not be offered, we attempt to exclude patients who are not regarded potential ICU candidates in Norway owing to low physical and/or cognitive function. Furthermore, we have limited knowledge on whether very elderly people in Norway might experience a questionnaire addressing critical illness and risk of dying as a burden. We prefer therefore a sampling method where the informants have a short face-to-face encounter with one of the investigators followed by the offer to re-contact by phone or e-mail in case of emotional distress related to completing the questionnaire. For these two reasons, we abandoned the idea of a mailed survey to a random generated population-based sample and decided to study a purposive sample of potential ICU candidates aged 80 years or more.

We plan to recruit study participants by approaching all patients ≥ 80 years at the orthopedic, ophthalmologic and ear, nose and throat outpatient clinics at Haukeland University Hospital consecutively. We will exclude patients who are blind, not fluent in Norwegian, or are not able to meet for the consultation without assistance as a rough surrogate measure of markedly reduced physical and / or cognitive function. We deem the patient populations of these outpatient clinics to be least skewed towards underlying comorbidities and chronic organ impairment compared to other medical or surgical outpatient clinics. The patients will receive an information sheet about the study upon registration, and if they are interested in participating they will receive a pair of cover letters, questionnaires and stamped return envelopes; one of each for the very elderly patient him- or herself, and one for the most likely designated proxy in the event of acute critical illness. The very elderly respondents, with age < 18 years being the only exclusion criterion, identify the potential proxy respondents. The participants are asked to complete the questionnaires by themselves and without consulting each other, and to return them by mail in the provided stamped envelope. No incentives or compensation will be offered, and no reminders will be sent. Patients having several outpatient appointments during the study period will only be approached once.

We will account for age and gender of very elderly patients approached, but not enrolled, as well as age and gender of the very elderly non-respondents. Will we not be able to account for any characteristics of non-respondents among potential proxies.

Sample size: We will use a sample size of at least 400 pairs of participants. We expect a response rate of more than 50%, and we plan to continue inclusion until we have reached at least 200 elderly respondents. For more details on the sample size calculations, see the ‘Analysis’ section below.

Survey construction: Table 1 summarizes the structure of the questionnaires. They start with a short summary of background information regarding intensive care in general, and expected risks and benefits for very elderly patients in particular. Then the participant is asked to make a treatment choice regarding four clinical vignettes; the very elderly person is asked only about his or her own preferences, while the proxy is asked to both indicate the likely whish of the very elderly person, and his or her own preference. Three response options are provided: wishing admission to intensive care, not wishing admission to intensive care, and wishing to not engage in the decision.

	Very elderly person (potential patient)		Potential proxy	
Cover / instructions / contact information (p.1) Background information (p.2)				
	Paragraph no.	Questions	Paragraph no.	Questions
Vignettes/scenarios 1–4	1-4	4 x 3	1-4	4 x 6
Family involvement in medical decision-making	5	5	5	3
Experiences with intensive care and advanced care planning	6	5	6	6
Demographics	7	7	9	7
Health / frailty	8	5	7	5
EuroQuol		6	8	6
Comments	9	1	10	1
Re-contact permission	10	1		
Pages / questions (total)	15 / 42		18 / 53	

Table 1: questionnaire structure

The vignettes are randomly chosen among 20 hypothetical patient histories of acute life-threatening illness causing a higher degree of acute organ failure (equaling > 2 SOFA points) [13].

All vignettes are built up in a similar way, containing three paragraphs, following the same template:

1. 2–3 sentences regarding the current diagnosis and acute organ failure. The type and frequency of diagnoses is representative for ICU admission diagnosis in elderly patients in Norway and Europe (table 2). For each questionnaire, there will be four vignettes – two framed as a history of a male patient, and two framed as a female patient. The vignettes will be presented in a random order.
2. 3-4 sentences describing dichotomous therapeutic options as either intensive care with sedation requirements and some kind of invasive organ support or ward care with conservative treatment and the possibility for symptom alleviation.
3. 3 sentences on the consequences of the choice. The survival outcome estimates are based on short- and long-term outcome data from the VIP2- study data-set (table 2). The estimated quality of life regarding physical and cognitive function of ICU survivors aged ≥ 80 years is based on published data from Norway, Finland, the Netherlands and Canada [14-17], and a systematic review on cognitive impairment after intensive care [18]. Outcomes are identical for all vignettes, but in 50% of the questionnaires, the expected outcome is framed as mortality and in 50% as survival. The same framing is used for all four vignettes in each questionnaire.

	VIP-2 (May 2018-May 2019)				NIR (May 2018-May 2019)			
ICU admission diagnosis	N (%)	Survival (%)			N (%)	Survival (%)		
		ICU	30 d	6 m		ICU	30 d	1 y
Overall	3921 (100)	73	75	40	3069 (100)	86	67	47
ARF	941 (24)	75	76	34	951 (31)	84		
Sepsis	392 (14)	68	70	33	338 (11)	86		
Shock	540 (14)	72	71	34	737 (24)	88		
Acute surgery	541 (14)	80	82	45	614 (23)	86		
Trauma	233 (6)	69	70	30	215 (7)	85		
Neuro	190 (5)	68	68	30	153 (5)	87		

Table 2: Main admission diagnosis and survival of very elderly (≥ 80 år) ICU patients in Europe (VIP-2 data set, personal communication, Hans Flaatten, April 2021) and in Norway (NIR (Norwegian Intensive Care Registry), personal communication, Reidar Kvåle, April 2021)

Furthermore, the survey covers items that may influence treatment preferences and proxy accuracy including: demographics, education, religion, previous experience with and / or communication about serious illness, comorbidity (Charlson Comorbidity Index, [19]), frailty (Clinical Frailty Scale, version 2, [20]), quality of life (EuroQol-5D-5L, registration ID: 30864, [21]) and projection (i.e. the proxy's own treatment preferences, [8]). Items were generated by a mapping review of the existing literature on elderly patients' treatment and end-of-life preferences and on proxy accuracy in general. Additional items where identified by discussions within the research group.

The questionnaires ask for the following free-text comments:

- Elaborating the treatment choice made after each scenario
- Expectations regarding family members contribution into the decisional process
- General comments

In order to allow for a longitudinal follow-up survey aiming at assessing very elderlies' treatment preferences and proxy accuracy stability over time, the respondents are asked to provide their name and address at the end of the questionnaire. The respondents are informed that providing name and address for follow-up is voluntary, about their right to withdraw at any time and that taking part in a longitudinal cohort will impact on data handling, i.e. data will be stored pseudonymously instead of anonymously.

The longitudinal follow-up will be a separate study with revised questionnaires and revised protocol according to the findings of the cross-sectional study. New ethical approval for the longitudinal follow-up will be sought.

The layout of the questionnaire was created in compliance with the guidelines for visual design of paper questionnaires by Statistics Norway [22].

Face / Content validity: The draft of the questionnaire has been evaluated by 9 health care professionals (4 senior ICU consultants, 2 junior anesthetists, 2 ICU nurse specialists, 1 research nurse, 2 geriatricians, 1 public health specialist) and 6 laymen (2 elderly, 4 possible proxy decision makers, of those 2 with higher education, but no health care professionals).

Pre-testing: (February/March 2020): We pre-tested a preliminary version of the questionnaire containing only one vignette and no questions regarding demographic or health-related information among 20 grandparent/parent pairs of medical students. Completed questionnaires were returned anonymously by mail. The response rate was 45% with 8 complete pairs and may have been adversely affected by the coincidental society lock-down due to the CoVID-19 outbreak.

We assessed whether the case vignette was feasible, and produced responses with sufficient data dispersion to assess proxy accuracy and factors that might impact on the choices made.

Elderly's preference	N	Son's / daughter's prediction			
		Wants ICU admission	Does not want ICU admission	Wants the doctor to decide	Unsure about the elderly's preference
Wants ICU admission	3	1	**1**	**1**	
Does not want ICU admission	1		1		
The doctor should decide	4	1		2	1
Unsure	0				

Table 3: Pre-test results (cases of apparent assumed similarity in red)

We reduced and adjusted the "uncertain" and "the doctor should decide" answer categories to "wishing to not engage in the decision" after the pre-test in order to more precisely match the Norwegian regulations, where patient preferences are an important information into the medical decision process, but the ultimate decisional authority remains with the treating physician(s). Additional space for free-text comments is provided, and the respondents are asked to elaborate the reason for their preference. Moreover, we abstracted confidence into the choices made as an independent item and ask the participant to indicate for each scenario how certain they feel about their answer regarding treatment preference on a five-point Likert scale.

The pretest also revealed cases of assumed similarity, where the son/daughter apparently decided according to his/her own preferences which were different from the preferences of their elderly mother / father (red numbers in table 2). None of the respondents commented on unpleasant feelings when confronted with a question regarding life-threatening illness, but several both elderly persons and their adult children volunteered that they perceived the question to be relevant, important, and not sufficiently addressed yet.

An interesting observation from the pre-test was that respondents who opted for their physician to decide had less or no free text comments, compared to respondents who made a clear choice.

Pilot testing: We plan to assess the penultimate versions of the questionnaires (one for the very elderly person, and one for the potential proxy) for face validity, and clinical sensibility as well as to pilot them regarding relevance, flow, arrangement and time to complete.

Validation method: We aim to recruit 10 very elderly people (≥ 80 years) and 10 family members of very elderly people (≥ 80 years) who likely would act as a designated proxy in case of an acute health related event through user representatives, the interest organization "Senior Norge", the volunteer service at Haukeland University Hospital and advertisements in public spaces, social media and local print media. We aim for balance regarding gender, educational and cultural background. Potential participants will get information about the project by phone, and upon verbal consent receive the questionnaire validation package by mail. The package contains an information letter with written consent, the respective questionnaire (vey elderly person or proxy, version 2), and an evaluation sheet comprising items regarding practical aspects, sensibility and validity of the questionnaire, alongside with an invitation to a group interview.

The participants are asked to complete the questionnaire and the evaluation sheet before the interview. They may keep the questionnaire and the evaluation sheet as an aid memoire during the interview, but are encouraged to not change their written answers. The evaluation forms will be collected after the interview. They do not contain any personal identifiable data.

The interviews will take place at Haukeland University Hospital, and will follow a standardized template. Two investigators will meet approximately 5 participants. The group interview will be chaired by the principal investigator (GLS), assisted by a co-investigator, who also will write minutes (MAS). An experienced intensive care nurse (BÅS) will be available during all interviews in case any participant requires assistance or comfort.

The content, wording and lay-out of the questionnaire and cover letter will be revised according to the data from the evaluation sheets and a synthesis of the focus group interviews. Data regarding validity and clinical sensibility of the questionnaire will be reported as numbers / percentages in the method chapter of the main study. Input from the focus group interview will also be used to inform about any possible additional ethical concerns not yet known to the investigators.

Analysis: We will report basic descriptive statistics (e.g., frequencies, means, and standard deviations) for the items included in the questionnaire.

To estimate the participants' preferences regarding life-sustaining treatment, we will calculate the proportion of responses in each category ('wants ICU admission', 'does not want ICU admission', 'does not want to engage in the decision'), along with 95% confidence intervals. With responses from 200 patients, we can estimate the preference proportions with an absolute margin of error less than 7%, based on 95% confidence intervals, which we deem sufficient. For example, if 50% of the respondents wanted ICU admission, the corresponding 95% confidence interval would be approx. 43%–57%.

To investigate factors associated with the participants' LST preference, we will use (mixed-effects) logistic regression analysis. The response variables will be a) having a preference ('wants ICU admission' or 'does not want ICU admission), b) wanting ICU admission (for the subset who have a preference), or c) 'does not want to engage in the decision'. Alternatively, we will use multinomial regression for the three preference categories. We will fit two types of models, with the following explanatory variables.

Model 1 (experimental variables):
Gender of vignette patient (two levels), survival vs. mortality framing (two levels).

Model 2 (experimental + observed variables):
Variables from model 1, and additionally age (continuous), gender (two levels), religion (three levels), comorbidity (continuous; Charlson Comorbidity Index), frailty score (continuous; Clinical Frailty

Scale), health-related quality of life (continuous; EQ-5D VAS), and experience with intensive care (two levels).

We will only have statistical power to detect large effects. For example, the effect of a binary predictor with a prevalence of 50% (e.g., the survival vs. mortality framing predictor) must correspond to an odds ratio of at least 2.33 (outcome 50% vs. 70%) for the power to be 80% or greater (with 200 participants). For continuous predictors, an odds ratio of 1.5 for the event rate at one standard deviation above the mean compared to the event rate at the mean, will be sufficient.

The above calculations are based on simple logistic regression, i.e., assuming that only *one* preference (from one patient vignette) is expressed for each participant. In practice, there will be four (correlated) preferences for each participant, and we will use statistical methods that take this into account (mixed-effects logistic regression instead of logistic regression). This will increase the statistical power; i.e., we will be able to detect lower odds ratios.

To assess the proxies' ability to predict their family member's preference, we will estimate the overall percentage agreement. Again, the absolute margin of error will be less than 7% (based on a 95% confidence interval). We will also estimate the agreement stratified by the family member's preference. Other measures of agreement (e.g., chance-corrected agreement) may also be calculated.

Furthermore, we will attempt to use (mixed-effects) logistic regression to examine variables associated with 'correct prediction' (and additionally stratified by the elderly's preference [23]). Only responses where the elderly has a preference ('wants ICU admission' or 'does not want ICU admission') will be included [24]. The analysis will only be carried out if enough elderly patients have a preference (we aim to have at least 5, and preferably 10 preferences, for each predictor variable that is included). The following predictors may be included:

Proxy's prediction, elderly's and proxy's certainty in the proxy's prediction of elderly's preference, proxy's preference, proxy's experience with intensive care, communication about end of life decisions, elderly's gender, proxy's gender, interaction between elderly's and proxy's gender, absolute difference in age between the elderly and the proxy, and proxy's assessment of elderly's frailty. (Predictors with high multicollinearity may be excluded.)

In all analyses where multiple responses are included for each participant or pair, we will use statistical methods that take this into account (e.g., mixed-effects logistic regression instead of ordinary logistic regression).

If free-text comments result in rich data, they will be analyzed by Systematic Text Condensation (STC) [25] and published separately.

4. Project organization

4.1. Research group:

Principal investigator:
Gabriele Leonie Schwarz, MD, SSAI and European Diploma of Intensive Care. Senior consultant at the Department of Surgical Services, Intensive Care Unit, Haukeland University Hospital.

Co-investigators:
Margrethe Aase Schaufel, MD, PhD, Associate Professor in Pain Medicine and Palliative Care, senior researcher and consultant, Department of Thoracic Medicine, Haukeland University Hospital.
Prof. Hans Flaatten, MD, PhD, Professor in Anaesthesia and Intensive care, Department of Clinical Medicine, University of Bergen. Coordinator of the European VIP network and principal investigator of the VIP study group, investigating outcomes and prognostic factors in very elderly intensive care patients.

Prof. Reidar Kvåle, MD, PhD, Professor in Anaesthesia and Intensive care, Department of Clinical Medicine, University of Bergen. Senior consultant, Department of Surgical Services, Intensive Care Unit, Haukeland University Hospital. Special research interest in very elderly patients' outcomes after ICU admission.
Prof. Ingrid Miljeteig, MD, PhD, Associate Professor in Medical Ethics, Department of Clinical Science, University of Bergen. Experienced researcher in priority setting and decision making.
Karl Ove Hufthammer, PhD, Biostatistician, Centre for Clinical Research, Haukeland University Hospital.
Elisabeth Skaar, MD, PhD, Specialist in Geriatric Medicine and Cardiology, Department of Heart Disease, Haukeland University Hospital.

Local Collaborators:
Prof. Roger Strand, Professor, Centre for the Study of the Sciences and Humanities, University of Bergen. Special research interest in "Uncertainty and complexity in the science-society interface".
Britt Ågot Sjøbø, Nurse specialist in Intensive Care and research nurse, Haukeland University Hospital, Master in Evidence Based Medicine.
Randi Hag, User representative, Senior Norge.

International Collaborator:
Karen E.A. Burns, MD, FRCPC, MSc, Staff Physician, Critical Care Medicine, St. Michael's Hospital. Clinician Scientist, Li Ka Shing Knowledge Institute of St. Michael's Hospital. Associate Professor, Department of Medicine, University of Toronto, Canada. Leader of a Canadian research program to characterize the unique aspects of the consent process in critical care.

4.2. Founding:

The project receives founding from Helse-Vest (the Western Norway Regional Health Authority), to cover 50% redemption of the principal investigator from clinical duties from March 2021 to December 2021, as well as user representative fees, and expenses for printing and postage.

None of the investigators have other bindings to declare or disclosures to make.

4.3. Plan / Milestones

Timeline	completed	completed	completed	Mai / June 2021	Juli / August 2021	September/ October 2021	November / December 2021
Survey develop-ment steps	Item generation	Item reduction Face / content validity assessment	Vignette feasibility (data dispersion)	Protocol write-up REC application	Pilot testing: - Relevance - Flow - Arrangement Clinical sensibility testing	Survey administration Data collection	Analysis Write-up
Approach	Mapping review Expert / laymen interviews	Expert / laymen interviews	Pre-test		Focus-groups (public engagement events) - Very elderly - Potential proxies	Recruitment of at least 400 outpatients	
Instrument version	0	1	1	2	2	3	

Table 4: study progress plan

4.3. Dissemination:

We plan to publish the results in a peer reviewed scientific medical journal.

Suggested authorship: G.L. Schwarz, E. Skaar, I. Miljeteig, K.O. Hufthammer, K.E.A. Burns, R. Kvaale, H. Flaatten, M.A. Schaufel

4.4. Plans for Implementation

The results of this project will be used to develop a clinical decision aid to guide intensivists when assessing very elderly patients with acute life-threatening illness, also incorporating illness severity scoring, frailty scoring, and assessment of capacity. The questionnaire if proven feasible in the proposed study will also serve as a template for further development of a European questionnaire for the conduction of an already proposed multinational survey [4].

5. User Involvement

Collaboration with the Norwegian Senior Advisory Organization, Senior Norge, has been formalized by cooperation with Randi Hag who will assist at all steps of the research process, especially by checking comprehension and wording during survey and interview guide construction and by input from a lay perspective during data collection and dissemination of the results. The protocol has been presented to the user advisory board of the Western Norway Regional Health Authority, too, and we aim to recruit one more user representative into the research group.

The contribution by the user representative(s) and the public engagement events, i.e. focus group interviews during the questionnaire validation process, will be reported according to the GRIPP2-SF checklist [26].

6. Ethical considerations and data security

The project will be conducted in coherence with the principles for medical research as described by the Helsinki Declaration [27]. Ethical approval will be sought from The Regional Committee for Medical and Health Research Ethics. The Regional Ethical Committee as well as the data protection officer at Haukeland University Hospital have already assessed the questionnaire validation project (focus group interviews) and waived consent, since no patients are involved and no identifiable, health related or otherwise sensitive data of the informants will be stored (REK-ID: 276403, 25.5.2021).

Written informed consent will be obtained from all participants of the focus group interviews before pilot and clinical sensibility testing.

Informed consent by the respondents of the survey will be regarded implicit by completing and returning the questionnaire. Personal data from anonymously returned questionnaires will be stored anonymously in a designated closed domain on a research server kept at Helse-Vest IKT. Data provided by respondents who consent to a longitudinal follow-up by entering their name and address, will be stored pseudonymously and the identification keys will be stored separately on another designated closed domain on a research server kept at Helse-Vest IKT. The identification keys will be deleted no later than five years after the responses given by the same respondent from the first and second survey are aligned. The participants will be explicitly informed about the possibility for either anonymous or pseudonymous data storage in the surveys cover letters.

Discussing end-of-life issues can be experienced as a burden and this will be addressed in the survey's cover letters and handled with special attention during the focus group interviews. Contact

details (phone and e-mail) of the principal investigator (GLS) will be provided not only for questions regarding the study but explicitly also for emotional support. In addition, an experienced intensive care and research nurse will be available in during the focus group interviews to take care of participants who might require an individual conversation or comfort. Notwithstanding, a recent study where 33 Norwegian nursing home residents and their next-of-kin where interviewed regarding end-of-life communication and shared decision making, revealed that a majority of the informants welcomed these conversations, and none withdrew due to emotional distress [28].

The study does not imply any additional blood samples or imaging and potential adverse effects are considered low.

7. References

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